FOURTH EDITION

HOSPITAL EPIDEMIOLOGY AND INFECTION CONTROL

C. Glen Mayhall

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Wolters Kluwer Health | Lippincott Williams & Wilkins

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Acquisitions Editor: Frances DeStefano
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Senior Manufacturing Manager: Benjamin Rivera
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Design Coordinator: Holly McLaughlin
Production Service: SPi Global

Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
LWW.com

Printed in China

Library of Congress Cataloging-in-Publication Data
Hospital epidemiology and infection control / editor, C. Glen Mayhall. — 4th ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-1-60831-300-6
ISBN-10: 1-60831-300-X
1. Nosocomial infections—Prevention. 2. Nosocomial infections—Epidemiology. 3. Cross infection–Prevention. I. Mayhall, C. Glen.
[DNLM: 1. Cross Infection—epidemiology. 2. Cross Infection—prevention & control. 3. Bioterrorism. 4. Infection Control—methods. WX 167]
RA969.H635 2012
614.4'4—dc23

2011015849

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10 9 8 7 6 5 4 3 2 1

With tremendous gratitude to all of my colleagues and authors who have made the commitment and worked so hard to provide excellent chapters for the four editions of this book.

PREFACE FOR THE FOURTH EDITION

Once again, I appreciate the opportunity to edit the Fourth Edition of Hospital Epidemiology and Infection Control. The Fourth Edition has 104 chapters prepared by 184 authors. It has the most changes between editions compared to those between the First and Second Edition and those between the Second and Third Edition. Nineteen chapters from the Third Edition were retired, and ten new chapters were added to the Fourth Edition. The authors of the chapters on computer fundamentals and on the personal computer collaborated on a single chapter for the Fourth Edition entitled "Using the Personal Computer for Healthcare Epidemiology." A chapter on meta-analysis was added to Section I, and another new chapter in this section integrates the information from the other chapters in the section to provide the reader with a useful approach to study design and data analysis. This author cites other chapters in the section by page number.

Once again, my good friend and colleague, Dr. David Birnbaum, provided guidance and direction on revision of Section II on Healthcare Quality Improvement. I particularly appreciate his suggestion on adding a chapter on working with the media on public communication.

Other new chapters include mechanisms of biofilm formation in staphylococci, microbiologic sampling of the environment in healthcare facilities, antimicrobial stewardship, and elements of design in the built environment of the healthcare facility. Biofilms have been recognized to be of importance in infections related to inanimate materials and devices inserted into patients. The chapter on environmental cultures was included, because when culture of the environment is indicated, the best data can be obtained when appropriate techniques are used to obtain the samples. The chapter on elements of design of the built environment is intended to be a companion chapter to the chapter on prevention of infections related to construction. Inclusion of a chapter on antimicrobial stewardship relates to the increasing resistance of healthcare-associated microorganisms and the need for defined programs to prevent antimicrobial resistance. The first two chapters in Section XIII provide an excellent background for the chapter on antimicrobial stewardship.

Many chapters in this edition have new coauthors and several chapters have been revised or rewritten by an entirely new set of authors.

A new feature for the Fourth Edition is that only 15 to 20 key references are located at the end of the chapters in the printed book while all references cited in the chapters are online. The numbers for the references that are only online are italicized in the text whereas the numbers for the references printed at the end of the chapters are not italicized in the text.

As for all of the editions of this reference text, my goal has been, and is, to bring together many of our colleagues with particular areas of expertise in Healthcare Epidemiology and other experts in related fields to provide a comprehensive and up-to-date reference text that the reader will find useful in the daily practice of Healthcare Epidemiology.

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ACKNOWLEDGMENTS

I greatly appreciate the excellent contributions made by my administrative assistant Denise R. Morris and the developmental editors Louise Bierig and Sarah Granlund for Lippincott Williams & Wilkins.

CONTENTS

SECTION V: EPIDEMIOLOGY AND PREVENTION OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY SPECIFIC PATHOGENS

SECTION XVI: HEALTHCARE EPIDEMIOLOGY AND INFECTION CONTROL IN SPECIAL SETTINGS FOR HEALTHCARE DELIVERY

SECTION XVII: BIOTERRORISM

SECTION I

Applied Epidemiology and Biostatistics in Healthcare Epidemiology and Infection Control

CHAPTER 1

Principles of Infectious Diseases Epidemiology

Lennox K. Archibald

Epidemiology is defined as the study of the factors determining the occurrence of diseases in human populations. It is an indispensable tool for characterizing infectious disease occurrences in medical institutions, communities, regions, or industry, and for determining the exposure–disease relationship in humans and the modes of acquisition and spread that are critical for treatment, control, and prevention of these infectious disease occurrences. Clinicians, microbiologists, and other personnel involved in the preventive and public health professions use epidemiologic methods for disease surveillance, outbreak investigations, infectious diseases outcome measurements, and observational studies to identify risk factors for various infectious diseases. Knowledge of these risk factors is essential for making decisions regarding further epidemiologic or microbiological investigations, directing research activities, implementing relevant prevention and control measures or interventions, and establishing public health policies. In the pharmaceutical and biomedical industries, the application of epidemiologic methods is integral to the investigation of intrinsic contamination of products, ascertainment and characterization of risk factors for contamination, and maintenance of quality assurance practices in the laboratory or manufacturing operations before distribution of products.

The use of epidemiology and the use of statistical methods to analyze epidemiologic data grew out of attempts to understand, predict, and control the great epidemics of our past; the diseases associated with those early epidemics were largely infectious. The study and implementation of infection control practices and interventions grew out of the need to understand and control the institutional epidemics of infectious diseases that complicate the care of the ill *(1,2)*. Thus, discussions of the principles of epidemiology begin with examples of methods that were first formalized in the study of transmissible microorganisms, many of which continue to cause problems today.

The term *hospital epidemiology* was a modern addition by workers in the United States *(3)*, as was the recognition of the potential use of epidemiologic methods in hospitals for the study and control of noninfectious diseases *(4)*. The term *nosocomial* infection has traditionally defined acute infections acquired in the hospital inpatient setting *(5)*. However, in the current era of managed care, healthcare systems in the United States have evolved from the traditional acute care hospital inpatient setting to a new integrated, extended care model that now encompasses hospitals, outpatient clinics, ambulatory centers, long-term care facilities, and the home. As expected, infections (and antimicrobial resistance among implicated pathogens) may be acquired at any of these levels of care. For this reason, the term *nosocomial infection* has been replaced by *healthcare-associated infection*. Except for the acute care hospitals, however, the relative importance of each of these levels of care as risk factors for the acquisition of healthcare-associated infections remains largely uncharacterized or unknown.

The terms *hospital epidemiology* and *infection control* remain synonymous in the minds of many, and both the terms and their associated programs have grown in definition and function over the past five decades. Interest in infection control has broadened from focused concerns

with puerperal sepsis and surgical site infection to full, scientifically tested programs of surveillance, prevention, and control of healthcare-associated infections acquired at other anatomic sites. Hospital epidemiology programs were among the earliest projects used to demonstrate the utility of the scientific method and statistics for characterizing and analyzing infectious diseases data and using the results of these analyses to improve the quality of care and patient outcomes. In the special environment of the acute care hospital, a natural repetition of earlier studies of population-based infectious diseases provided the basis for epidemiologic investigations.

Surveillance data generated from epidemiologic studies may be used to determine the need for clinical or public health action; assess the effectiveness of prevention, intervention, or control programs, or diagnostic algorithms; or set priorities for rational or appropriate use of limited microbiology resources, planning, and research. An understanding of epidemiology is important for quantifying and interpreting microbiology and pharmaceutical data, and for application of these data to clinical practice, quality assurance, hypothesis generation during investigation of outbreaks and other adverse events, rational prescribing policies, and public health.

Data from epidemiologic and microbiological studies can inform diagnostic and therapeutic practice and indicate areas for allocation of already scarce resources. For example, one of the perennial problems that clinicians and microbiologists face is how to differentiate between true bacteremia and blood culture contamination resulting from coagulase-negative staphylococci, which are the most frequently isolated microorganisms in blood cultures (6). Blood culture contamination can occur during venipuncture if the skin is not adequately cleaned, after the blood draw at the time of inoculation of blood into the culture bottle, or at some point during processing of blood culture bottles in the microbiology laboratory. To make an informed decision on true bacteremia versus contamination, clinicians and microbiologists need to be familiar with the epidemiology of bloodstream infections in different clinical settings and be able to integrate these data with the relevant clinical and microbiology information at hand so that a decision could be made whether or not to initiate antimicrobial therapy or request additional, supplemental investigations that might facilitate the decision-making process.

DEFINITIONS

In the application and discussion of epidemiologic principles, standard definitions and terminology have been widely accepted *(7,8)*. The definitions of some commonly used terms are outlined in this section:

Attack rate A ratio of the number of new infections divided by the number of exposed, susceptible individuals in a given period, usually expressed as a percentage. Other terms are the *incidence rate* and the *case rate*.

Attributable mortality indicates that an exposure was a contributory cause of or played an etiologic role leading to death.

Attributable risk The measure of impact of a causative factor. The attributable risk establishes how much of the disease or infection is attributable to exposure to a specific risk factor. It is a proportion where the numerator is the difference between the incidence in exposed and unexposed groups and the denominator is the incidence for the exposed group.

Bias The difference between a true value of an epidemiologic measure and that which is estimated in a study. Bias may be random or systematic. There are three types of bias: selection bias, information bias, and confounding. Selection bias is a distortion in the estimate of effect resulting from the manner in which parameters are selected for the study population. Information bias depends on the accuracy of the information collected. Confounding arises from unrecognized factors that may affect interpretation of epidemiologic data. Unrecognized, systematic bias presents the greatest danger in studies by suggesting relationships that are not valid (see also Chapter 2).

Carrier An individual (host) who harbors a microorganism (agent) without evidence of disease and, in some cases, without evidence of host immune response. This carriage may take place during the latent phase of the incubation period as a part of asymptomatic disease or may be chronic following recovery from illness. Carriers may shed microorganisms into the environment intermittently or continuously, and this shedding may lead to transmission. Shedding and potential transmission may be increased by other factors affecting the host, including infection by another agent.

Case An individual in a population or group recognized as having a particular disease or condition under investigation or study. This definition may not be the same as the clinical definition of a case.

Case–fatality rate A ratio of the number of deaths from a specific disease divided by the number of cases of disease, expressed as a percentage.

Cluster An aggregation of relatively uncommon events or diseases in time and/or space in numbers that are believed to be greater than are expected by chance alone.

Colonization The multiplication of a microorganism at a body site or sites without any overt clinical expression or detected immune reaction in the host at the time that the microorganism is isolated. Colonization may or may not be a precursor of infection. Colonization may be a form of carriage and is a potential source of transmission.

Communicability The characteristic of a human pathogen that enables it to be transmitted from one person to another under natural conditions. Infections may be communicable or noncommunicable. Communicable infections may be endemic, epidemic, or pandemic.

Communicable period The time in the natural history of an infection during which transmission to susceptible hosts may take place.

Confounding An illusory association between two factors when in fact there is no causal relationship between the two. The apparent association is caused by a third variable that is both a risk factor for the outcome or disease

and is associated with but not a result of the exposure in question.

Contact An exposed individual who might have been infected through transmission from another host or the environment.

Contagious Having the potential for transmission.

Contamination The presence of an agent (e.g., microorganism) on a surface or in a fluid or material—therefore, a potential source for transmission.

Cumulative incidence The proportion of at-risk persons who become diseased during a specified period of time.

Endemic The usual level or presence of an agent or disease in a defined population during a given period.

Epidemic An unusual, higher-than-expected level of infection or disease by an agent in a defined population in a given period. This definition assumes previous knowledge of the usual, or endemic, levels.

Epidemic curve A graphic representation of the distribution of defined cases by the time of onset of their disease.

Epidemic period The time period over which the excess cases occur.

Hyperendemic The level of an agent or disease that is consistently present at a high incidence and/or prevalence rate.

Immunity The resistance of a host to a specific agent, characterized by measurable and protective surface or humoral antibody and by cell-mediated immune responses. Immunity may be the result of specific previous experience with the agent (wild infection), from transplacental transmission to the fetus, or from active or passive immunization to the agent. Immunity is relative and governed through genetic control. Immunity to some agents remains throughout life, whereas for others, it is short-lived, allowing repeat infections by the same agent. Immunity may be reduced in extremes of age, through disease, or through immunosuppressive therapy.

Immunity: cell-mediated versus humoral Cell-mediated immune protection, largely related to specific T-lymphocytic activity, as opposed to humoral immunity, which is measured by the presence of specific immunoglobulins (antibodies) in surface body fluids or circulating in noncellular components of blood. Antibodies are produced by B lymphocytes, also now recognized to be under the influence of T-lymphocytic functions.

Immunogenicity An agent's (microorganism's) intrinsic ability to trigger specific immunity in a host. Certain agents escape host defense mechanisms by intrinsic characteristics that fail to elicit a host immune response. Other agents evoke an immune response that initiates a disease process in the host that increases cellular damage and morbidity beyond the direct actions of the microorganism itself. These disease processes may continue beyond the presence of living microorganisms in the host.

Incidence The ratio of the number of new infections or disease in a defined population in a given period to the number of individuals at risk in the population. "At risk" is frequently defined as the number of potentially exposed susceptible persons. Incidence is a measure of the transition from a nondiseased to a diseased state and is usually expressed as numbers of new cases per thousands (1,000, 10,000, or 100,000) per year.

Incidence rate or density Similar to the incidence but members of the at-risk population may be followed for different lengths of time. Thus, the denominator is the sum of each person's time at risk (i.e., total person-time of observation).

Incubation period The period between exposure to an agent and the first appearance of evidence of disease in a susceptible host. Incubation periods are typical for specific agents and may be helpful in the diagnosis of unknown illness. Incubation periods may be modified by extremes of dose or by variations in host immune function. The first portion of the incubation period following colonization and infection is frequently a silent period, called the *latent period*. During this time, there is no evidence of host response(s) and evidence of the presence of the infecting agent may not be measurable. However, transmission of the microorganism to other hosts, though reduced during this period, is a recognized risk (e.g., chicken pox, hepatitis B virus, human immunodeficiency virus [HIV]). Measurable early immune responses in the host may appear shortly before the first signs and symptoms of disease, marking the end of the latent period. Signs and symptoms of disease commonly appear shortly thereafter, marking the end of the incubation period.

Index case The first case to be recognized in a series of transmissions of an agent in a host population. In semiclosed populations, as typified by chronic disease hospitals, the index case may first introduce an agent not previously active in the population.

Infection The successful transmission of a microorganism to the host with subsequent multiplication, colonization, and invasion. Infection may be clinical or subclinical and may not produce identifiable disease. However, it is usually accompanied by measurable host response(s), either through the appearance of specific antibodies or through cell-mediated reaction(s) (e.g., positive tuberculin test results). An infectious disease may be caused by the intrinsic properties of the agent (invasion and cell destruction, release of toxins) or by associated immune response in the host (cell-mediated destruction of infected cells, immune responses to host antigens similar to antigens in the agent).

Infectivity The characteristic of the microorganism that indicates its ability to invade and multiply in the host. It is frequently expressed as the proportion of exposed patients who become infected.

Isolation The physical separation of an infected or colonized host, including the individual's contaminated body fluids and environmental materials, from the remainder of the at-risk population in an attempt to prevent transmission of the specific agent to the latter group. This is usually accomplished through individual environmentally controlled rooms or quarters, hand washing following contact with the infected host and environment, and the use of barrier protective devices, including gowns, gloves, and, in the case of airborne agents, an appropriate mask.

Morbidity rate The ratio of the number of persons infected with a new clinical disease to the number of persons at risk in the population during a defined period; an *incidence rate* of disease.

Mortality rate The ratio of those infected who have died in a given period to the number of individuals in the defined population. The rate may be *crude*, related to all causes, or *disease-specific*, related or *attributable* to a specific disease in a population at risk for the disease.

Odds The ratio of the probability of an event occurring to the probability of it not occurring.

Pandemic An epidemic that spreads over several countries or continents and affects many people.

Pathogenicity The ability of an agent to cause disease in a susceptible host. The pathogenicity of a specific agent may be increased in a host with reduced defense mechanisms. For some agent–host interactions, the resultant disease is due to the effects of exaggerated or prolonged action of defense mechanisms of the host.

Prevalence The ratio of the number of individuals measurably affected or diseased by an agent in a defined population at a particular point in time. The proportion of the population having the disease during a specified time period, without regard to when the process or disease began, defines the period prevalence.

Pseudo-outbreak Real clustering of false infections or artifactual clustering of real infections. Often it is identified when there is increased recovery of unusual microorganisms.

Rate An expression of the frequency with which an event occurs in a defined population. All rates are ratios. Some rates are proportions; that is, the numerator is a part of the denominator. A comparable rate is a rate that controls for variations in the distribution of major risk factors associated with an event.

Ratio An expression of the relationship between a numerator and a denominator where the two are usually distinct and separate quantities, neither being a part of the other.

Relative risk The ratio of the incidence rate of infection in the exposed group to the incidence rate in the unexposed group. Used to measure the strength of an association between exposures or risk factors and disease.

Reservoir Any animate or inanimate niche in the environment in which an infectious agent may survive and multiply to become a source of transmission to a susceptible host. Medical care workers and patients constitute the main animate reservoir for microorganisms associated with healthcare-associated infections; water-related sources are important inanimate reservoirs that have been implicated in outbreaks related to dialysis units and to air conditioning systems.

Secular trend Profile of the changes in measurable events or in the incidence rate of infection or disease over an extended period of time; also called a *temporal trend*.

Sensitivity For surveillance systems, the ratio of the number of patients reported to have an infection divided by the number of patients who actually had an infection.

Specificity For surveillance systems, the ratio of the number of patients who were reported not to have an infection divided by the number of patients who actually did not have an infection.

Sporadic Occurring irregularly and usually infrequently over a period of time.

Surveillance The ongoing systematic collection, analysis, and interpretation of healthcare data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those contributing data or to other interested groups who need to know. Surveillance was popularized by Langmuir and others at the Centers for Disease Control and Prevention (CDC) and has been the basic method in infection control programs in the United States since the 1960s.

Susceptibility A condition of the host that indicates absence of protection against infection by an agent. This is usually marked by the absence of specific antibodies or specific measures of cell-mediated immunity against the infecting microorganism.

Transmission The method by which any potentially infecting agent is spread to another host. Transmission may be direct or indirect. *Direct transmission* may take place by touching between hosts, by the projection of large droplets in coughing and sneezing onto another host, or by direct contact by a susceptible host with an environmental reservoir of the agent. *Indirect transmission* may be vehicle-borne, airborne, or vector-borne. In *vehicle-borne transmission*, contaminated environmental sources, including water, food, blood, and laundry, may act as an intermediate source of an infectious agent for introduction into a susceptible host. The agent may have multiplied or undergone biologic development in the vehicle. In *airborne transmission,* aerosols containing small (1–5 μm) particles may be suspended in air for long periods and inspired into the lower respiratory tract to become a site of infection in a host. These infectious particles may be generated by evaporation of larger particles produced in coughing and sneezing (*Mycobacterium tuberculosis*), by mechanical respiratory aerosolizers (*Legionella*), or by wind or air currents (fungal spores). In *vector-borne transmission,* arthropods or other invertebrates may carry or transmit microorganisms, usually through inoculation by biting or by contamination of food or other materials. The vector may be infected itself or act only as a mechanical carrier of the agent. If the vector is infected, the agent may have multiplied or undergone biologic development in the vector. This type of transmission has been of little importance for healthcare-associated infections in the United States.

Virulence The intrinsic capabilities of an agent to infect a host and produce disease and a measure of the severity of the disease produced. In the extreme, this is represented by the number of patients with clinical disease who develop severe illness or die—the case–fatality rate.

EPIDEMIOLOGIC METHODS APPLIED TO INFECTIOUS DISEASES

The classic epidemiologic methods are essential for the study, characterization, and understanding of the various infections that occur in healthcare settings, communi-

ties, or regions. Such methods are used to determine the exposure–disease relationship in humans; establish the modes of acquisition, mechanisms of transmission, and spread; identify risk factors associated with infection and disease; characterize and relate causal factors to an infectious disease; determine or select appropriate methods of prevention and control; or guide rational application and practice of clinical microbiology methods. These epidemiologic methods were developed in an attempt to control common errors in observations that occur when one studies the association of one event (a risk or causal factor) with another later event (the outcome or disease).

Epidemiologic study methods are grouped as either *observational* or *experimental*. Observational epidemiologic methods are further classified as either *descriptive* or *analytic. Observational studies* are conducted in natural, everyday community or clinical settings, where the investigators observe the appearance of an outcome but have no control over the environment or the exposure of people or product to a risk factor or suspected etiologic agent, a specific intervention or preventive measure, or a particular therapeutic regimen.

Descriptive Epidemiology

Observational descriptive studies establish the case definition of an infectious disease event by obtaining data for analysis from available primary (e.g., medical records) or secondary (e.g., infection control surveillance) sources. These data enable the characteristics of the population that has acquired the infection to be delineated according to (a) "person" (age, sex, race, marital status, personal habits, occupation, socioeconomic status, medical or surgical procedure or therapy, device use, underlying disease, or other exposures or events); (b) "place" (geographic occurrence of the health event or outbreak, medical or surgical service, place of acquisition of infection, or travel); and (c) "time" (preepidemic and postepidemic periods, seasonal variation, secular trends, or duration of stay in hospital). The information from descriptive studies might provide important clues regarding the risk factors associated with infection, and in each case it is hoped that an analysis of the collected data might be used to generate hypotheses regarding the occurrence and distribution of disease or infection in the population(s) being studied.

Analytic Epidemiology

Observational analytic studies are designed to test hypotheses raised by the findings in descriptive investigations. The objectives of these studies are (a) to establish the cause and effects of infection in a population and (b) determine why a population acquired a particular infection in the first place. The three most common types of observational analytic studies are cohort studies, case–control studies, and prevalence or cross-sectional studies.

Cohort Studies In cohort studies, hypotheses that have been generated from previous (descriptive) studies are tested in a new population. A population of individuals (a cohort) that is free of the infection or disease of interest is recruited for study. The presence or absence of the suspected (hypothesized) risk factors for the disease is recorded at the beginning of the study and throughout the observation period. All members of the cohort population (e.g., all premature infants admitted to a neonatal intensive care unit during a defined time period) are followed over time for evidence or appearance of the infection or disease and classified accordingly as exposed or unexposed to specific risk factors. If the observation period begins at the present time and continues into the future or until the appearance of disease, the study is called a *prospective cohort study*. If the population studied is one that in the past was apparently free of the markers of disease on examination of records or banked laboratory specimens, it may be chosen for study if data on exposure to the suspected risk factors for disease also are available. The population may be followed to the present or until the appearance of disease. This type of study, common in occupational epidemiology, is called a *historical* or *retrospective cohort study*.

A key requirement of a cohort study is that participants be reliably categorized into exposed and unexposed groups. *Relative risk*, that is, the ratio of the incidence of the outcome in the exposed group to the incidence in the unexposed group, is used to measure the strength of an association between exposures or risk factors and disease. Cohort studies have the advantage of enabling identification and direct measurement of risk factors associated with disease, determination of the incidence of infection and disease, and ascertainment of the temporal relationship between exposure and disease. In cohort studies, observational bias may be less of a limitation on the validity or results, since the information on the presence of risk factors is recorded before the outcome of disease is established. To ensure sufficient numbers for analysis, cohort studies require continual follow-up of large populations for long periods unless the disease under investigation is one of high incidence. Cohort studies are, in general, more expensive and time-consuming to conduct and are not suitable for the investigation of uncommon infections or conditions. However, they render the most convincing nonexperimental approach for establishing causation.

Case–Control Studies In a case–control study, individuals (cases) who are already infected, ill, or meet a given case definition are compared with a group of individuals (controls) who do not have the infection, disease, or other outcome of medical interest. In contrast to cohort studies, participants in a case–control study are selected by manifestation of symptoms and signs, laboratory parameters, or a specific condition, disease, or outcome. Thus, the search for exposure of case and control subjects to potential risk factors remains a retrospective one. For case–control studies, the measure of association between exposures or risk factors and health outcome is expressed as an odds ratio, that is, the ratio of the odds of an exposure, event, or outcome occurring in a population to the odds in a control group, where the odds of an event is the ratio of the probability of it occurring to the probability of it not occurring.

The presence of significant differences in the exposure to risk factors among case versus control subjects suggests an etiologic (causal) association between those factors and the infection or disease defined by cases. Case–control methods are useful for studying infections, events, or outcomes likely associated with multiple risk factors or

low incidence rates; for investigating situations in which there is a long lag-time between exposure and outcome of interest; and for establishing etiologic associations or causation of a disease, infection, or other outcome when there is no existing information about the cause or source. In an attempt to reduce bias, control subjects might be selected from individuals matched with cases for selected characteristics, such as age, gender, socioeconomic status, or other variables not suspected or under investigation as risk factors. Compared with cohort studies, case–control studies may be conducted in relatively shorter time, are relatively less expensive, or may require a smaller sample size to execute. Limitations of case–control studies include selection bias in choosing case and control subjects; recall bias in which study subjects might have difficulty in remembering possible exposures; incomplete information on specific exposures; or risk factor data may be difficult to find (or remember). Case–control studies are not used to measure incidence or prevalence rates and, generally, are not capable of establishing temporal relationships between an exposure and outcome.

Prevalence or Cross-Sectional Studies In prevalence studies, the presence of putative risk factors and the disease under investigation is recorded in a survey of a study population at a specific point in time or within a (short) time period. The rates of disease among those with and without the suspected risk factors are compared. Thus, cross-sectional studies can establish association but not causation for suspected risk factors. Prevalence studies are relatively inexpensive and can be carried out rapidly if well-planned. However, they do not allow the ascertainment of risk factors at the beginning of disease nor do they enable one to establish a temporal sequence of risk factors preceding the infection or other outcome of interest. Point prevalence, period prevalence, and seroprevalence surveys are examples of cross-sectional studies.

Experimental Epidemiology

In *experimental studies*, the investigator controls an exposure of individuals in a population to a suspected causal factor, a prevention measure, a therapeutic regimen, or some other specific intervention. These exposure modalities are *randomly* allocated to comparable groups, thereby minimizing confounding factors. Both the exposed and unexposed groups are monitored thereafter for specific outcomes (e.g., appearance of infection or disease, evidence of effective prevention or control of the disease, or cure). Experimental studies often are used to evaluate antimicrobial or vaccine treatment regimens and are generally expensive to conduct. Within healthcare settings, studies that examine restriction of certain antimicrobials or promotion of use of alternative antimicrobials for the control of antimicrobial resistance could be considered under the category of experimental. For ethical reasons, it is rarely possible to expose human populations to potential pathogens or to withhold a preventive measure that could potentially be beneficial to the patient. Unfortunately, animal hosts are not naturally susceptible to many agents of human disease. Thus, one has to be careful when extrapolating epidemiologic findings in animal experimental studies to the control of infections in human subjects.

Quasi-experimental studies: more recently, there has been an increase in the number of published papers describing results from these studies. This type of study shares the design characteristics of experimental studies but lacks random assignments of study subjects. Quasi-experimental studies are useful where randomization is impossible, impractical, or unethical. The main drawbacks of quasi-experimental studies are their inability to eliminate confounding bias or establish causal relationships.

EPIDEMIOLOGY OF INFECTION AND DISEASE

The epidemiology of infectious disease presents two processes for discussion: (a) the epidemiology of the determinants leading to infections in hosts and (b) the epidemiology of the appearance and extent of disease related to the infection in those hosts. It is common to discuss health and disease as the result of a series of complex interactions between an agent of change, the host that is the target of the agent's actions, and the mutual environment in which the host and agent are found. In studies of healthcare-associated infections, the agents are the microorganisms associated with the infections, the hosts are the patients under care or their healthcare workers, and the common environment is the acute care hospital, intensive care unit, outpatient, home, or other healthcare venues.

The interactions determining the probability of a microbiologic agent causing infection in a host may be simply presented by an equation of infection:

$$I_p = (D \times S \times T \times V)/H_d,$$

where I_p is the probability of infection, D is the dose (number of microorganisms) transmitted to the host, S is the receptive host site of contact with the agent, T is the time of contact (sufficient for attachment and multiplication or not), and V represents virulence, the intrinsic characteristics of the microorganism that allow it to infect. The denominator in the equation (H_d) represents the force of the combined host defenses attempting to prevent this infection.

Any reduction in host defenses (represented by the denominator) in such an equation allows infection to take place with a similar reduction in one or more of the agent factors in the numerator. Infection may take place with a smaller dose of microorganisms. Infection may take place at an unusual site. The contact time for a microorganism to fix to an appropriate surface may be briefer, or infection may take place with an agent of lesser virulence, one that does not cause infection in the normal host. These reductions in the host defense characteristics, represented by the denominator, and the reduction of requirements to infect for the agent are typical of the interactions that allow opportunistic infections in compromised hosts, represented by many patients under care in modern hospitals. In this model, equation of infection, the environment might be considered the background or playing field on which the agent–host interaction takes place. A number of additional models of the interaction of agent, host, and environment have been suggested to help understand these processes. The three models in Figure 1-1—the seesaw model, the

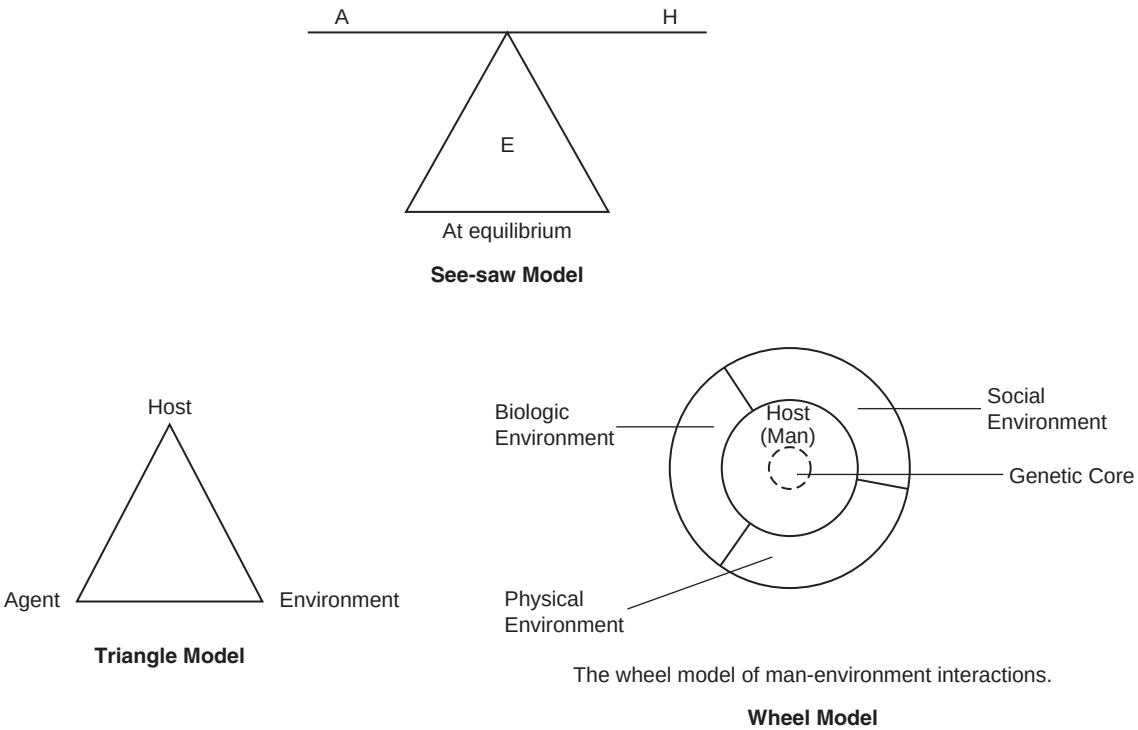

FIGURE 1-1 Models of interactions of agent, disease, and environment. (See-saw model from Fox JP, Elveback L, Gatewood L, et al. Herd immunity. *Am J Epidemiol* 1971;94:179–189, by permission of Oxford University Press. Triangle model and wheel model from Mausner JS, Kramer S, eds. *Mausner & Bahn epidemiology—an introductory text*. Philadelphia, PA: WB Saunders, 1985.)

triangle model, and the wheel model—have been frequently cited *(9,10)*. Each attempts to simply visualize the interplay between the three components.

INTERACTIONS OF AGENT, HOST, AND ENVIRONMENT

All outcome events (infection or disease) have multifactorial causes. For some infectious diseases, a single unique factor or agent is *necessary* and *sufficient* for the disease to appear. This is exemplified by measles or rabies. It is only *necessary* for the host to be exposed to and infected by an agent (the measles virus or the rabies virus) for that disease to develop. For other infectious diseases, the single factor of infectivity of the agent is *necessary* but not *sufficient* to cause disease in the host. *M. tuberculosis*, polio virus, hepatitis A, and many other agents *necessary* for specific disease in a human host infect without causing disease in a majority of cases. Within the hospital setting, exposure to a specific microorganism or colonization of an inpatient with an agent, such as vancomycin-resistant *enterococcus* (VRE) or *Staphylococcus aureus*, may be *necessary* but not *sufficient* to generate disease, which only develops through complex interactions between other contributory factors, such as age, state of debilitation, immune or nutritional status, device use, invasive procedures, antimicrobial usage, or susceptibility of the microorganism to available antimicrobials. The fact of the infection in these cases is not *sufficient* to produce disease in the host without the contribution of these latter elements in the host and the environment.

Agent

The agents causing healthcare-associated infectious diseases are microorganisms ranging in size and complexity from viruses and bacteria to protozoa and helminths. Bacteria, fungi, and certain viruses have been the agents most recognized and studied as causes of healthcare-associated infections *(11)*. For transmission to take place, the microorganism must remain viable in the environment until contact with the host has been sufficient to allow infection. Reservoirs that allow the agent to survive or multiply may be animate, as exemplified by healthcare worker carriage of staphylococci in the anterior nares or throat (12,*13–15*), or the inanimate environment, as demonstrated by *Pseudomonas* spp. colonization of sink areas, *Legionella* in hot or cold water supply systems *(16–19)*, *Clostridium difficile* spores on computer keyboards, or *Serratia marcescens* growing in contaminated soap or hand lotion preparations *(20–22)*.

Certain intrinsic and genetically determined properties of a microorganism are important for it to survive in the environment. These include the ability to resist the effects of heat, drying, ultraviolet light, or chemical agents, including antimicrobials; the ability to compete with other microorganisms; and the ability to independently multiply in the environment or to develop and multiply within another host or vector. Intrinsic agent factors important to the production of disease include infectivity, pathogenicity, virulence, the infecting dose, the agent's ability to produce toxins, its immunogenicity and ability to resist or overcome the human immune defense system, its ability to replicate only in certain types of cells, tissues, or hosts (vectors), its

ability to persist or cause chronic infection, and its interaction with other host mechanisms, including the ability to cause immunosuppression (e.g., HIV).

Once transferred to a host surface, the agent may multiply and colonize without invading or evoking a measurable host immune response *(23–25)*. The presence of an agent at surface sites in the host does not define the presence of an infection. Nonetheless, patients so colonized may act as the reservoir source of transmission to other patients *(26)*.

If infection takes place, a measurable immune response will develop in most hosts even if the infection is subclinical. The success of this process for the agent is increased in the nonimmune host and is most successful in the nonimmune, immunocompromised host. A microorganism's ability to infect another host vector (e.g., yellow fever virus in mosquitoes) or another nonhuman reservoir (e.g., yellow fever virus in the monkey) is important in the epidemiology of certain infectious diseases in world populations at large but plays little role in healthcare infection epidemiology.

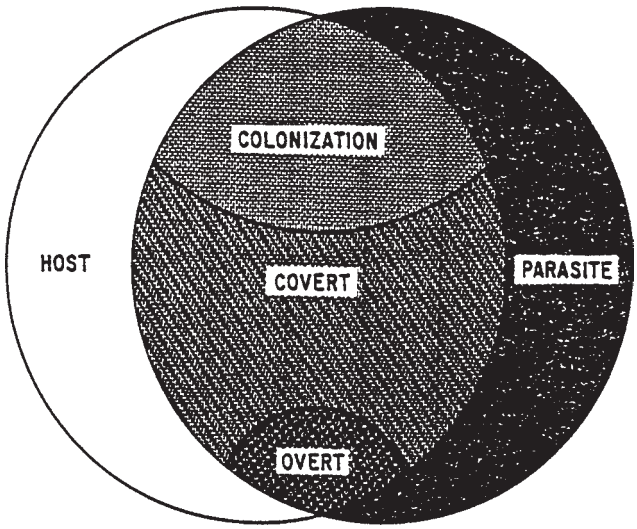

FIGURE 1-2 Venn diagram of agent–host interactions. An interaction between host and parasite may result in infection. Infection consists of colonization and an infectious disease. An infectious disease may be either covert (subclinical) or overt (symptomatic). (From Hoeprich PD, ed. *Infectious diseases*. Hagerstown, MD: Harper & Row, 1972:40.)

Host

Infection depends on exposure of a susceptible host to an infecting agent. Exposure of the susceptible host to such agents is influenced by age, behavior, family associations, occupation, socioeconomic level, travel, avocation, access to preventive healthcare, vaccination status, or hospitalization. Whether or not disease takes place in the infected host and the severity of disease when it appears depend not only on the intrinsic virulence factors of the agent but more importantly on the pathogenicity of the interactions between the agent and the host. The host immune defenses attempt to prevent infection. Thus, any reduction in host defenses may allow infection to take place with a smaller dose of microorganisms or at a body site that is not usually susceptible to infection. A combination of reductions in host defense characteristics and the requirements for an agent to cause infection are typical of the interactions that allow acquisition of opportunistic infections in immunocompromised patients. A commonly cited model indicating the potential interactions between agent and host and the relationships among colonization, infection, and clinical and subclinical disease is shown in Figure 1-2 *(27)*.

Host factors important to the development and severity of infection or disease may be categorized as intrinsic or extrinsic. Intrinsic factors include the age at infection; birth weight; sex; race; nutritional status *(28)*; comorbid conditions (including anatomic anomalies) and diseases; genetically determined immune status; immunosuppression associated with other infections, diseases, or therapy; vaccination or immunization status; previous experience with this or similar agents; and the psychological state of the host *(29)*. Colonization of the upper and lower respiratory tracts is more likely when the severity of illness increases in critically ill patients. This, along with other host impairments (e.g., reduced mucociliary clearance or changes in systemic pH), allows colonization to progress to invasive infection. Moreover, other clinical conditions may lead to an alteration in epithelial cell surface susceptibility to binding with bacteria, leading to enhanced colonization *(23–25)*. Extrinsic factors include invasive medical or surgical procedures; medical devices, such as intravenous catheters or mechanical ventilators; sexual practices and contraception; duration of antimicrobial therapy and hospitalization; and exposure to hospital personnel.

Environment

The environment provides the mutual background on which agent–host interactions take place and contains the factors that influence the spread of infection. Environmental factors include (a) physical factors such as climatic conditions of heat, cold, humidity, seasons, and surroundings (e.g., intensive care units, outpatient clinics, long-term care facilities, or water reservoirs); (b) biologic factors (e.g., intermediary hosts such as insect or snail vectors); and (c) social factors (e.g., socioeconomic status, sexual behavior, types of food and methods of preparation, and availability of adequate housing, potable water, adequate waste disposal and healthcare amenities). These environmental factors influence both the survival and the multiplication of infectious disease agents in their reservoirs and the behavior of the host in housing, occupation, and recreation that relate to exposure to pathogens. Food- and water-borne diseases flourish in warmer months because of better incubation temperatures for the multiplication of the agent and recreational exposures of the host, whereas respiratory agents appear to benefit from increased opportunities for airborne and droplet transmission in the closed and closer living environments of the winter. In US hospitals, the frequency of hospital-acquired *Acinetobacter* spp. infections is increasing in critical care units and has been shown to be seasonal in nature *(30)*. The seasonal variation in the incidence of this pathogen is thought to be due to changes in climate—summer weather increases the number of *Acinetobacter* spp. in the natural environment and transmission of this microorganism in the hospital environment during this season *(30)*.

Within healthcare settings, the components of the agent, host, and environment triad interact in a variety of ways to produce healthcare-associated infections. For example, the

intensive care unit is now considered the area of highest risk for the transmission of healthcare-associated pathogens in US hospitals (31). Moreover, methicillin-resistant *S. aureus* (MRSA), VRE, and ceftazidime-resistant *Pseudomonas aeruginosa* are endemic in many intensive care units in these hospitals (31). The emergence of vancomycin-resistant *S. aureus* in US institutions highlighted the unwelcome but inevitable reality that this pathogen may become endemic in acute care settings (32). A complex interaction of contributory factors, such as inadequate hand washing and infection control practices among healthcare workers, fluctuating staffing levels, an unexpected increase in patient census relative to staffing levels in the intensive care unit, or an unprecedented increase in the number of severely ill patients with multiple invasive devices, could all contribute to the acquisition of hospital infections caused by one of these endemic microorganisms *(33,34)*. Adding to the complexity of the process would be the unquantifiable mechanism of transmission of the agent from host to healthcare worker, healthcare worker to healthcare worker, and host to environment. Thus, acceptable measures for the prevention and control of healthcare-associated infection dictate that the healthcare epidemiologist looks at and analyzes the interrelationships among all components of the triad of agent, host, and environment (31).

It is well-known that the social environment is extremely significant in determining personal behavior that affects the direct transmission of agents, such as HIV via breast milk in regions of high HIV endemicity, gram-negative microorganisms via artificial nails worn by healthcare workers in US intensive care units *(35)*, and pathogens that cause sexually transmitted diseases. What must be understood to be equally relevant is the impact of other factors in the social environment, such as the distribution of and access to medical resources; the use of preventive services *(36–38)*; the enforcement of codes in food preparation, infection control practices, or occupational health practices; the extent of acceptance of breast-feeding for children *(39–41)*; and the acceptance of advice on the appropriate use of antimicrobials (*42–44*,45,*46*). Also, there must be an appreciation by patients, relatives, and healthcare workers alike that at-risk patients (e.g., those born very prematurely have severe congenital abnormalities, the very elderly, or those with premorbid end-stage cardiac or pulmonary disease), who have numerous indwelling medical invasive devices, or who have undergone multiple invasive procedures or surgical procedures would be particularly susceptible to healthcare-associated infections that are likely nonpreventable. There must be an informed and ethically sound willingness to reject the extraordinary application of medical technology, including the inappropriate or repeated use of resistance-inducing antimicrobials when clinical evidence and experience suggest that the condition of the sick patient is untreatable or irreversible.

Special Environments

Microenvironments, including military barracks, dormitories, day-care centers, chronic disease institutions, ambulatory surgery and dialysis centers, and acute care hospitals, provide special venues for agent–host interactions. Historically, epidemics in these institutional environments provided the experience that drove the development and acceptance of control measures, guidelines, and infection control programs. Acute care hospitals, especially those offering regional secondary and tertiary care, remain the dominant examples of these environments. Changing patterns of outpatient practice, home healthcare, and technical advances in medicine have resulted in increasingly severely diseased and injured populations being managed in acute care facilities. Data from CDC demonstrate that the changing healthcare environments in the United States are resulting in larger intensive care unit populations while there has been a general decrease in the number of general medical beds (31).

Special units for intensive medical or surgical care for extensive burns, trauma, transplantation, and cancer chemotherapy frequently house patients with increased susceptibility to infection (47). In these patients, reduced inocula of pathogens or commensals are required to cause infection, infection may take place at unusual sites, and usually nonpathogenic agents may cause serious disease and death. Frequent opportunistic infections in these patients require repeated, broad, and extended therapy with multiple antimicrobials, leading to increasingly resistant resident microbial populations (31,*46*).

The emergence or reemergence in this setting of pathogens resistant to all available antimicrobials is taking place, a situation that has not been present since the 1950s *(48)*. For example, in some institutions during the early 1990s, >80% of VRE isolates were documented as being resistant to all available antimicrobials *(49)*. Similarly, spiraling healthcare costs have been the major factor leading to the current shift toward managed care in the United States. The process has resulted in the downsizing of hospital workforces to cut costs and reduce patient charges. As a result, more severely ill patients are being managed or treated as outpatients or at home. For example, central venous catheters may be placed in the hospital, and kept *in situ* for long-term home infusion therapy. The trade-off is minimum exposure to the hospital environment with decreased costs to the patient. On the other hand, a patient with a central venous catheter in the home environment may be potentially at risk of bloodstream infections due to contamination of lines, dressing, and infusates in a care environment where infection control practices are not as well understood, practiced, or regulated.

INFECTION, COLONIZATION, AND SPECTRUM OF DISEASE

Infection is the successful transmission of a microorganism to a susceptible host, through a suitable portal of entry, with subsequent colonization, multiplication, and invasion. The source of a microorganism (the primary reservoir) may be animate (e.g., humans, mammals, reptiles, or arthropods) or inanimate (e.g., work surfaces, toys, false fingernails, toiletries, or soap). *Disease* is the overt damage done to a host as a result of its interaction with the infectious agent: it represents a clinically apparent response by or injury to the host after infection, with the affected person showing symptoms or physical signs that may be characteristic of infection with the invading pathogen. Thus, disease is the outcome of an infectious process, and

a *pathogen* is any microorganism with the capacity to cause disease in a specific host.

Unapparent or subclinical infection is a frequent occurrence where the infected person may not manifest any symptoms, signs, disability, or identifiable disease. For example, in patients who acquire *Salmonella typhi* infection (typhoid fever), a chronic infection of the gallbladder may develop with asymptomatic fecal excretion of the pathogen for years after the acute event. Patients in HIV-endemic countries may have *M. tuberculosis* bloodstream infections despite having normal chest radiographs and no symptoms or signs suggestive of underlying pulmonary disease *(50)*. Persons with subclinical infection are sometimes referred to as *carriers*. Subclinical infection may be recognized through laboratory testing of blood or other appropriate body material from the host. These tests may indicate evidence of an immune response to infection, the presence of antigens characteristic of the microorganism, abnormal cellular function in response to infection, or the presence of the microorganism itself.

Colonization is the presence of a microorganism in or on a host, with growth and multiplication, but without any overt clinical expression or detected immune reaction in the host at the time the microorganism is isolated. An infectious agent may establish itself as part of a patient's flora or may cause low-grade chronic disease after an acute infection. For example, 20% of healthy adults are persistent carriers of *S. aureus* in the anterior nares without any manifestation of clinical illness (*51*,52,*53*). However, under suitable conditions, patient populations colonized with *S. aureus* are at an increased risk of having infection and disease develop *(54–58)*. Once colonization or infection is established in a susceptible host, the agent may enter a silent or latent period during which there is no clinical or typical laboratory evidence of its presence. Thereafter, the host may manifest signs and symptoms of mild disease without disability, exhibit rapid or slow progression of disease, or progress to either temporary or chronic disability. Ultimately, the patient may die or have a complete recovery and return to health without sequelae.

The outcome of an infection is determined by the size of the *infecting dose*, the site of the infection, the vaccination status of the host, the speed and effectiveness of the host immune response, other intrinsic host factors (e.g., nutritional status), or promptness of instituting and effectiveness of the therapy. These factors together with intrinsic properties of a microorganism, such as its infectivity, pathogenicity, virulence, and incubation period, determine the course and progress of an infection, and manifestation of disease. *Infectivity* is the characteristic of the microorganism that indicates its ability to invade and multiply in a susceptible host to produce infection or disease; it is expressed as the proportion (i.e., the *attack rate*) of patients who become infected when exposed to an infectious agent. The basic measure of infectivity is the minimum number of infectious particles required to establish infection. Pathogens like polio or measles viruses have high infectivity.

The *pathogenicity* of an infectious agent is a measure of its ability to cause disease in a susceptible host. Thus, while the measles virus has a relatively high pathogenicity (i.e., few subclinical cases), the poliovirus has a low pathogenicity (i.e., most cases of polio are subclinical). The measure of pathogenicity is the proportion of infected persons with clinically apparent disease. The pathogenicity of an agent that is usually innocuous may be increased in a host with reduced defense mechanisms. For some agent–host interactions, the resultant disease is due to the effects of exaggerated or prolonged defense mechanisms of the host. The *virulence* of a microorganism is its intrinsic capability of infecting a host to produce disease. It follows that a pathogen might have varying degrees of virulence. Thus, although the nonencapsulated form of *Haemophilus influenzae* is a common inhabitant of the upper respiratory tract of healthy humans and causes localized infection without bacteremia (e.g., conjunctivitis or otitis media in children), the more virulent encapsulated type b form causes more invasive disease and is an important cause of meningitis or epiglottitis. If the disease is fatal, virulence can be measured with the case–fatality rate. For example, the rabies virus almost always produces fatal disease in humans and is therefore an extremely virulent agent.

The ability to diagnose an infection or disease depends on the degree to which typical symptoms and physical signs develop in patients, the appropriateness of diagnostic tests, and the sensitivity and specificity of these tests for the particular infecting agent. Whether an infecting agent produces clinical or subclinical infections depends on the agent and host factors, for example, age or immune status. Thus, *P. aeruginosa,* a ubiquitous pathogen that thrives in aquatic environments and vegetation, seldom causes disease in healthy humans. However, in debilitated, hospitalized patients, such as those with burns, critical care patients with multiple *in situ* invasive medical devices, or those who are on prolonged mechanical ventilation, this pathogen remains an important cause of ventilator-associated pneumonia in US hospitals *(59)*.

Certain agents may be associated with a variety of different syndromes that depend on age and vaccination status of the host, previous infection with the agent, and agent-related mechanisms that remain unclear. Thus, *Strongyloides* spp., a nematode that is endemic in many parts of the world, including Southeast Asia and some parts in the southeastern United States, can cause asymptomatic infection or be associated with several syndromes ranging from mild epigastric discomfort and chronic skin rashes to life-threatening hyperinfection that results in gram-negative bacteremia, pneumonia, and multisystem disease in immunosuppressed patients, including solid organ transplant recipients or patients with chronic airways disease who are steroid-dependent *(60–63)*. These differences in host–agent interactions underscore the difficulty in establishing causation and the importance of confirmatory laboratory evidence to precisely identify the causal agent associated with syndromes of infectious disease.

Once colonization or infection is established in a susceptible host, the agent may enter a silent or latent period during which there is no clinical or usual laboratory evidence of its presence. Thereafter, the host may manifest signs and symptoms of mild disease without disability, may have a rapid or slow progression of disease, or may progress to either temporary or chronic disability, or, ultimately, death. Alternatively, the patient may have a complete recovery and return to health without sequelae. In other instances, the entire process may be inapparent

or subclinical without evidence of disability or disease. Subclinical cases may be recognized through laboratory testing of blood or other body fluids of the host. These tests may indicate evidence of abnormal cellular function (abnormal liver function tests), the presence of an immune response to infection (antibody to hepatitis B virus core antigen), the presence of antigens characteristic of the microorganism (positive test for hepatitis B virus surface antigen), or the presence of the microorganism itself.

The ability to diagnose an infection or disease is obviously easier in clinical cases and much easier in severe clinical cases wherein the typical signs and symptoms of the disease are apparent and routine tests are diagnostic of the agent. The ratio of clinical to subclinical infections varies widely by agent and is influenced by certain host factors, such as age and immune status. Certain agents may be associated with a variety of different syndromes that depend on age and vaccination status of the host, previous infection with the agent, and agent-related mechanisms that remain unclear. Poliovirus is less likely to appear as a paralytic syndrome in children, and Coxsackie virus B infections may appear as myocarditis one year and more prominently as meningoencephalitis the next. Respiratory syncytial virus infections may appear as bronchiolitis in infants and as a common cold syndrome in their older caregivers. Since the ability to diagnose an infection or disease caused by a specific pathogen depends partly on the degree to which typical symptoms and physical signs develop in patients, variation in the clinical manifestation of disease underscores the difficulty in establishing causation, the importance of clinical awareness of syndromic variations of certain infections, and the importance of confirmatory laboratory evidence to precisely identify the causal agent associated with syndromes of disease outbreaks. Evans provides a detailed and excellent review of the principles and issues in establishing causation in infection and disease *(64)*.

MECHANISM OF SPREAD

Transmission

For infection to take place, microorganisms must be transferred from a reservoir to an acceptable entry site on a susceptible host in sufficient numbers (the infecting dose) for multiplication to occur. The infecting dose of a microorganism may depend in varying degrees on infectivity, pathogenicity, or virulence of the microorganism itself. The entire transmission process constitutes the *chain of infection*. Within the healthcare setting, the reservoir of an agent may include patients themselves, healthcare workers (e.g., nares or fingernails), tap water, soap dispensers, hand lotions, mechanical ventilators, intravascular devices, infusates, multidose vials, or various other seemingly innocuous elements in the environment.

Direct transmission from another host (healthy or ill) or from an environmental reservoir or surface by direct contact or direct large-droplet spread of infectious secretions is the simplest route of agent spread. Examples of direct-contact transmission routes include kissing (infectious mononucleosis), shaking hands (common cold [rhinovirus]), or other skin contact (e.g., contamination of a wound with staphylococci or *Enterococcus* spp. during trauma, surgical procedures, or dressing changes). Transmission of *Neisseria meningitidis*, group A streptococcus, or the respiratory syncytial virus (an important cause of respiratory infection in young children worldwide) by large respiratory droplets that travel only a few feet is regarded as a special case of direct-contact transmission.

Vertical transmission of infection from mother to fetus is another form of direct-contact transmission that may occur through the placenta during pregnancy (e.g., HIV, rubella virus, hepatitis B virus, or parvovirus), by direct contact of the infant with the birth canal during childbirth (group B streptococci), or via breast milk (HIV).

Indirect-contact transmission may occur via the hands of people, contaminated inanimate objects (fomites), various work surfaces, food, biological fluids (e.g., respiratory, salivary, gastrointestinal, or genital secretions, blood, urine, stool), invasive or shared medical devices, or through arthropod or animal vectors. Indirect-contact transmission is the most common mechanism of transfer of the microorganisms that cause healthcare-associated infections and commonly occurs via the hands of healthcare workers, their clothing, or instruments like stethoscopes or thermometers. Rapid dissemination of agents, such as respiratory syncytial virus or the influenza virus, may occur in day-care centers through salivary contamination of shared toys and games. *C. difficile* is an important diarrheal agent transmitted from patient to patient in acute care hospitals. Its transmission is abetted by its spore-forming ability to survive in the environment, and its selection and promotion in patients by the repeated and prolonged use of certain antimicrobials (65). Medical devices contaminated with blood-borne pathogens, including hepatitis B and C viruses, cytomegalovirus, and HIV, are sources of infection for both patients and medical care personnel in healthcare institutions *(66,67)*. Some viruses can remain viable for extended periods under suitable conditions. For example, Hepatitis B virus is relatively stable in the environment and remains viable in dried form for at least 7 days to 2 weeks on normal working surfaces at room temperature *(68)* This property has led to Hepatitis B virus transmission among dialysis patients through indirect contact via dialysis personnel or work surfaces in the dialysis unit *(69,70)*. Examples of other sources of healthcare-associated infections that occur through indirect contact include bacterial or viral contamination of musculoskeletal allograft tissues, intrinsic contamination of infusates or injectable medications, liquid soap, or contaminated medications prepared in the hospital pharmacy (*20*,*71*,72,*73–75*). The continuing presence of *Pseudomonas* spp. and other gram-negative rods in potable water supplies acts as an important reservoir for these agents and a readily available source for hand transmission to patients, especially the severely ill *(19,76)*.

Airborne transmission is another mechanism of indirect transfer of pathogens. Microorganisms transmitted by this method include droplet nuclei (1–10 μm) that remain suspended in air for long periods, spores, and shed microorganisms. The airborne transfer of droplet nuclei is the principal route of transmission of *M. tuberculosis*, varicella, or measles. The transmission of *Legionella* spp. through the

air in droplet nuclei from cooling tower emissions, and from environmental water sites, such as air-conditioning systems, central humidifiers, and respiratory humidification devices, is another important example of this type of spread (*77–79*,80,*81*). *C. difficile*–associated disease, the most common cause of healthcare-associated gastrointestinal infection in the United States, is frequently acquired through the transmission of spores via hospital work surfaces and the hands of healthcare workers (65,82). In fact, *C. difficile* may become endemic if its spores are propagated by air currents throughout an institution. Fungal spores can be an important cause of healthcare-associated infections. Spores of invasive fungi, such as *Aspergillus* spp., may be carried over long distances in hospitals to cause severe infections in immunosuppressed patients. The risk of spore contamination was highlighted by an outbreak of *Curvularia lunata* (a black fungus) among silicone breast implant recipients, who had undergone the breast augmentation procedures in an operating room that was erroneously maintained at negative pressure resulting in high spore counts in the operating room environment (operating rooms are supposed to be maintained at net positive pressures relative to adjacent areas). The surgeons had not implemented a closed system for inflating the breast prostheses with saline; instead, they had inflated the silicone prostheses using syringes filled with saline drawn up from a sterile bowl exposed to the ambient operating room environment. The end result was contamination of sterile saline in the open bowl with *C. lunata* spores, which were then injected inadvertently into the breast prostheses *(83)*. In some settings (e.g., burn units), staphylococci have been thought to spread on skin squamous cells that have been shed from patients or healthcare personnel. The importance of this mode of transmission, however, is not thought to be of great significance in other care settings. More recent data suggest that *S. aureus* is a common isolate in oropharyngeal cultures *(13)*. Although the epidemiologic implications of this finding remain uncharacterized, the ramification for infection control in healthcare facilities would be enormous if indeed the chain of infection for *S. aureus* includes oropharyngeal secretions or droplet nuclei. More recently, the emergence of extensively drug-resistant (XDR) strains of *M. tuberculosis* (i.e., strains resistant to practically all second-line agents) has again highlighted the importance of airborne transmission and the fact that the underlying reason for XDR emergence stems from poor general tuberculosis control and the subsequent development of multi-drug resistant (MDR)-tuberculosis (84,*85*).

Vector-borne transmission by arthropods or other insects is a form of indirect transmission, and may be mechanical or biologic. In mechanical vector-borne transmission, the agent does not multiply or undergo physiologic changes in the vector; in biologic vector-borne transmission, the agent is modified within the host before being transmitted. Although the potential for microorganism carriage by arthropods or other insect vectors has been described *(86,87)*, this type of transmission has not played any substantial role in the transmission of healthcare-associated infections in the United States. In tropical countries with endemic dengue, yellow fever, or malaria, vector-borne transmission is relatively more important, requiring screening of patients or other interventions, and preventive measures not ordinarily required for patients in colder climates.

Reservoirs

Humans are the primary reservoir for *Neisseria gonorrhoeae*, *S. typhi*, HIV, Hepatitis B and C viruses, or *Shigella* spp. Animals (zoonoses) harbor the rabies virus, *Yersinia pestis, Leptospira* spp., or *Brucella* spp. Environmental reservoirs include the soil (*Histoplasma capsulatum, Clostridium tetani*, and *Bacillus anthracis*) and water (*Legionella* spp., *P. aeruginosa, Serratia* spp., and *Cryptosporidium* spp.). In critical care units, reservoirs in ventilation circuits often harbor gram-negative pathogens, such as *P. aeruginosa, Serratia* spp., or *Acinetobacter* spp. For some infections, the interaction between host, agent, and environment might include an extrinsic life cycle of the agent outside of the human host. The interplay of such factors can add significant layers of epidemiological complexity in properly understanding the cause of an outbreak or in characterizing the chain of infection.

INCUBATION PERIOD AND COMMUNICABILITY

The *incubation period* is the time between exposure to an infectious agent and the first appearance of evidence of disease in a susceptible host. The incubation period of a pathogen usually is typical for that class of microorganisms and may be helpful in diagnosing unknown illness or making a decision regarding further diagnostic testing. The first portion of the incubation period after colonization and infection of a person is frequently a silent period, called the *latent period*. During this time, there is no obvious host response, and evidence of the presence of the infecting agent may not be measurable or discernible. Measurable early immune responses in the host may appear shortly before the first signs and symptoms of disease, marking the end of the latent period. Incubation periods for a microorganism may vary by route of pathogen inoculation, and the infecting dose. For example, brucellosis may be contracted through direct contact with blood or infected organic material, ingestion of raw dairy products, or through airborne transmission in a laboratory or abattoir; these various modes of transmission result in an incubation period for brucellosis that is highly variable, ranging from 5 days to several months. Incubation periods for other common microorganisms are as follows: 1 to 4 days for the rhinovirus (the common cold) or influenza virus; 5 to 7 days for herpes simplex virus; 7 to 14 days for polio virus; 6 to 21 days for measles virus; 10 to 21 days for chickenpox virus; 20 to 50 days for hepatitis A virus and the rabies virus; and 80 to 100 days for hepatitis B virus.

The *communicable period* is the time in the natural history of an infection during which transmission may take place. Generally, microorganisms that multiply rapidly and produce local infections are associated with short incubation periods. For example, enterotoxin-producing *S. aureus* undergoes such rapid multiplication in unrefrigerated food that symptoms of food poisoning may become manifest within 1 to 6 hours of ingestion of the contaminated meal. Microorganisms that cause disease that depend on

hematogenous spread or multiplication in distant organs tend to have longer incubation periods. HIV antibodies are generally detectable 1 to 3 months after the initial exposure, whereas the HIV-infected person might remain asymptomatic for years. Cytomegalovirus, a blood-borne pathogen that frequently causes posttransplant or post-transfusion infection, generally causes illness 3 to 8 weeks after initial exposure.

OUTBREAKS, EPIDEMICS, AND EPIDEMIC INVESTIGATION

An infectious disease outbreak or epidemic is defined as an increase in the occurrence of infection or disease above the baseline or background rate, in a given area in a specific patient population. Epidemics may originate from a common source or be propagated from person to person. Common source epidemics appear when susceptible persons have mutual exposure to the same agent in the same time period. If the exposure to an infectious agent happens at a single event at a single time and place, such as at a church dinner, it is called a *point source epidemic*. When this happens, the affected (exposed) patients usually have a similar incubation period, and the average time from the onset of first symptoms back to the initial, common exposure event is the natural incubation period of the agent. If the agent is known, its identified incubation period helps to define the time of the common event. For example, onset of symptoms of food poisoning caused by *S. aureus* usually occurs within 1 to 6 hours; symptoms due to *Shigella* spp. usually occur within 24 to 48 hours. If exposure to an infecting agent is continuous, as in a hospital room with an air-conditioner contaminated with *Legionella* spp., episodes of *Legionella* pneumonia among hospital inpatients may appear sequentially. Sewage from a treatment plant seeping into a water supply is another example of continuous source exposure in which a persistent increase above an expected level extends beyond a single incubation period.

Propagated epidemics occur when serial direct or indirect transmission of a microorganism occurs from susceptible host to susceptible host (e.g., person-to-person spread of *Malassezia pachydermatis*, a microorganism with a short incubation *(88)*), or it may occur at a more leisurely pace as in transmission of an agent from a carrier to a susceptible individual (e.g., transmission of *Nocardia farcinica* from the hands of a colonized healthcare worker to a surgical site *(89)*). Thus, investigation of an epidemic requires a prioritized and systematic approach to the gathering and analysis of data with careful attention to epidemiologic and clinical detail and correct interpretation of microbiological and other laboratory information.

Investigating an Epidemic

The first and most critical step in an outbreak investigation is ascertaining that an epidemic does indeed exist. This step assumes some previous information on the usual or endemic rate of occurrence of the infection or disease under study. When there is a perceived increase in the occurrence of an infection without reference to a baseline level, the aggregation of case-patients is classified as a *cluster*. Many clinical microbiology laboratories that serve large teaching hospitals or other healthcare institutions maintain computerized, retrospective line listings of infection or colonization caused by pathogens that are endemic in the institution. Such line listings are readily available on request and enable documentation of endemic infection rates.

The first hint of an outbreak or an unusual cluster of infections may be the appearance of a microorganism from epidemiologically related sources noticed by the clinician, infection control team, pharmacy, or laboratory personnel. The microbiology laboratory has been likened to an early warning, laboratory-based surveillance system for the detection of outbreaks *(11,90)*. For example, laboratory technologists might be the first to suspect the presence of an outbreak of healthcare-associated infections by being alert and noting in a line listing the existence of an unusual cluster of isolates of a particular morphology, species, or antimicrobial susceptibility profile. End-of-the-day scrutiny of routine line listings of microorganisms growing in cultures by a staff microbiologist might herald the presence of a cluster of infections or antimicrobial-resistant microorganisms in a specific hospital inpatient service that would have otherwise been overlooked or missed by the clinician or healthcare epidemiologist. Or perception by an astute pharmacist of overprescribing of antimicrobials for infections caused by an unusual microorganism could be a lead to ascertainment of a putative cluster or outbreak.

Computerized laboratory records, line listings, and culture reports that have been retrospectively archived constitute an invaluable source of site-specific, baseline data on endemic infection rates with which to compare current perceived increases in infection rates for various patient populations in a facility. If a comparison of epidemic and preepidemic infection rates suggests the presence of an outbreak, the clinical microbiology personnel on the team conducting the outbreak investigation must then ensure that all isolates and relevant specimens from patients associated with the putative outbreak are saved for culture or other analyses that might become necessary later on in the investigation. Thus, the initial investigation and characterization of outbreaks or clusters of infection must necessarily involve the laboratory *(91)*.

To determine the existence of an outbreak, one must understand the etiology of the infection or disease. If the syndrome is unrecognized, a consensus case definition or criteria for the condition must be formed. This case definition must be fulfilled for each event that is judged to be associated with the epidemic. The case definition may include a medical sign or symptom; a syndrome; an abnormal laboratory test (e.g., a raised white blood cell count); the isolation of an etiological agent (e.g., positive blood cultures for bacteremia); or one of the serologic tests, such as those for serum immunoglobulin levels (e.g., immunoglobulin M group), that suggest acute or recent infection. The case definition for epidemics of unknown etiology might include combinations of clinical and laboratory parameters. Depending on the data available at the onset of an investigation, a case definition may include classification of the ill as (a) definite cases, (b) probable cases, or (c) possible cases.

Case definitions of healthcare-associated infections usually involve clinical, epidemiologic, and laboratory parameters and delineate the patients (*person*) who have specific symptoms or syndromic features, the period (*time*) during which the symptoms began or were recognized, the location (*place*) of the problem, and the infecting agent and anatomic site of infection (*what*). If the case definition is microorganism-based, a careful review of the existing microbiology records usually is all that is needed to identify case-patients and determine numerator and denominator data for the calculation of comparable rates. After a case definition has been formulated, the outbreak investigators must identify and ascertain case-patients. This step may be accomplished by calling hospitals, clinics, health departments, physicians' offices, schools, or workplaces, or careful examination of patients' medical, surgical, or laboratory records, patient census listings, administrative staffing records, death certificates, or existing surveillance data, such as frequency of medical device or antimicrobial use. Laboratory records play a vital role in this undertaking by providing confirmatory data on pathogen identification, site of infection, antimicrobial susceptibility testing profiles (antibiograms), or microorganism biochemical profiles (biotype number).

In industry, annual product reviews analyze the assorted quality parameters that intersect with a given product, such as reviewing the number of laboratory deviations, the number of confirmed batch failures, or the number of manufacturing/testing changes. If available, such data are helpful in investigations of national or international outbreaks, such as those associated with widespread distribution of an intrinsically contaminated drug, device, or other product. Within healthcare systems, comparable quality systems are found largely in clinical laboratories. For example, in the microbiology laboratory, quality reviews similar to those performed in the pharmaceutical industry include systematic analyses of batch failures of reagents; monitoring culture media quality and variability of set incubation temperatures for incubators; quality assurance checks of antimicrobial-impregnated disks and adherence to standards set by the Clinical and Laboratory Standards Institute for antimicrobial susceptibility testing; regular assessments of the ability of microbiology personnel to accurately identify or characterize "unknown" isolates from the American Type Culture Collection; or weekly checks of the optical density cutoff points for spectrophotometers used in serological testing. Data from these reviews are indispensable for outbreak investigations, especially when an outbreak is linked epidemiologically to practices and procedures in the laboratory (see Chapter 9).

When an infection outbreak is recognized only by the presence of a cluster of patients with a specific syndrome, idiosyncratic clinical features, or pyrogenic reactions, and the case definition contains only clinical or epidemiologic parameters, initial cultures of relevant body sites may be negative. In these instances, it is vital that the laboratory be involved in all subsequent decision making in the outbreak investigation, particularly regarding the types of cultures, specimens, serologic tests, or assays that should be considered to assist in determining the source or cause of the outbreak. Such additional investigations may include testing large volumes of dialysis fluid or water for endotoxin, performing specialized serologic tests for *Salmonella* spp., or molecular genotyping. These indispensable roles of the laboratory underscore the interdependency of epidemiology and laboratory disciplines during the investigation of an outbreak where the suspected pathogen is absent or not initially apparent, and the direction of the subsequent investigation may require specialized laboratory tests or assays that become obvious only after an epidemiologic evaluation (see Chapter 95).

After case ascertainment, the next steps are to prepare a line listing of the patients who meet the case definition and construct an *epidemic curve* by plotting the number of cases (*y*-axis) over time (*x*-axis), and identify on a geographic map the location of the cases. The line listing should contain the basic demographic data and characteristics that are relevant to the outbreak, and should include the features of the outbreak in terms of person, place, and time that were established by the case definition.

Critical variables in an outbreak investigation include the following: (a) When did the exposure take place? (b) When did the disease begin? (c) What was the incubation period for the disease? If any two of these are known, the third can be calculated. The epidemic curve can graphically suggest the temporal relationship between acquisition of infection or disease and index case, the existence of a common source, the incubation period of an infectious agent, or the mode of transmission. In addition, the epidemic curve can be used to determine the probable period of exposure to a source: first look-up the average, median, and range of the relevant incubation period of the suspected infection in question. This information can be obtained from a recognized reference source (e.g., the *Control of Communicable Diseases Manual (7)*. The median incubation period is the time when 50% of case-patients would have acquired the infection. A rapid assessment would be to count back the average incubation period from the median case-patient and the minimum incubation period from the earliest case-patient. There are limitations in extrapolating inferences from an epidemic curve. For example, the curve might not have a "classic" shape, especially if the outbreak is small. Moreover, an observed shape may be consistent with more than one interpretation; intermittent exposures to a common source may look like person-to-person exposure, or the incubation period may remain unknown.

With an initial count of the cases completed, one can determine the rates of infection and illness in the population by age group, birth weight, gender, ethnic origin, religious affiliation, socioeconomic status, water supply, food ingestion, device use, treatment regimens, or other factors that appear to be historically associated with the individuals infected. On the basis of this preliminary analysis, a hypothesis is generated to identify the high-risk population. One may consider conducting a case–control epidemiologic study to compare ill persons (case-patients) with randomly selected persons who have remained well (control group) to identify exposures significantly associated with cases. The contrast between cases and controls is then determined by calculation of the odds ratios and

confidence intervals for each exposure. Alternatively, one may conduct a cohort study in which attack rates are compared through calculation of relative risks and confidence intervals for persons exposed and not exposed to a specific risk factor. Not all case-patients can be expected to fit the hypothesis because a background rate of endemic infections or disease must be assumed for many infectious agents (e.g., *Enterococcus* spp. in healthcare facilities). Using the hypothesis, one searches for additional case-patients, both to increase the numbers for statistical study and to include persons with mild or subclinical disease, who might otherwise escape evaluation.

With the additional findings, the data are analyzed and an interpretation of the events is prepared. If the hypothesis is supported, it is confirmed in a final report; if not, the data are reviewed for alternative hypotheses, and another round of testing and analyses is begun. On the basis of the analyses and the supported hypothesis, intervention and follow-up programs are outlined, including both short-term and long-term control measures. Finally, the findings are reported formally to local and regional authorities, public health agencies, and medical and public groups, indicating the nature of the outbreak and recommendations for future prevention and control.

The Role of Epidemiology and Microbiology in the Investigation of Outbreaks

Traditionally, the most important function of the microbiology laboratory during outbreak investigations has been to accurately identify outbreak pathogens, to conduct relevant antimicrobial susceptibility testing, and to determine the clonality (similarity) of outbreak pathogens based on whatever phenotypic or genotypic typing methods are available to the laboratory. These functions now encompass all stages of outbreak investigations. There are two different approaches to an investigation of infectious disease outbreaks: (i) to conduct extensive culture surveys to identify the source of the outbreak (*laboratory-based investigation*) or (ii) to conduct an epidemiologic investigation with subsequent epidemiology-directed environmental or personnel cultures or assays (epidemiologic investigation with laboratory confirmation). Experience from CDC suggests that the former "shot-gunning" approach creates much superfluous work and may be counterproductive, because risk factors or environmental reservoirs that are epidemiologically relevant could potentially be missed altogether, or the wrong source identified *(92)*. Initial culture surveys of the environment or personnel without a prior epidemiologic investigation may appear to identify or "implicate" the causal agent or person, but also may represent secondary contamination or colonization rather than the true source. This may result in erroneous recommendations or interventions, or inappropriate actions against staff members who are not in any way epidemiologically associated with disease transmission. Other published data from CDC suggest that an epidemiology-directed approach is generally more accurate and less costly for identifying the source and mode of transmission of outbreak pathogens *(93,94)*.

In many CDC outbreak investigations, subsequent laboratory studies have indeed confirmed the epidemiologic findings *(93–95)*; moreover, there have been occasions when the investigators of an outbreak have had to draw conclusions solely on the epidemiologic findings without laboratory confirmation, because relevant microbiological specimens often are discarded before the decision to conduct a formal investigation is made *(74,75)*. Random culture surveys of personnel, products, or the environment without a prior epidemiologic investigation may be misdirected, expensive, unsustainable, or costly in terms of human and laboratory resources and should not be performed before comparative epidemiologic studies are completed.

Epidemiologic principles are particularly important when addressing the issue of intrinsic microbial contamination of a product within an industrial plant. Intrinsic contamination of a normally sterile product may be detected in-house through quality assurance surveillance, such as end-product sampling, or it may manifest as a common-source outbreak of local, national, or international proportions *(73)*. If a pharmaceutical product is suspected to be associated with an infectious disease outbreak, integration of epidemiology and microbiology remains vital to conducting a successful outbreak investigation (the principles have been described earlier). Such an approach has been used to successfully investigate a nationwide outbreak of sterile peritonitis due to intrinsic endotoxin contamination of peritoneal dialysis solution from a single manufacturer, infections among recipients of contaminated allograft tissues, and fungal infection of saline-filled silicone breast implants *(83,96)*.

Epidemiologic methods are used to investigate and relate causal factors to an outbreak and are essential for understanding the mechanisms of infection acquisition and transmission, determining risk factors, and directing the application and practice of clinical microbiology methods. The information from epidemiologic and descriptive studies may provide important clues regarding the causes of or risk factors associated with infections, and may be used to generate causal hypotheses.

To test a hypothesis, one may attempt to identify the high-risk population and design appropriate microbiologic studies and culture surveys. Thus, the laboratory service must be able and prepared to collect relevant specimens through liaison with the epidemiologist, culture or process these specimens using reproducible, quality-controlled methods, and disseminate the information back to other outbreak coinvestigators in a timely manner.

In summary, the following issues must be considered when interpreting environmental culture data: (a) surfaces by themselves do not transmit disease; transmission from surfaces is more likely mediated by personnel who might not have maintained scrupulous aseptic conditions resulting in cross contamination of patient care items; (b) for environmental sampling, there are no benchmarks or standards to compare data generated from different culture methods; and (c) epidemiology is essential for interpreting environmental cultures—just because a pathogen is isolated from an environmental culture does not necessarily mean that there is a problem. The classic steps in the recommended investigation of an epidemic are outlined in Table 1-1.

TABLE 1-1

Steps in Investigating an Epidemic

- Confirm the existence of an epidemic
- Establish a case definition that reflects time, place, and person
- Ascertain cases and create a line listing
- Create an epidemic curve
- Determine the extent and characteristics of cases by rapid survey
- Formulate a working hypothesis
- Test the hypothesis through epidemiologic studies
- Initiate appropriate microbiology or other laboratory studies that are directed by the epidemiologic data
- Analyze all cases for interpretation
- Reassess hypothesis if not proven and initiate additional studies where warranted
- Draw conclusions and inferences from investigation
- Communicate with relevant personnel and recommend appropriate control and preventive measures (exit interviews and preliminary report)
- Continue postoutbreak surveillance for new cases
- Reevaluate control measures
- Prepare a formal written report and disseminate findings in a published manuscript

PREVENTION AND CONTROL

Measures for the prevention and control of communicable diseases are directed at various links in the *chain of infection*. These include interventions to (a) eliminate or contain the reservoirs of infectious agents or curtail the persistence (endemicity) of a microorganism in a specific setting; (b) interrupt the transmission of infectious agents; or (c) protect the host against infection and disease. This approach calls for a detailed knowledge of the epidemiology of infectious diseases in a variety of settings or environments.

Modifying Environmental Reservoirs

Interventions chosen to modify a reservoir depend on whether the reservoir is *animate* or *inanimate*. *Quarantine*, the restriction of movement of individuals who have been exposed to a potentially transmissible agent for the entire incubation period of the infection, is now rarely used to control human disease in healthcare settings and has been replaced, largely, by active surveillance of exposed individuals in acute care hospitals or long-term care facilities. Animate reservoirs (i.e., carriers) include healthcare personnel who are colonized with potential pathogens in their nares or hands, relatives (or pets) who visit patients in intensive care units, or patients known to be colonized or infected with a particular healthcare pathogen and are moved from one unit to another within a given institution, or are transferred from one hospital to another. Since disease is often subclinical, it may be difficult to recognize and separate silent carriers from susceptible persons.

Treatment of humans to eradicate their carriage of transmissible pathogens that are typically found in healthcare settings has had variable success. For example, treatment to eradicate VRE often yields mixed results *(97–99)*; whereas, there has been limited success in the eradication of MRSA among hospital inpatients (100,*101–103*) and in the community (*104*). There are no compelling data that show an association between eradication of gram-negative carriage among patients or healthcare personnel and reduced rates of transmission. Thus, removal of an individual healthcare worker, known to be a reservoir for a potentially transmissible pathogen, from a healthcare setting (e.g., bone marrow unit or surgical intensive care unit) with susceptible patients might be the only control or preventive option. Human carriers of transmissible pathogens may be isolated from susceptible individuals, who are not colonized or infected, for the duration of their stay at the institution or for as long as they harbor the microorganism (*105*,106). Finally, ethical issues arise when the decision is made to expose asymptomatic carriers or colonized but well persons to medical therapy that might have serious side effects, or render them susceptible to adverse events, such as healthcare-associated infections, disease, or undue morbidity.

In healthcare settings, reservoirs of a transmissible pathogen might be limited solely to the inanimate environment. Thus, appropriate control measures might include removing contaminated fruit, flowers, intravenous infusates, hand lotions, toys, white coats, stethoscopes, or other objects deemed to be potential reservoirs; appropriate handling of sewage and medical waste per published guidelines; ensuring that scrupulous aseptic techniques are maintained during invasive procedures or line insertion; or destroying the agent in the environmental niche (e.g., work surfaces in an intensive care unit, medicine preparation areas, or moisture reservoirs in mechanical ventilators) by chemical or physical means. In some healthcare settings, such as medical or intensive care units, microorganisms, such as VRE or *C. difficile*, may remain endemic or persistent despite identification and appropriate treatment or elimination of reservoirs. Such persistence may require periodic enhanced environmental cleaning of the concerned unit to curtail the endemicity of the pathogen (107). The importance of modifying environmental reservoirs for the control and prevention of infectious disease is sustained by the fact that much of the reduction in disease and death from infectious diseases in the industrialized world during the 20th century has been attributed to purification of potable water by filtration and chlorination, improvements in the cooking, processing, and inspection of food, and advancements in housing, nutrition, and sanitary disposal of human waste (*108*).

Interrupting Transmission

Many of the features of interventions necessary for interrupting the transmission of infection are identical to those included in the interventions necessary for modifying inanimate environmental reservoirs discussed above. The most important addition to these has been in the behavioral changes necessary to support improvements in the area of personal hygiene, specifically in the washing of hands between tasks in the preparation of food, caring for children, and caring for the sick (*109,110,*111). In the control of healthcare-associated infections, the use of appropri-

ate barriers, including the use of gloves, gowns, and eye protection, has been emphasized to prevent the transmission of blood-borne pathogens (e.g., HIV and hepatitis B) between patients and healthcare workers, as has the use of high-filtration masks for protection from respiratory transmission of influenza or tuberculosis (*105*,106). Although one of the key measures for the prevention and control of healthcare-associated infections remains the routine washing of hands before, between, and after patient contacts in healthcare settings, compliance or adherence to hand washing protocols among healthcare professionals—a behavioral attribute—remains wanting *(112)*; this is not surprising since as far back as 1996, Goldmann et al. found that National Guidelines seldom are studied thoroughly by physicians, and, if they are read, they rarely are incorporated into everyday practice *(46)*. Compounding the problem is the growing body of evidence that hand hygiene is but one factor in the complex interplay of host, agent, and the environment that facilitates transmission.

For a microorganism like VRE, transmission is enabled by one or more of the following factors: (a) the degree of hand hygiene among healthcare personnel; (b) the inherent properties of the microorganism that enable it to remain viable *days to weeks* on dry, inert environmental surfaces, coats, or ties; (c) the proportion of patients in the unit of concern who are colonized with VRE; (d) the proportion of patients who are inherently susceptible to infection; (e) selective pressure of vancomycin use in the unit; and (f) adherence to prevention efforts among healthcare personnel. Given the above, it follows that complete adherence to a strict hand hygiene policy alone will not necessarily preclude intrahospital transmission of VRE.

One method commonly used to interrupt transmission of pathogens in healthcare settings is the isolation of patients known to be colonized or infected with a particular pathogen in a separate area so as to reduce the probability of transmission of infection to other patients. This method may include allocation of these cohorted patients to specific healthcare workers to avoid transmission of the pathogen by the healthcare workers themselves.

Protecting the Host

The risk of acquisition and transmission of infectious diseases among patient populations in healthcare settings is better characterized if the patients' immune status or immune response is known. Immunization is the most effective method of individual and community protection against epidemic diseases, and can be active or passive. Through active immunization, smallpox, one of the major global communicable diseases, was eradicated *(113–115)*. Although polio has been eliminated from large areas, including all of the Americas (80), and indigenous transmission of wild poliovirus types 1 and 3 infection has been interrupted in all but four countries worldwide (Afghanistan, India, Nigeria, and Pakistan), there were still 1,655 cases reported in 2008 *(116)*. The occurrences of other childhood diseases have been substantially reduced, including diphtheria, pertussis, tetanus, measles, mumps, rubella, and infections of *H. influenzae* type B *(36,117,118)*. Since one of the main goals of epidemiology is to identify subgroups in the patient population that are at high risk for infection and disease, a knowledge of the vaccination status of patients is essential for the prevention of infection or disease. Institutional immunization programs have been recommended as part of the occupational health services of healthcare facilities for some time, but compliance for all healthcare workers has only recently come under mandate. Evaluation of patients for immunization during hospital admission is another program widely recommended but incompletely implemented. The residual endemic problems and periodic outbreaks of these vaccine-preventable diseases in both populations at large and in healthcare institutions have been largely the result of failure of the delivery programs for the vaccines. These have been due to poor funding, poor prioritization of the programs, the lack of political will, and the lack of organization of the vaccine effort—not to failure of the vaccine to immunize *(38)*.

Passive immunization with hyperimmune or standard immunoglobulins is another intervention valuable in a small group of diseases, including certain genetic and acquired immunodeficiency diseases, primary antibody-deficiency disorders, hypogammaglobulinemia in chronic lymphocytic leukemia, measles, hepatitis A, varicella-zoster, hepatitis B, and HIV infections in children *(36)*. Hyperimmune globulin preparations are obtained from blood plasma donor pools preselected for high antibody content against a specific antigen (e.g., hepatitis B immune globulin, varicella-zoster immune globulin, cytomegalovirus immune globulin, and respiratory syncytial virus immune globulin). Although active searches have been carried out for other kinds of immunomodulating agents (e.g., interferons and cytokines) and biologics that heighten host immune function and protect the host from infection or disease, there are no data that indicate such treatment modalities play any significant role in the prevention and control of healthcare-associated infections.

Administering antimicrobials to ensure the presence of an anti-infective agent at the site of a potential infection is a more recent addition to the control programs protecting the host. The use of a single dose or short course of preoperative antimicrobials to reduce the probability of infection with agents commonly seen following certain procedures has become a standard part of surgical practice *(119)*.

Profound cellular and humoral immunosuppression may ensue in patients following chemotherapy or radiotherapy of certain malignancies, or may be a consequence of the primary disease process. Therapy-related immunosuppression occurs during or following bone marrow transplantation or may be a sequelae of therapeutic regimens used to prevent rejection of transplanted organs. The use of local and systemic anti-infectives in these patients has either prevented infection or mitigated the duration and severity of infection, leading to reduced morbidity and mortality, and improved outcomes *(120–123)*. The use of preprocedure (e.g., surgery or dental) antimicrobial prophylaxis in individuals with a history of rheumatic heart disease is also a standard recommendation to prevent bacterial endocarditis *(124–126)*. Unfortunately, one of the side effects of repeated short courses of antimicrobials has been the appearance of significant resistance to these agents among pathogens associated with healthcare-associated infections (31,*127*,*128*). This problem has been aggravated by overprescribing of antimicrobials for nonbacterial infection by some practitioners, over-the-counter

sale of antimicrobials in many parts of the world, and the use of subtherapeutic doses of growth promoters in animal husbandry in the United States and other countries (*129–131*,132).

HEALTHCARE-ASSOCIATED INFECTIONS AND INFECTIOUS DISEASES

Inherent in the measures for the prevention and control of healthcare-associated infections is the ongoing education of healthcare workers in infection control practices and procedures through guidelines published by CDC *(133,134)*, and the implementation of surveillance measures to detect changes in the incidence or prevalence rates of infections caused by microorganisms commonly associated with healthcare-associated infections. The acute care hospital (inpatient, outpatient, and intensive care unit) settings and long-term care and home healthcare facilities provide special settings for the interaction of the agents of infection and patients and healthcare workers. The ongoing study of the basic epidemiologic features of agent–host interactions in these environments has led to recommendations for wide application of, and extensive testing of, surveillance, prevention, and control programs, which have proven highly successful. Descriptions of the special features of the investigations and interventions of these programs are the topics of the chapters to follow.

Despite falls in overall rates of healthcare-associated infections involving the bloodstream, respiratory tract, surgical wounds, and urinary tract, rates of infections caused by *antimicrobial-resistant* pathogens have been increasing across the United States. Thus, control of antimicrobial resistance in the 2000s remains inextricably linked to the control of transmission of healthcare-associated, *antimicrobial-resistant* pathogens and the infections they cause. The seriousness of the problem was underscored in an editorial by Muto, who made the point that "for as long as CDC has measured the prevalence of hospital-acquired infections caused by multidrug-resistant microorganisms, it has been increasing" *(135)*. The myriad of articles in the medical literature has in effect helped explain this failure since much of the data originated in facilities that had implemented untried control programs or had already instituted considerably ineffective programs.

Acute care hospital (inpatient, outpatient, and intensive care unit) settings, free standing medical and surgical centers, long-term care facilities, and the home provide special settings for the interaction of the agents of infection and hosts (i.e., patients, relatives, and healthcare workers alike). The ongoing study of the basic epidemiologic features of agent–host interactions in these environments has led to evidence-based recommendations for healthcare-associated infections surveillance, and prevention and control programs, which have proved highly successful. For example, the Society for Healthcare Epidemiology of America (SHEA) has established evidence-based guidelines to control the spread of MRSA and VRE in acute care settings (136). The tenets of the SHEA guidelines are based on identification and containment of spread through (a) active surveillance cultures to identify the reservoir for spread; (b) routine hand hygiene; (c) barrier precautions for patients known or suspected to be colonized or infected with epidemiologically important antimicrobial-resistant pathogens, such as MRSA or VRE; (d) implementation of an antimicrobial stewardship program; and (e) decolonization or suppression of colonized patients (136). Numerous reports presented at the SHEA annual meetings over the past 5 years have repeatedly shown control of endemic or epidemic MRSA and VRE infections through implementation of the SHEA guidelines. There is now growing evidence that active surveillance cultures do indeed reduce the incidence rates of MRSA and VRE infections and that programs described in the SHEA guidelines are effective and cost-beneficial (137,*138*,*139*). Many other studies have since established that identification of patients colonized with MRSA or VRE on admission to hospital for critical care may enhance implementation of interventions to decrease infection (*140*).

Despite all of the resources put into surveillance activities for healthcare-associated infections in facilities throughout the nation, there remain several obstacles that hinder progress in the control of these infections. These include (a) substantial variation in surveillance activities from one medical center to another and in the collection, aggregation, and use of surveillance data; (b) lack of designated staff healthcare epidemiologists to proactively aggregate, manage, and analyze surveillance data, and apply the results effectively; (c) failure of healthcare facilities to use effective control measures or inconsistent implementation of such measures (e.g., surveillance cultures not being performed as recommended); (d) lack of commitment and prescience among healthcare providers and administrative personnel alike in appreciating the fact that the initial outlay of financial resources that is necessary for employing healthcare epidemiologists and infection preventionists and executing surveillance activities and preventive measures could actually result in improved patient outcomes and substantial savings.

In conclusion, epidemiologic methods can enhance and strengthen evidence-based infection prevention and control through the design and conduct of studies to ascertain risk factors for infection and disease, establish the appropriateness of laboratory testing (e.g., the clinical significance of positive blood cultures), or determine best outcome correlates. In addition, familiarity with infectious diseases epidemiology enables characterization of community or healthcare-associated infections, the pathogens that cause these infections and their respective antimicrobial susceptibility profiles, and risk factors that cause (or are associated with) infection. Such data allow cost-effective patient care in hospitals with adequate resources, and enable development of logical, evidence-based preventive policies that could be applied to hospitals without sophisticated epidemiologic or laboratory support. Finally, the integration of epidemiologic and microbiologic principles is necessary for the development of robust surveillance systems for tracking emerging infections and antimicrobial resistance, for the effective conduct of infection control activities and outbreak investigations, and for informed clinical and public health decision making, research, and management practices.

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CHAPTER 2

Modern Quantitative Epidemiology in the Healthcare Setting

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I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of Science, whatever the matter may be. *Lord Kelvin*

The job of the hospital epidemiologist is an intensely political one, into which we can occasionally interject some science. *Jonathan Freeman*

This chapter is about quantitative epidemiology, a term without a formal definition. However, epidemiology can be defined as "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to control of health problems" *(1)*. "Distribution" refers to rates of disease overall and in various subgroups; for example, what percent of patients having cardiac surgery develop a surgical site infection? Assembling such rates requires an important series of steps, including determining which diseases are important, how they should be defined, and by what practical means they can be measured. "Study of … determinants of health-related states," or risk factors for disease, is the part of the definition closest to quantitative epidemiology. For example, what determines whether one patient gets a surgical site infection while another does not, or why the infection rate is higher at one hospital than at another? "Application of this study to control of health problems" is the all-important final step, requiring wisdom, judgment, and political savvy. Given the difficulty of this final step, we should at least be sure that we have done the best possible job at quantitative epidemiology, that is, of analyzing and presenting the data needed for decision making.

In one sense, epidemiology is merely "quantified common sense." For example, the simple observation that "our infection rate is higher than theirs because our patients are sicker than theirs" describes what epidemiologists call confounding. Confounding bedevils a variety of activities in healthcare epidemiology, including the comparisons of disease rates among hospitals that underlie interhospital comparisons (benchmarking) and quality assurance programs. Simply comparing crude infection or death rates among hospitals, without accounting for factors such as severity of illness, leads to obviously incorrect conclusions. While the concept of confounding may be intuitive, there is considerable complexity in application of the methods of quantitative epidemiology to deal with confounding.

It is difficult to determine the boundary between quantitative epidemiology and a related discipline, statistics. Many healthcare epidemiologists have taken introductory statistics courses, but such entry-level courses are becoming less and less adequate with each passing year. A study of articles in a prominent medical journal showed substantial increases in the use of advanced methods such as multiple regression (from 5% of articles in 1978–1979 to 51% of articles in 2004–2005), survival methods (from 11% to 61%), and power analyses (from 3% to 39%) *(2)*. In 2004 to 2005, 79% of the articles used methods beyond the scope of introductory statistics courses. Greater knowledge of quantitative epidemiology/statistics is needed both to interpret the infection control literature and to practice healthcare epidemiology.

HISTORY OF EPIDEMIOLOGY

A famous early example of applied epidemiology is the work of Dr. John Snow, a physician in London during the cholera epidemic of 1855 (3). At that time, the germ theory of disease had not been accepted and the pathogen causing cholera, Vibrio cholerae, was unknown. Whereas the prevailing view during this period was that disease was caused by a miasm or cloud, Snow inferred from epidemiologic evidence that cholera was a water-borne illness. He constructed a spot map of cholera cases and noted a cluster of cases near a water pump on London's Broad Street, the so-called Broad Street pump. This early use of a spot map to find the putative cause of an outbreak is an example of descriptive epidemiology. He also

[1]The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

performed several analytic studies, noting that the rate of cholera was higher for people who obtained water from more polluted areas of the Thames. His well-known intervention was to remove the handle from the Broad Street pump, thereby preventing the use of this contaminated water, after which cases of cholera in the vicinity were said to have decreased. This example illustrates that epidemiologists can define the mechanism of disease spread and institute control measures before the agent causing disease is discovered. More recent examples of this power of epidemiology include Legionnaires' disease and human immunodeficiency virus disease; for both diseases, the mechanism of spread and means of prevention were inferred by epidemiologists before the microbe was discovered in the laboratory.

DESCRIPTIVE VERSUS ANALYTIC EPIDEMIOLOGY

In descriptive epidemiology, we describe characteristics of the cases and generate hypotheses. The line list of cases, case series, epidemic curves, and spot maps are examples. In analytic epidemiology, we use comparison groups, calculate statistics, and test hypotheses. Many outbreaks and other problems in healthcare epidemiology can be solved by thoughtful examination of descriptive data without the use of analytic epidemiology. However, the increasingly complex nature of healthcare and associated illness demands that we have a firm grounding in analytic or quantitative epidemiology, which is the main focus of this chapter.

MEASURES OF FREQUENCY

Proportions (synonyms are *probability*, *risk*, and *percentage*) are the simplest way to represent how often something occurs. A proportion is the ratio of a part to the whole; that is, the numerator of the ratio is included in the denominator. The proportion with disease is the number of people who get the disease divided by the total number at risk for the disease; that is, proportion ill = number ill/(number ill + number well). The probability of pulling an ace from a deck of cards is 4/52 = 7.7%. Proportions can be represented by a fraction (e.g., 0.077) or a percentage (e.g., 7.7%) and can range from 0 to 1.0 or from 0% to 100%. Proportions cannot be >1.0 or 100% since, using proportions, each entry in the denominator can have at most one entry in the numerator. A proportion is unitless, because the numerator and denominator have the same units. The proportion is the measure of frequency used in cohort studies and to calculate the relative risk.

Odds represent the ratio of a part to the remainder or the probability that an event will occur divided by the probability that it will not occur. Unlike in proportions, the numerator of the ratio is not included in the denominator. The odds of a disease occurring equal the number of people with the disease divided by the number without the disease; that is, odds of illness = number ill/number well. The odds of pulling an ace from a deck of cards are 4/48 = 8.3%. Note that the odds of illness are always higher than a corresponding proportion ill, because the denominator is smaller for odds. Odds are unitless and have bounds of zero to infinity. Odds are used in case–control studies and to calculate the odds ratio.

A rate, in contrast to proportions and odds, has different units of measure in the numerator and denominator, as in 55 miles/hour or 20 healthcare-associated infections/1,000 observed patient-days. A rate can have any value from zero to infinity. Rates are used in incidence density analyses.

Common Usage

The proportion ill, especially in outbreaks, is often called an "attack rate," although strictly speaking it is a misnomer to refer to a proportion as a rate. This chapter follows common usage in using the following terms interchangeably with proportion ill: percent ill, attack rate, and rate of illness.

Cumulative Incidence Versus Incidence Density

In a cumulative incidence study, time at risk is not taken into account; the denominator is the total number of persons at risk, and the proportion with disease (or proportion with potential risk factors for disease) is calculated. The cohort and case–control studies presented in the following section are examples of cumulative incidence. In an incidence density study, time at risk is accounted for; the denominator is person-time at risk and a rate of illness (e.g., infections per 1,000 patient-days) is calculated. This type of study is considered later in this chapter.

BASIC STUDY DESIGN

There are three types of analytic study: cohort, case–control, and cross-sectional. The goal of analytic epidemiologic studies is to discover a statistical association between cases of disease and possible causes of disease, called *exposures*. A first step in any such study is the careful definition of terms used, especially defining what clinical and laboratory characteristics are required to indicate a case of disease.

The Cohort Study and Relative Risk

Prospective Cohort Study There are several subtypes of cohort study, but all have certain common features and are analyzed the same way. In the prospective cohort study, we identify a group of subjects (e.g., persons or patients) who do not have the disease of interest. Then, we determine which subjects have some potential risk factor (exposure) for disease. We follow the subjects forward in time to see which subjects develop disease. The purpose is to determine whether disease is more common in those with the exposure ("exposed") than in those without the exposure ("nonexposed"). Those who develop disease are called "cases," and those who do not develop disease are "noncases" or "controls."

A classic example of a prospective cohort study is the Framingham study of cardiovascular disease, which began in 1948 (3). Framingham is a city about 20 miles from Boston with a population of about 300,000, which was considered to be representative of the US population. A random sample of 5,127 men and women, age 30 to 60 years and without evidence of cardiovascular disease, was enrolled in 1948. At each subject's enrollment, researchers recorded gender and the presence or absence of many exposures, including smoking, obesity, high blood pressure, high cholesterol, low level of physical activity, and family history of cardiovascular disease. This cohort was then followed forward in time by examining the subjects every 2 years and daily checking of the only local hospital for admissions for cardiovascular disease.

Note several features of this study. The study was truly prospective in that it was started before the subjects developed disease. Subjects were followed over many years and monitored to determine if disease occurred, that is, if they became "cases." This is an incidence study, in which only new cases of disease were counted (because persons with cardiovascular disease in 1948 were not eligible for enrollment). In an incidence study, it is necessary to specify the study period, that is, how long the subjects were allowed to be at risk before we looked to see whether they had developed disease.

The Framingham study allowed investigators to determine risk factors for a number of cardiovascular disease outcomes, such as anginal chest pain, myocardial infarction (heart attack), death due to myocardial infarction, and stroke. One finding of this study was that smokers had a higher rate of myocardial infarction than nonsmokers. An advantage of this study design is that it is very flexible, in that the effect of many different exposures on many different outcome variables can be determined. The disadvantages are the time, effort, and cost required.

Relative Risk Performing hospital surveillance for surgical site infections (SSIs) is an example of a prospective cohort study. Assume that during one year at hospital X, 100 patients had a certain operative procedure. Of these, 40 were wound class 2 to 3 and 60 were class 0 to 1. Note that wound class was determined before it was known which patients were going to develop SSI; this makes it a prospective cohort study. A subgroup or sample of patients was not selected; that is, the entire group was studied. When the patients were followed forward in time, the following was found: of 40 patients with class 2 to 3 procedures, 10 developed SSI; of 60 patients with class 0 to 1 procedures, 3 developed SSI.

Cohort study data are commonly presented in a 2×2 table format. The general form of the 2×2 table is shown in Table 2-1, and the 2×2 table for this SSI example is shown below. Notice that the columns denote whether disease (SSI) was present and the rows whether exposure (wound class 2–3) was present. In this example, exposed means being class 2 to 3 and nonexposed means being class 0 to 1. In the 2×2 table below, the total number of cases is 13, total noncases is 87, total exposed is 40, total nonexposed is 60, and total patients is 100.

TABLE 2-1

The 2 × 2 Table and Associated Formulas

Exposure	Disease: Yes	Disease: No	
Yes	a	b	$a + b = h_1$
No	c	d	$c + d = h_2$
	$a + c = v_1$	$b + d = v_2$	N

Exposed cases = a
Exposed noncases = b
Nonexposed cases = c
Nonexposed noncases = d
Total cases = $a + c = v_1$
Total noncases = $b + d = v_2$
Total exposed = $a + b = h_1$
Total nonexposed = $c + d = h_2$
Total subjects = $a + b + c + d = n$

$$\text{Relative risk} = \frac{\%\text{ ill exposed}}{\%\text{ ill nonexposed}} = \frac{a/(a+b)}{c/(c+d)}$$

$$\text{Odds ratio} = \frac{ad}{bc}$$

Expected values (where "ea" denotes "the expected value of cell a")
ea = $h_1 v_1 / n$
eb = $h_1 v_2 / n$
ec = $h_2 v_1 / n$
ed = $h_2 v_2 / n$

$$\text{chi-square} = \frac{(a-\text{ea})^2}{\text{ea}} + \frac{(b-\text{eb})^2}{\text{eb}} + \frac{(c-\text{ec})^2}{\text{ec}} + \frac{(d-\text{ed}^2)}{\text{ed}}$$

Alternate "calculator" formula: chi-square = $(ad - bc)^2(n - 1)/(a + b)(c + d)(a + c)(b + d)$

Disease: Surgical Site Infection

Exposure	Yes	No	
Class 2–3	10	30	40
Class 0–1	3	57	60
	13	87	100

In the exposed group, the proportion ill = 10/40 = 0.25 or 25%. In the nonexposed group, the proportion ill = 3/60 = 0.05 or 5%. We compare the frequency of disease in the exposed versus nonexposed groups by calculating the relative risk (often called risk ratio). The relative risk of 5.0 means that patients in wound class 2 to 3 were five times more likely to develop SSI than were patients in wound class 0 to 1.

$$\text{Relative risk} = \frac{\%\text{ ill exposed}}{\%\text{ ill nonexposed}} = \frac{\%\text{ ill class } 2-3}{\%\text{ ill class } 0-1} = \frac{a/(a+b)}{c/(c+d)} = \frac{25}{5} = 5.0$$

Retrospective Cohort Study A retrospective cohort study is started after disease has developed. A study period

(start date and stop date) is decided upon. Using patient records, we look back in time to identify a group (cohort) of subjects that did not have the disease at the start time. We then use patient records to determine whether each cohort member had a certain exposure. Again using patient records, we determine which cohort members developed disease during the study period. Finally, we calculate the percent with disease in those with the exposure and those without the exposure and compare the two.

The following is an example of a retrospective cohort study based on the SSI example above. Hospital X noted that the overall SSI rate of 13% was higher than in previous years. We want to determine whether a new surgeon (surgeon A) was responsible for the increase. The prospective surveillance system did not routinely record the surgeon performing each procedure, so we pull the records from each procedure and record whether or not surgeon A was involved. We find that surgeon A operated on 20 patients,3 of whom later developed SSI. Among the 80 other patients, 10 developed SSI. The percent ill in the exposed group (surgeon A) = 3/20 = 15%. The percent ill for other surgeons (nonexposed) = 10/80 = 12.5%. The relative risk = 15%/12.5% = 1.2.

The interpretation is that patients operated on by surgeon A were 1.2 times (or 20%) more likely to develop disease than patients operated on by other surgeons. Factors to consider in deciding whether surgeon A is truly a cause of the problem are presented below (see Interpretation of Data, Including Statistical Significance and Causal Inference).

To review, this was a retrospective cohort study, since data on the exposure were collected from patient records after we knew which patients had developed SSI. The retrospective nature of data collection is sometimes irrelevant and sometimes a problem. For certain types of data, such as length of hospital stay or death, retrospective data collection will be as good as prospective. However, determining other factors, such as which ancillary personnel treated a given patient, may be difficult to do after the fact, and retrospective studies using such data may be less valid.

Observational Versus Experimental Studies Epidemiologic studies are generally observational; that is, the investigator collects data but does not intervene in patient care. Patients, physicians, nurses, and random processes all play a part in determining exposures in the hospital. The goal of observational studies is to simulate the results of an experimental study (see Quasi-Experimental Studies)

In an experimental study, a group (cohort) of subjects is identified and the investigator assigns some of them to receive treatment A (exposed) and the remainder to receive an alternate treatment B (nonexposed). The patients are followed forward in time, the cases of disease are recorded, and the rates of illness and relative risk are calculated as usual. The experimental study is a special type of a prospective cohort study where the two exposure groups are assigned by the investigator.

Cohort Studies With Subjects Selected Based on Exposure In this type of cohort study, subjects are selected based on exposure. We select two subgroups: one that is exposed and one that is nonexposed. Both groups are followed forward in time to see how many develop disease. Consider the SSI example and surgeon A above. We study all 20 patients operated on by surgeon A (exposed); of the 80 patients operated on by other surgeons, we randomly select 40 (nonexposed). Thus, only 60 patients of the original group of 100 are included in this study.

Note that this is a type of cohort study, not a case–control study. In a case–control study, the subjects are chosen based on whether or not they have disease. In this study, subjects were chosen based on whether or not they had exposure.

The disadvantage of this type of cohort study, where the subjects are selected based on exposure, is that only one exposure (i.e., the exposure that you selected subjects on) can be studied. However, this type of study is very useful for studying an uncommon exposure. In the SSI surveillance example used above, consider the situation if there had been 500 surgical procedures, and surgeon A had performed only 20 of them. If you performed a cohort study of the entire group, you would have to review 500 charts, which would waste time and effort. Instead, you could perform a cohort study of the 20 procedures performed by surgeon A (exposed), and 40 randomly selected procedures performed by other surgeons (nonexposed). The second alternative would be much more efficient.

Cohort Studies—Summary Cohort studies can be prospective or retrospective, observational or experimental. They usually include a whole group of subjects, but studying two subgroups selected based on exposure is also possible. The 2×2 table layout and calculations are the same for all types of cohort studies. All have in common that subjects are chosen without regard to whether they develop disease.

The Case–Control Study and Odds Ratio

In a case–control study, we choose subjects for study based on whether they have disease. Since we have to know which subjects developed disease before we select them, case–control studies are always retrospective. We usually study those with disease (cases) and choose a sample of those without disease (controls). We usually study one to four controls per case. The more controls, the greater the chance of finding statistically significant results. However, there is little additional benefit from studying more than four controls per case. Controls are usually randomly selected from subjects present during the study period who did not have disease.

Example: Case–Control Study of Surgical Site Infections This is the same example presented in the section on cohort study and relative risk. At hospital X, 100 patients had a certain operative procedure, 40 class 2 to 3 (exposed) and 60 class 0 to 1 (nonexposed), and 13 developed SSI. To perform a case–control study, we select the 13 patients with SSI (cases) and also study 26 patients who had surgical procedures but did not have SSI (controls). We studied two controls per case, but could have studied fewer or more controls. The controls were randomly chosen from all patients who had the surgical procedure under study but did not develop SSI. From their

medical records, we find which of the subjects had class 2 to 3 procedures and which had class 0 to 1 procedures. Our data showed that, of 13 cases, 10 had class 2 to 3 procedures. Of 26 noncases, 9 had class 2 to 3 procedures. The 2×2 table for this example is as follows:

Disease: Surgical Site Infection

		Yes	No	
Exposure	Class 2–3	10	9	
	Class 0–1	3	15	
		13	26	39

In a case–control study, we cannot determine the percent ill in the exposed or nonexposed groups, or the relative risk. In this example, note that the percent ill among class 2 to 3 is NOT = 10/(10 + 9) = 52.6%. However, we can validly calculate the percent of cases that were exposed, 10/13=76.9%, and the percent of noncases that were exposed, 9/26 = 34.6%. Note that the cases were much more likely to have the exposure than were the controls. Most importantly, we can calculate the odds ratio (also called the relative odds; Table 2-1) as follows:

$$\text{Odds ratio} = \frac{ad}{bc} = \frac{10 \times 15}{9 \times 3} = \frac{150}{27} = 5.6$$

We can interpret the odds ratio as an estimate of the relative risk. Using the case–control method, we estimated that patients in class 2 to 3 were 5.6 times more likely to develop SSI than were patients in class 0 to 1. Note that the odds ratio is similar to, but slightly higher than, the relative risk (5.0) we calculated previously. If the frequency of disease is not too high, that is, is less than approximately 10%, the odds ratio is a good approximation of the relative risk.

The meanings of the letters (i.e., *a*, *b*, *c*, and *d*) used to represent the 2×2 table cells are different in cohort versus case–control studies (Table 2-1). For example, in a cohort study, *a* denotes the number of cases of disease among exposed persons; in a case–control study, *a* denotes the number exposed among a group of cases. Although this distinction may not be clear to the novice, it will suffice to keep in mind that in a case–control study, it is not valid to calculate percent ill or relative risk, but it is valid to calculate an odds ratio.

A more in-depth explanation of the odds ratio is as follows. In a case–control study, we actually measure the odds of exposure among those with disease and the odds of exposure among those without disease. The ratio of these two odds is the exposure odds ratio; if equal to 2.0, this would be interpreted as "the odds of exposure are twice as high in those with disease versus those without disease." However, the exposure odds ratio is not a very useful quantity. Fortunately, it can be proven mathematically that the exposure odds ratio equals the disease odds ratio. Therefore, using our example of 2.0, we can say that the odds of disease are twice as high in those exposed versus those not exposed, which is closer to being useful. Finally, we use the odds ratio as an approximation of the relative risk (where the frequency of disease is not too high) and say simply that those with exposure are twice as likely to get disease.

Selection of Controls Selection of controls is the critical design issue for a case–control study. Controls should represent the source population from which the cases came; represent persons who, if they had developed disease, would have been a case in the study; and be selected independently of exposure *(4)*. It is always appropriate to seek advice when selecting controls, and may be worthwhile to select two control groups to compare the results obtained with each.

An example of incorrect selection of controls is provided by a case–control study of coffee and pancreatic cancer (3,5). The cases were patients with pancreatic cancer, and controls were selected from other inpatients admitted by the cases' physicians but without pancreatic cancer. The finding was that cases were more likely to have had the exposure (coffee drinking) than the controls, which translated into a significant association between coffee drinking and pancreatic cancer. The problem was that the controls were not selected from the source population of the cases (cases did not arise from hospital inpatients) and thus were not representative of noncases. The physicians admitting patients with cancer of the pancreas were likely to admit other patients with gastrointestinal illness; these control patients were less likely to be coffee drinkers than the general population, possibly because they had diseases that prompted them to avoid coffee. A better control group might have been healthy persons of similar age group to the cases.

More contemporary examples of problematic control selection are studies of the association between vancomycin receipt and vancomycin resistance (6). Cases are often hospitalized patients who are culture positive for vancomycin-resistant enterococci. Controls have often been selected from patients who were culture positive for vancomycin-sensitive enterococci. Using this control group, case-patients will be more likely to have received vancomycin than the controls, resulting in a significant association and elevated odds ratio. The problem is that controls were not representative of the source population and were less likely to have received vancomycin than other patients, since vancomycin would have suppressed or eliminated vancomycin-sensitive microorganisms. Better control groups would be hospital patients similar in age and severity of illness to the cases.

A potential problem is that hospital patients without a positive culture may include some patients who had the microorganism but were not cultured. Inclusion of these patients as controls would bias the odds ratio to 1.0 (null result). An alternative method is to limit controls to those with at least one clinical culture performed. However, this may not be preferable since it results in selection of sicker controls ("severity of illness bias") and also biases the odds ratio toward 1.0 *(7)*. Another way to look at this issue of potential "contamination" of the control group with unrecognized cases is as follows: in a study design called the case-cohort study, cases are compared with subjects chosen from all patients (i.e., from both cases and noncases); then, the *ad*/*bc* statistic equals the relative risk rather than the odds ratio; therefore, inadvertent inclusion of noncases in the control group when performing a case–control study may "bias" the odds ratio toward the relative risk and thus be advantageous.

Comparison of Cohort Versus Case–Control Studies

Cohort studies may be prospective or retrospective, but case–control studies are always retrospective. A major advantage of cohort studies is that we can calculate the percent ill and the relative risk. Cohort studies are less subject to bias than case–control studies. The potential disadvantages of cohort studies are that they are more time-consuming and expensive and may require study of a large group to collect information on a small number of cases.

Prospective cohort studies are the premier type of observational study. They provide the strongest evidence; are less subject to bias in collecting exposure data, since exposure is recorded before the subjects develop disease; and are flexible in that it is possible to study many exposures and diseases. The disadvantage is that it may be necessary to follow subjects over a long period of time to determine whether they develop disease.

The advantages of the case–control study are that we can determine risk factors while studying a relatively small group of patients; we can study as many risk factors as desired; and case–control studies are usually quicker, easier, and cheaper than cohort studies. The disadvantages are that the percent ill and relative risk are not determined; only one disease can be studied at a time; and the selection of controls can be subtle and introduces the chance of error. Deciding which is the most appropriate control group for a particular study is a matter of opinion about which even well-trained epidemiologists may disagree.

Cross-Sectional or Prevalence Study

A third type of study (besides cohort and case–control) includes only subjects who are present in a locality at one point in time. Exposure and disease are ascertained at the same time. Depending on the way the subjects were selected, a cross-sectional study may be analyzed as a cohort study or a case–control study.

A cross-sectional study is clearly not an incidence study, which would include as cases only those free of disease at the start of the study and who develop disease during the study period. However, if an entire group present at one point in time is studied, the results can be analyzed in a 2×2 table similar to that used for cohort studies. The formula used to calculate a relative risk in a cohort study would yield a prevalence ratio in a cross-sectional study. If the group present at one point in time is sampled as in a case–control study (i.e., the cases and a random selection of noncases are studied), then the odds ratio formula could be used to calculate a prevalence odds ratio.

Incidence Versus Prevalence

Incidence includes only new cases of disease with onset during a study period; the denominator is the number of subjects without disease at the beginning of the study period. Incidence measures the rate at which people without the disease develop the disease during a specified period of time; it is used to study disease etiology (risk).

Prevalence includes both new and old cases that are present at one time and place, measuring the proportion of people who are ill. The commonest measure of prevalence is point prevalence, which is the proportion of individuals who are ill at one point in time. Point prevalence is a unitless proportion. A different measure of prevalence, period prevalence, is the proportion of persons present during a time period with disease. Period prevalence has been criticized as an undefined mixture of both prevalent and incident cases without quantitative use, but is occasionally seen.

Prevalence studies are the ideal way to measure disease burden and plan for needed resources. For example, if we wanted to know how many isolation rooms would be needed for patients with resistant microorganisms, we would want to know average prevalence, that is, the total number of patients with recognized drug-resistant microorganisms of either new or old onset in the hospital at any given time.

Prevalence can also be used as a simple, quick, and dirty way to measure disease frequency and risk factors, but such estimates may be biased by length of stay. It is often said that prevalence equals incidence *times* duration. That is, prevalence is higher if either incidence is higher or if the duration of the illness is longer. In hospital studies, prevalence is greatly influenced by length of stay and mortality. For example, assuming that ascertainment of vancomycin-resistant enterococci is stable, the prevalence of vancomycin-resistant enterococci in a hospital may decrease because of an effective prevention program, or because patients with this microorganism are being discharged sooner or dying more commonly than had been the case previously.

Point prevalence and incidence density are mathematically linked; in a steady-state or dynamic population, one can be derived from the other. Prevalence can be derived from incidence density and distributions of durations of disease, and incidence density may be derived from prevalence and distributions of durations to date of disease *(8–11)*.

INTERPRETATION OF DATA, INCLUDING STATISTICAL SIGNIFICANCE AND CAUSAL INFERENCE

Measures of Size of Effect and their Interpretation

The relative risk and the odds ratio measure the size of effect, that is, the magnitude of the association between an exposure and a disease. A relative risk of 1.3 shows a modest association, whereas a value of 20 shows a large association. In general, odds ratios are interpreted in the same manner as relative risks.

Because the relative risk = percent ill exposed/percent ill nonexposed, the relative risk can fall into three categories. First, if the two percents are approximately equal, the relative risk is approximately 1.0; this is a null result showing no association between exposure and disease. Second, if the percent ill is higher in the exposed group, the relative risk is >1.0; exposure is apparently associated with disease, is a risk factor for disease, and may be a cause of disease. Third, if the percent ill is higher in those without exposure,

the relative risk is <1.0; exposure is again apparently associated with disease, but in this instance the exposure prevents disease. An example of a preventive exposure is vaccine use; persons who are "exposed" to the vaccine have a lower rate of disease than those not exposed, leading to a relative risk <1.0. Interpretation of odds ratios as equal to, greater than, or less than 1.0 is similar. To intelligently interpret relative risks and odds ratios, we must in addition understand statistical significance and the distinction between association and causation (presented below).

Relative risks can be interpreted as a percent increase or decrease. For example, a relative risk of 1.5 could be interpreted in two ways: disease is 1.5 times more likely in exposed than in nonexposed, or disease is 50% more likely in exposed than in nonexposed. Similarly, a protective relative risk of 0.6 could be interpreted in two ways: illness was 0.6 times as likely in exposed than in nonexposed, or illness was 40% less likely in the exposed group.

Statistical Significance and *p* Values

For a given group and time period, an association between exposure and disease might occur due to chance alone. For example, suppose that over many years the rate of SSI at hospital A is the same as that of other hospitals. However, during a given quarter, the rate at hospital A may be higher or lower than average by chance alone. To tell us the probability that the SSI rate at hospital A differed from the rate at other hospitals due to chance alone, we commonly use two measures of statistical significance, the *p* value and the confidence interval.

The *p* value measures the probability that a given result, or one more extreme, could have happened by chance alone if there was no association between exposure and diseases. Because computer packages calculate *p* values automatically, it is more important to know how to interpret than to calculate them. *P* values range from >0 to 1.0. By convention, a *p* value ≤.05 indicates statistical significance. This means that there is a ≤5% or ≤1/20 chance that the result we found (or one more extreme) could have occurred by chance alone; exposure is associated with disease. Another way of stating this is that we are 95% certain that this observed difference did not arise by chance alone. If the *p* value is >.05, the result is not considered statistically significant and could well have happened by chance alone; we do not have evidence that exposure is associated with disease.

The .05 cutoff was not chosen for any particular reason but now is very commonly used. There is not a meaningful difference between *p* values of .04 and .06; although the latter would not usually be considered statistically significant, in fact there is only a 6% chance that such a result could have occurred by chance alone. The adoption of the arbitrary .05 standard has its unfortunate aspects and is subject to interpretation after considering all of the sources of bias described below. Some published manuscripts describe interesting or important studies where the *p* value did not reach .05, thus allowing readers to make their own determinations of biologic importance.

Small epidemics, or epidemics that are stopped before there are sufficient cases to demonstrate statistical significance at the .05 level, may be biologically very important, so epidemiologists who work with observational data in hospitals should not consider statistical *p* values to be of primary interest. Biologic importance and size of effect are much more compelling than *p* values in the face of an ongoing problem in a hospital.

In biostatistical terms, significance testing can be viewed as follows. We assume the null hypothesis that there is no true difference in rate of illness between the exposed and nonexposed groups. We then compute the *p* value, that is, probability of the results (or results more extreme) under the null hypothesis. If the *p* value is low, then apparently the null hypothesis was wrong, and we reject the null hypothesis and embrace the alternative hypothesis, namely, that there is a true difference between exposed and nonexposed (see Chapter 3).

Type I Versus Type II Error The *p* value required for statistical significance is commonly called the chance of type I error. This means that if we conclude that hospital A has a high (or low) rate of illness based on a *p* value of .05, there is a 5% chance that we are drawing this conclusion in error. The type I error then indicates the chance of concluding that a difference in rates exists when in fact there is no true difference. Type II error measures the opposite problem—that there really is a difference between the two rates but we erroneously conclude that they are the same. The power of a study (discussed below) = 1—the probability of type II error.

Methods of Calculating p Values *P* values for 2×2 tables may be calculated by the chi-square or Fisher exact methods. The chi-square *p* value is valid when an expected value (Table 2-1) is not <5; if an expected value is <5, the Fisher exact results should be used. Computer packages commonly calculate expected values and print out a suggestion to use the Fisher exact *p* value if appropriate. In addition to a simple or uncorrected chi-square value, computer packages may compute a continuity corrected (or Yates corrected) value. The formula for continuity correction involves subtracting 0.5 from each cell in the 2×2 table. There are usually not great differences among these chi-square values, and many authorities suggest using the simple or uncorrected value.

The calculation of chi-square value does not differ depending on whether data are from a cohort, case–control, or cross-sectional study. However, the computation of chi-square value is different for incidence density data. Calculation of chi-square value is shown in Table 2-1 and Question 3 in Appendix 1 at the end of this chapter. Later in this chapter we suggest some shareware programs that perform these calculations. When one has the value for chi-square, one can determine the *p* value by looking it up in a table or by using a statistical program. In Excel, the CHIDIST function calculates the *p* value for a given chi-square value and number of degrees of freedom.

P values may be one-tailed or two-tailed. Two-tailed *p* values are usually twice as great as one-tailed values. A two-tailed *p* value assumes that the rate in the exposed group could have been either higher or lower than in the unexposed group due to chance alone. A one-tailed value recognizes only one of these two possibilities. For example, suppose that a study showed rates of illness significantly lower among those exposed to a putative toxin

than among those not exposed; if the intent had been to conclude that the "toxin" might actually be protective, we should use a two-tailed test; however, if the intent had been to consider such a finding to be spurious and probably due to chance alone and conclude that the toxin has no effect, then we should use a one-tailed test. Although there is no uniform agreement as to whether one- or two-tailed results should be used, the majority of authors use two-tailed *p* values. This suggests that, for uniformity and ease of comparison among studies, two-tailed *p* values should be the standard.

One-tailed tests are standard for noninferiority studies, which are becoming more common in the literature. An example is a trial of whether hepatitis A vaccine is inferior to the standard method, immune globulin, for postexposure prophylaxis *(12)*. Hepatitis rates were 4.4% among those vaccinated and 3.3% among those receiving immune globulin (relative risk = 1.35, two-tailed confidence interval = 0.7–2.67, one-tailed upper confidence limit = 2.40). Since the one-tailed upper confidence limit did not overlap a predetermined relative risk of 3.0, the authors concluded that the vaccine was noninferior. If the rate of hepatitis A had been lower among those receiving vaccine than immune globulin, the authors would have dismissed the finding and not concluded that the vaccine was better. Given this intent, a one-tailed test was appropriate for this study, as it is for other noninferiority trials.

Confidence Intervals

The second way to judge statistical significance is the confidence interval for a relative risk or odds ratio. The confidence interval combines the concepts of size of effect (relative risk) and strength of association (*p* value). A 95% confidence interval means that, roughly speaking, we are 95% sure that the true relative risk lies between the upper and lower confidence interval limits. For example, assume that a study showed a relative risk of 5.0 with a 95% confidence interval of 1.47 to 17.05. Our best guess is that the relative risk is 5.0, which seems quite high, but we are 95% sure that it lies between 1.47 and 17.05. This is much more informative than simply reporting the probability of our results under the null hypothesis (*p* value). An additional benefit of the confidence interval is humility; a wide interval points out the uncertainty in our results.

If a 95% confidence interval does not cross 1.0, the result is statistically significant at the .05 level. Remembering the formula for the relative risk, a relative risk >1.0 with a 95% confidence interval excluding 1.0 means that we are 95% sure that the rate of illness in the exposed group is greater than the rate of illness in the nonexposed group.

Causal Inference: Association Versus Causation

A statistical association between an exposure and a disease does not necessarily mean that the exposure caused the disease. Sir Bradford Hill first described a set of logical criteria by which associations could be judged for potential causality. Fulfillment of Hill's criteria does not guarantee that an association is causal, but failure to meet these criteria generally excludes the possibility of causality. These criteria have changed somewhat over time, but here is a version appropriate for healthcare epidemiology:

1. Size of effect can be estimated by the relative risk. Large effects are more likely to be causal than small effects. The magnitude of a credible relative risk must depend on the magnitude of the potential sources of bias. Generally, a relative risk >2.0 or <0.5 in a well-done study is difficult to ignore.
2. Strength of association can be measured by the *p* value. A relatively weak association can more easily be the result of random or systematic error. A *p* value near .05 would be considered a weak association. The same information is better presented by the statement that a relative risk 95% confidence bound near 1.0 would be evidence of a weak association.
3. Consistency: A particular effect should be reproducible in different populations and settings.
4. Temporality: The cause must precede the effect.
5. Biologic gradient: There should be a dose–response effect. More exposure should lead to more outcome.
6. Plausibility of the biologic model: There should be a reasonable biologic model to explain the apparent association. This includes Hill's criteria of coherence, experimental evidence, and analogy.

ERRORS IN EPIDEMIOLOGIC STUDIES

Epidemiologic studies, even observational studies, involve people and are usually expensive. Therefore, the practical goal is to design a study that requires the least resources yet will provide a good-enough answer to a question. Since the perfect epidemiologic study will never be done, every epidemiologist has to be an expert on sources of error in measurement. For every question or every study, one must review the potential sources of error, estimate their likely direction and magnitude, and then decide what overall effect these distortions might have on the result of the study.

It is worthwhile to distinguish random variation, random error, and systematic error. Random variation is the statistical phenomenon of variability due to chance alone, and is sometimes called background or noise. If we were measuring SSIs, the true underlying SSI rate would vary each month according to many factors, including the mix of surgeons and patients involved; assuming hypothetically that these factors could be held stable, the SSI rate would still vary each month because of chance alone (i.e., random variation). On the other hand, random and systematic *errors* are produced by inaccuracies in finding or recording data. Random error would occur if we incorrectly measure the SSI rate to be higher than it actually is during some months and lower than it actually is in other months; over many months, these random errors in measurement balance each other and the average value would be correct. Systematic error would occur if we consistently measured the SSI rate as higher or lower than the true rate, and an average over many months would be wrong; systematic error is also called *bias*. We define validity as getting the right answer, or alternately as a lack of bias.

A related concept is *precision,* which may be functionally defined as the width of the confidence interval. A narrow

confidence interval indicates high precision; that is, we are confident that the true value is within a narrow range. A confidence interval is narrower when both random variation and random error are low and vice versa. A larger sample size leads to a narrower confidence interval and greater precision. Precision may also be improved by modifying the study design to increase the statistical efficiency by which information is obtained from a given number of study subjects.

Selection Bias or Berkson's Bias

Selection bias occurs when inappropriate subjects are chosen for a study. An example is a study of mortality rates in patients with versus without bacteremia. The problem is that blood cultures are selectively obtained from patients who appear septic, and thus mildly ill patients who may have unrecognized bacteremia are not included as cases. Therefore, cases are not representative of all patients with bacteremia. Including only the sicker cases leads to an overestimate of the mortality associated with bacteremia. Other examples of selection bias are given in the section on selection of controls for case–control study. Selection bias cannot be corrected by data analysis techniques. In traditional surveillance, however, where no selection of subjects occurs, selection bias is not usually a problem.

Misclassification or Information Bias

After subjects are chosen, errors in classification of exposure or outcome are called *misclassification*. For example, suppose that one is comparing postsurgical infections between thoracic and general surgeons. In this hypothetical hospital, the thoracic surgeons do routine urine cultures for all patients with urinary catheters, sputum cultures for all intubated patients, and vascular catheter tip cultures when catheters are removed. However, the general surgeons obtain cultures only when they feel it is necessary. A comparison of infection rates shows higher infection rates for the thoracic surgeons when all that has really happened is that infection status has been misclassified.

Misclassification may be differential or nondifferential. Differential misclassification means that, in a case–control study, exposure is incorrectly determined to a differing extent among those with versus without disease or, in a cohort study, that disease is incorrectly determined to a differing extent among those with versus without exposure. Differential misclassification may bias the calculated relative risk away from the null value of 1.0, making the relative risk either falsely high (for risk factors with relative risk >1.0) or falsely low (for protective factors with relative risk <1.0). Conversely, nondifferential misclassification would mean that exposure was recorded incorrectly to a similar extent for those with and without disease, or disease was recorded incorrectly to a similar extent in those with and without exposure. This type of misclassification biases the relative risk toward the null value of 1.0.

Note that mere low sensitivity does not mean that data are not useful. The reliability of data primarily depends on how consistent the sensitivity remains in the data collection. National data on sexually transmitted diseases and food-borne illnesses such as salmonella gastroenteritis have a consistent sensitivity of around 0.01 or 1%, but these data remain useful because the sensitivity has been relatively constant at that level over time, so that secular increases or decreases are evident. Data with higher levels of sensitivity but greater variability are actually less reliable in making valid comparisons. Benchmarking comparisons among facilities should be attempted only when a practitioner has some measure of the comparative sensitivities of data from different populations.

A Broader View of Bias

Bias can be more generally defined as a systematic deviation from the truth: any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth *(13)*. In the analysis phase of a study, if one has a strong preconceived idea of what the answer should be, then a biased analysis and interpretation of the data may result. If one keeps analyzing and reanalyzing data with a view to finding something statistically significant to publish, eventually a satisfactory result will be found. This has been expressed as "If you torture data enough, it will confess to anything." Publication bias results when studies that show a statistically significant difference between study groups are published, whereas other studies of the same topic that did not show such a difference remain unpublished.

Inaccuracy of Hospital Surveillance

Errors in routine hospital surveillance for healthcare-associated infections could result in either reporting of spurious episodes of infection or lack of reporting of true infections. In practice, the latter problem is much more common. Patients with true healthcare-associated infections escape detection because (a) not all relevant data are present in the medical record or laboratory reports; (b) the data collector may overlook relevant data; and (c) the physician did not order appropriate tests to detect the infection. Estimates of the loss of sensitivity due to (a) and (b) above are shown in Table 2-2. In this table, all sensitivities are related to a composite standard, including data from multiple independent surveys of the medical record, bedside examination, and microbiology laboratory records.

The effect of point (c) above was measured in the Study of the Efficacy of Nosocomial Infection Control (SENIC) (14,*15*). The overall culturing rate, which was the proportion of patients with signs or symptoms of any infection that had at least one appropriate culture done, was 32% in 1970 and 40% in 1975 to 1976 (14). The proportion of febrile patients from whom at least one appropriate culture was obtained was 28% in 1970 and 45% in 1975 (14). These measures varied substantially from 5% to 95% by hospital type and region of the country. Patients in academic hospitals in the northeast United States had the highest likelihood of being appropriately cultured. It follows that patients in such hospitals were more likely to have a healthcare-associated infection documented. For urinary tract infections, pneumonias, and bacteremias, the lack of availability of objective data was a major determinant of observed rates of infection *(15)*.

The National Nosocomial Infections Surveillance (NNIS) system, now replaced by the National Healthcare Safety Network (NHSN), conducted a study of the accuracy of reporting healthcare-associated infection rates in intensive care unit patients (16). The sensitivity in this study was greatly improved over that found in the SENIC

TABLE 2-2

Sensitivities of Methods of Case-Finding for Healthcare-Associated Infections Quantifying Only Omissions from Limited Data Sources and Errors by Surveyors

Method	*Study (Reference)*	*Sensitivity*
Reference standard: Duplicate surveys + Record review + Bedside examination + Laboratory tests		
	UVA, BCH, CDC (23)[a]	1.00
Single survey: Record review + Bedside examination + Laboratory tests		
	BCH	0.98
Physician self-reports	CHIP (23)[a]	0.14–0.34
Micro laboratory reports	CHIP (23)[a]	0.33–0.65
Micro laboratory reports	UK *(82)*	0.71
Kardex clues (50% sample)	UVA (23)[a]	0.69–0.85
Record review (100% sample)	UVA (23)[a]	0.90
Kardex clues	UK *(82)*	0.49
Ward Ilaison	UK *(82)*	0.58
ICD-9 coded dx	BCH (22)	0.02–0.35
ICD-9 coded dx	Yale *(83)*	0.57
SENIC pilot record review	CDC *(84)*	0.66–0.80
SENIC project record review	CDC *(85)*	0.05–0.95
NNIS	CDC (16)	0.30–0.85

Note: The effects of failure of physicians to evaluate patients with suspicious clinical episodes were not included in these measures. These data do not include losses from unresolved clinical episodes.
[a]Some of these results have previously been summarized in Freeman and McGowan (23).
UVA, University of Virginia; BCH, Boston City Hospital; CDC, Centers for Disease Control and Prevention; CHIP, Community Hospital Infection Protocol; UK, United Kingdom; Yale, Yale University; NNIS, National Nosocomial Infections Surveillance; SENIC, Study of the Efficacy of Nosocomial Infection Control.
(Adapted from Freeman J, McGowan JE Jr. Methodologic issues in hospital epidemiology. I. Rates, case finding, and interpretation. *Rev Infect Dis* 1981;3:658–667.)

project, as the NNIS hospitals correctly reported the majority of infections that occurred. Still of concern, however, was the continuing wide range in the sensitivity that varied from 30% to 85%, depending on the site of infection. In this study, substantial numbers of healthcare-associated infections were missed by prospective monitoring and a different large group was missed by retrospective chart review.

The implications of these findings for benchmarking rates among hospitals are obvious. There is a disincentive for physicians and hospitals to self-report healthcare-associated infections, and this leads to the paradox that hospitals that do the worst job of collecting data and documenting infections report the lowest rates.

External Validity (Generalizability)

The sections above on bias and errors concern internal validity; that is, are we measuring correctly within the population we selected? External validity or generalizability asks the question, are our results applicable in other settings? Generalizability is always a matter of opinion. A lack of bias does not guarantee generalizability. A perfectly done epidemiologic study may or may not be generalizable to a larger population.

Epidemiologists frequently choose to study unrepresentative samples of subjects in order to answer a scientific question cleanly, cheaply, practically, or safely. Although not widely generalizable, a study result may be scientifically sound for the population on which the study was performed. In a randomized trial, for example, potential study subjects and their physicians must determine that it is safe for the study subjects to accept any of the study treatments before they can be randomized. Patients who have a contraindication to one of the treatments cannot be included in the study on the chance that they might be randomized to the contraindicated treatment. Thus, many treatable patients must ordinarily be excluded from randomized trials, rendering the sample of patients on whom the trial is actually performed highly unrepresentative of the population as a whole *(17)*. This lack of representativeness does not indicate that the study is epidemiologically biased, but it may limit the generalizability of the study result to a larger population.

The Collaborative Antibiotic Prophylaxis Efficacy Research Study (CAPERS) of antibiotic prophylaxis for clean (herniorrhaphy and breast) surgery used both experimental and observational components *(18,19)*. In the experimental component, 1,218 patients were randomized to receive or not receive prophylaxis; patients were not included in this study if they or their physicians did not provide consent. In the observational component, 3,202 other patients received prophylaxis at the discretion of their surgeons. Both components showed that about half of the SSIs were prevented by antibiotic prophylaxis. In this particular instance, the result of the randomized trial turned out to be generalizable to the larger group, but this need not have been so.

ACCOUNTING FOR TIME AT RISK

Because many healthcare-associated infections are related to time at risk, and because average lengths of hospital stay are decreasing, state-of-the-art studies must use methods that account for time at risk. Studies of mortality present a similar challenge: we all have one death per lifetime, and that is unavoidable, but it matters very much just when that death occurs. Methods used to account for time at risk include incidence density methods and survival analysis.

Incidence Density

Incidence density studies are a type of cohort study where the denominator is the total person-time at risk for all subjects, rather than the number of subjects. Commonly used denominators in healthcare-related incidence density studies are patient-days (vascular or urinary), catheter-days, and ventilator-days. Of the four most commonly studied healthcare-associated infections, three are device-related and are best studied using incidence density methods: catheter-associated bloodstream infections (BSIs), ventilator-associated pneumonias, and catheter-associated urinary tract infections (20).

Only one of the four (SSI) is best studied using cumulative incidence methods; that is, the denominator is the number of surgical procedures.

If the event being studied is an infection, then incidence density is the number of infections in a specified quantity of person-time in the population at risk. The population at risk is composed of all those who have not yet suffered an infection. After a patient acquires an infection, that patient would be withdrawn from the population at risk. All hospital days for each patient who never acquired an infection would be included in the pool of days at risk, but for a patient who became infected only those hospital-days before the onset of the infection would be included.

Incidence density is the instantaneous rate of change or what used to be called the force of morbidity. For convenience in healthcare epidemiology, healthcare-associated infection rates are usually expressed as the number of events in 1,000 hospital-days, because this usually produces a small single- or double-digit number, but we could have used seconds or years.

The basic value of this measure can be seen when comparing healthcare-associated infection rates in two groups with large differences in time at risk, for example, in short-stay patients versus long-stay patients, or infection rates with peripheral venous catheters versus implanted ports. By contrast, if one looks at events that come from a point source, such as eating vanilla ice cream at a church supper, or events that are not time related, like acquiring tuberculosis during bronchoscopy with a contaminated bronchoscope, the attack rate or cumulative incidence is an excellent measure of incidence. SSIs are usually thought of as having a point source—the operation; therefore, cumulative incidence methods are adequate for studies of SSI.

An incidence density rate = total events/total time at risk for an event. If we have an exposed and nonexposed group, then we define the rate ratio = rate ill in exposed/rate ill in nonexposed. The rate ratio is a measure of the size of effect analogous to the relative risk used in cumulative incidence studies. Rate ratios are sometimes called incidence density ratios, relative risks, or risk ratios. Rate ratios are interpreted in a similar manner to relative risks; a rate ratio of 2 means that disease incidence was twice as great in the exposed group than in the nonexposed group. Note that the units for the denominators of incidence density divide out, so that you will find the same incidence density ratio no matter whether you use time units of seconds or millennia. *P* values for the rate ratio may be calculated by a chi-square or binomial exact method.

Multiple Events in a Single Patient

Standard statistical tests assume that each observation in a data set is independent, having no linkage with other observations. A corollary is that each subject in a study should contribute at most one event to a data set; that is, we should study only first events in an individual. If this rule is not followed, the calculated confidence intervals and *p* values may not be valid. However, it is well-known that a subset of patients will have multiple episodes of infection and other adverse outcomes. Also, patients with a first event are more likely to suffer a second (*21*,*22*,23,24,*25*). For quantitative analyses, these nonindependent events cannot simply be summed. The biologic and statistical import of 5 infections per 100 discharges would be entirely different depending on whether it represented five sequential infections in a single patient or five first infections in 5 different patients.

Furthermore, a first healthcare-associated infection becomes a risk factor for a second, and risk factors for multiple infections are different from the risk factors for a first infection. The simplest way to cope with multiple incident events in the same individual is to restrict quantitative analyses to first events. A second method is to stratify by number of previous infections, for example, study the effect of exposures on risk of first infection, then on risk of second infection, and so on. These individual strata would then be combined into a summary relative risk. However, this method also violates the independence rule for conventional data analyses. A third alternative is to use statistical methods designed for longitudinal or correlated data. This type of analysis is technically complex (see Longitudinal Analysis and Repeated Measures, below).

Survival Analysis

Survival analysis is a second method for accounting for time at risk (3). Survival analysis usually consists of the familiar Kaplan–Meier plot, where at time zero survival begins at 1.0 or 100% and gradually falls off as subjects are followed forward in time. Survival can literally mean not dying, or it can mean remaining free of infection or whatever outcome variable is being studied. The opposite of survival is termed "failure," which again may either mean death or onset of another adverse event. An extremely useful feature of survival analysis is that it can make use of subjects who are lost to follow-up or die of a disease other than that of interest; these subjects are called "censored" since we don't know if they would have failed if we had been able to follow them for a longer period of time.

Statistical packages automatically plot survival curves for two or more groups and calculate a *p* value for the difference between the two groups. Median survival (the follow-up time when the probability of survival is 0.5 or 50%) is often reported. The Kaplan–Meier plot represents a univariable analysis. Multivariable survival analysis is accomplished via regression models, the most common of which is the Cox model (discussed below).

CONFOUNDING AND EFFECT MODIFICATION

Confounding

Confounding can be defined as "a situation in which a measure of the effect of an exposure on risk is distorted because of the association of the exposure with other factor(s) that influence the outcome under study" *(1)*. An intuitive example given in the chapter introduction was "our infection rate is higher than theirs because our patients are sicker than theirs." We can set up an experimental study to measure the effect of only one exposure at a time, but in observational studies where several exposures may act jointly to produce disease, we often need to use statistical techniques to tease out the independent effect of any one exposure.

TABLE 2-3

Sample Data: Simple and Stratified Analyses

a. Numbers of Patients Total and Infected, Hospitals A vs. B

	High-Risk Patients		*Low-Risk Patients*		
Hospital	*Total*	*Number Infected*	*Total*	*Number Infected*	*Overall Infection Rate*
A	900	90	100	1	91/1,000 = 9.1%
B	100	10	900	9	19/1,000 = 1.9%

b. Simple (Crude) Analysis: Effect of Hospital

Hospital (Exposure$_1$)	*Total Patients*	*No. (%) Infections*	*Relative Risk*
A	1,000	91 (9.1)	4.8
B	1,000	19 (1.9)	—

c. Stratified Analysis: Effect of Hospital Stratified by Patient Risk

Patient Risk (Exposure$_2$)	*Hospital (Exposure$_1$)*	*Total Patients*	*No. (%) Infections*	*Relative Risk*
High	A	900	90 (10)	$RR_1 = 1.0$
High	B	100	10 (10)	—
Low	A	100	1 (1)	$RR_2 = 1.0$
Low	B	900	9 (1)	—

Note: Mantel–Haenszel summary relative risk (RR_{MH}) = 1.0.

Example of Confounding by Severity of Illness Let's hypothetically assume that we were studying healthcare-associated infections at two hospitals, A and B. In our simplified example, there are two types of patients: high-risk patients who have a 10% risk of disease per hospitalization and low-risk patients who have a 1% risk. During a time period, hospitals A and B both admit 1,000 patients, but hospital A admits 900 high-risk and 100 low-risk patients, whereas hospital B admits 100 high-risk and 900 low-risk patients. Using hospital A as the exposed group, the relative risk is 9.1/1.9 = 4.8; that is, the risk of infection after admission to hospital A was 4.8 times higher than after admission to hospital B (Table 2-3).

This is an example of confounding. We are primarily interested in the relationship between one exposure (hospital A, which we shall denote as exposure$_1$) and disease. However, the effect of a second exposure (high- vs. low-risk patient, denoted by exposure$_2$) confuses or confounds our ability to measure the effect of exposure$_1$. This occurs because of an unequal mix of exposure$_2$ among the exposure$_1$ groups (high-risk patients comprise 90% of hospital A admissions but only 10% of hospital B admissions).

Stratified Analysis Stratification is an important method to detect and control for confounding. First, we compute a simple or crude relative risk by our usual 2 × 2 table methods (Table 2-3b). Second, we perform a stratified analysis: we calculate two relative risks (RRs), designated RR_1 and RR_2. In the above example of hospitals A and B, RR_1 measures the effect of hospital A among high-risk patients and RR_2 the effect of hospital A among low-risk patients (Table 2-3c). In this example, both RR_1 and RR_2 are equal to 1.0. Third, with the help of a statistical program, we compute a Mantel–Haenszel summary relative risk (RR_{MH}), which is a weighted average of RR_1 and RR_2. In this example, the RR_{MH} was also 1.0 (i.e., null result), indicating that there was no association between hospital and infection after adjusting for patient risk.

There was an obvious case-mix difference between hospitals A and B. The RR_{MH} is our prediction of what the crude relative risk would have been if there had not been a case-mix difference between the hospitals. Calculating an RR_{MH} is a way of adjusting for a potential confounding exposure, and thus the RR_{MH} is a type of adjusted relative risk. Other methods of calculating an adjusted relative risk include indirect standardization and regression modeling (these methods are presented later in this chapter).

Calculation of Mantel–Haenszel Relative Risk and Odds Ratio If there are i strata, the four cells of the 2 × 2 table are designated a_i, b_i, c_i, and d_i; the total number of subjects in each stratum is $n_i = a_i + b_i + c_i + d_i$; and $\sum$ indicates the sum over all i strata:

$$\text{Mantel–Haenszel summary relative risk} = \frac{\sum a_i(c_i + d_i)/n_i}{\sum c_i(a_i + b_i)/n_i}$$

$$\text{Mantel–Haenszel summary odds ratio} = \frac{\sum (a_i d_i)/n_i}{\sum (b_i c_i)/n_i}$$

Recognizing Confounding The following is a simple functional definition of confounding: if the adjusted relative risk differs to a meaningful extent from the crude relative risk, then confounding is present. There is no statistical test or firm guide for how great the difference must be.

In the hospital A versus B example above, the RR_{MH} of 1.0 differed substantially from the crude relative risk of 4.9, so confounding was obviously present. We say that the effect of $exposure_1$ (hospital A vs. B) was confounded by the effect of $exposure_2$ (high- vs. low-risk patients). In order for confounding to occur, both of the following are required: $exposure_2$ must be associated with disease and $exposure_1$ must be associated with $exposure_2$.

Additional Examples of Confounding Older age, female gender, and instrumentation of the urinary tract are risk factors for urinary tract infections. If we want to measure the effect of instrumentation alone, a simple 2×2 table analysis will be confounded by the effects of the other two variables. However, confounding can be adjusted for if one has data on the confounders (age and gender) and uses an appropriate statistical method.

Investigators in the SENIC project reported a relative risk of 0.94 for healthcare-associated infections in hospitals with infection surveillance and control programs compared with those lacking such programs, or a preventive effect of 6%. One could argue that this small apparent preventive effect could have been due to confounding factors that were imperfectly measured and adjusted for. Measurement of such small differences may be beyond the capabilities of statistical methods applied to observational data.

Quality assurance (26–28) is an area of healthcare epidemiology beset with difficulties posed by confounding variables. The degree to which the unalterable characteristics of the individual patient determine the inherent susceptibility to infection and probability of death are only partially defined, yet must be controlled for to make interhospital quality assurance comparisons meaningful *(29)*. After adjustment for severity of illness, using objective comparisons, it is often difficult to detect differences in hospital care that led to excess mortality *(30)*.

Methods to Deal with Confounding We can prevent confounding in the design phase of a study by doing a randomized trial or by doing a matched case–control study. We can adjust for the effects of confounding in the analysis phase by stratification, by standardization, or by performing regression analyses.

Randomization Randomized trials are rarely used because of their expense and difficulty, but are an effective way to avoid confounding. The magic of randomization is that it produces groups that are similar with respect to both known and unknown confounders. The previously mentioned CAPERS contained both a randomized component, which produced an unconfounded result, and an observation component, which required logistic regression to adjust for multiple confounding variables *(18,19)*.

Matched Case–Control Studies In a simple case–control study, the controls are usually a random sample of all noncases. In a matched case–control study, controls are selected by matching one or more noncases with each case according to some potentially confounding variable. For example, if we wanted to study the effects of an exposure on risk of vancomycin-resistant enterococcus, we would want to control for some well-known risk factors for vancomycin-resistant enterococcus. Therefore, for each case we could select some controls that were closest to the case in a measure of severity of illness such as Apache II score and antimicrobial receipt. To analyze the matched data, we do not do a simple 2×2 table analysis. Instead, we would perform a stratified analysis, where each case and its associated controls form one stratum. The Mantel–Haenszel summary odds ratio is then used rather than the simple odds ratio.

A matched design makes sense only if the potential confounders are well known and one has no need to study them further. In the matched study, one cannot calculate an odds ratio or *p* value for the variables that were used to match the controls (Apache II score and antimicrobial receipt, in the example above). To produce an unbiased odds ratio, we must analyze the data using the stratified method outlined above, thus reducing flexibility in the analysis phase. Also, the *p* value calculated in a matched study will be higher than that from a conventional 2×2 table, reducing the chance of finding a statistically significant result. Rather than matching, well-trained epidemiologists usually prefer to select a random sample of noncases and adjust the data using a multivariable method. However, matching clearly makes sense if an important confounding variable is common in cases and rare in noncases; under such conditions, if random sampling is done, only a few of the controls will have the confounding variable, and much effort will be expended to collect data on controls that have little relevance.

Standardization There are two methods of standardization, direct and indirect. Direct standardization is rarely used in healthcare epidemiology and is not presented here. However, indirect standardization is commonly used in healthcare surveillance. This method is typically used when stratum-specific event rates are available from a large reference population (e.g., a large number of facilities) and we want to compare a smaller group (e.g., a single facility) to this reference population. Any outcome event can be studied by indirect standardization. When applied to infections, indirect standardization produces a standardized infection ratio (SIR) and when applied to deaths a standardized mortality ratio is produced.

The following example of indirect standardization (Table 2-4) uses the incidence density approach to calculate rates and rate ratios *(31)*. We want to compare the BSI rate at a single dialysis center, center X, with the average rate of a large reference group. At center X, we observed 101 BSIs during 3,395 patient-months of follow-up, for a BSI rate of 2.97 per 100 patient-months. The crude rate ratio comparing center X to all centers was 1.67, indicating that the risk of BSI was 1.67 times higher (or 67% higher) at center X.

Vascular access type is a potential confounding variable. Rates of BSI from the reference group vary widely from 0.25 to 8.73 BSIs per 100 patient-months among four vascular access types (Table 2-4). If center X treats more patients with high-risk vascular access (e.g., tunneled or nontunneled catheters) than other centers, we would

TABLE 2-4

Example of Indirect Standardization to Calculate a Standardized Infection Ratio

Vascular Access Type	*BSI Rate[a] All Centers*	*Patient-Months, Center X*	*Expected BSI, Center X*
Fistula	0.25	1,709	4.27
Graft	0.53	528	2.80
Tunneled catheter	4.84	958	46.37
Nontunneled catheter	8.73	200	17.46
Total	—	3,395	70.9

Note: Crude rate ratio = rate at Center X/rate at all centers = 2.97/1.78 = 1.67.
Standardized infection ratio = actual BSI/expected BSI = 101/70.9 = 1.42.
[a]Rate per 100 patient-months. BSI rate for all centers from reference (31).
BSI, bloodstream infection.

expect more BSI at center X. We want to determine the intrinsic risk of BSI at center X if the mix of vascular access types at center X were the same as that at all centers.

To calculate an SIR, we first determine the expected numbers of BSI at center X for each access type by multiplying the all-center rates by the center X denominators (e.g., for nontunneled catheters, $0.0873 \times 200 = 17.46$). Second, we sum the expected values for the four access types to get total expected BSIs = 70.9. If the BSI rates at center X were the same as the all-centers rates, we would have expected 70.9 BSIs at center X. Finally, the SIR is calculated as the ratio of the actual to expected BSIs. The SIR is interpreted as an adjusted rate ratio; that is, after adjusting for vascular access type, the rate of BSI at center X is 1.42 times higher than that at other centers. Notice that the SIR or adjusted rate ratio (1.42) was lower than the crude value (1.67), indicating a minimal degree of confounding by vascular access type.

Effect Modification (Interaction)

Using the terminology of exposure$_1$, exposure$_2$, and outcome, we say that effect modification is present when the effect of exposure$_1$ and exposure$_2$ together is different from what would have been predicted by their independent effects. Cigarette smoking and asbestos exposure as joint causes of lung cancer are a familiar example. Each of these is a risk factor for lung cancer individually, but when both are present, the risk of cancer is particularly high; that is, the relative risk when both are present is even higher than would be predicted from the sum or product of the two individual relative risks. The carcinogenic potential of asbestos fibers is thought to result from their unusual size, which allows them to migrate easily through the lung tissue. In smokers, these fibers become coated with the carcinogenic materials in cigarette smoke, and thus asbestos fibers become a uniquely efficient system for the delivery of powerful carcinogens from cigarettes into lung tissue. Thus, there is biologic plausibility to the epidemiologic finding of effect modification.

Recall that in the example of confounding involving hospitals A and B presented earlier (see Example of Confounding by Severity of Illness, above), the stratum-specific relative risks were equal (i.e., $RR_1 = RR_2$, Table 2-3). In contrast, effect modification would have been present if RR_1 and RR_2 were found to differ. Unlike the situation with confounding, statistical tests may be used to determine whether effect modification is present (see Chapter 3, Breslow–Day test). An example of effect modification is presented below (see Example of Confounding and Effect Modification, and Example of Logistic Regression Model: Healthcare-Associated Infection and Neonatal Mortality, and Tables 2-7 and 2-11).

Although a single RR_{MH} can be calculated when effect modification is present, this is not recommended; instead, report RR_1 and RR_2 separately. The value of identifying effect modification and reporting separate relative risks is to identify subgroups where a certain exposure is a greater or lesser problem, or in which certain treatments may be more or less effective.

Examples of Stratified Analyses

Stratification is a powerful tool to investigate confounding and effect modification. Stratification is simple, intuitive, and accessible, because the data remain visible in tables, and the origin and validity of surprising results can be investigated immediately by reference to the tables containing the data.

Example of Confounding Without Effect Modification In the following example, the effect of healthcare-associated infections (exposure) on mortality (disease) was studied in the neonatal intensive care unit at the Utah Medical Center (32). Note that in this instance healthcare-associated infection, which we usually consider to be the disease or outcome, was instead considered the exposure. The crude relative risk was 2.46, indicating an association between infection and death (Table 2-5). However, if low birth weight is also a cause of death acting jointly with healthcare-associated infection, and infection occurs preferentially in low-birth-weight infants, then the crude relative risk is incorrect, having been confounded by birth weight. To investigate this possibility, we can stratify by birth weight and see how the answers change (Table 2-6). Note that, for simplicity, we have left out several lines from each table.

Adjusting for birth weight produced an adjusted relative risk of 1.89, which represents a substantial change from the crude value of 2.46 (Table 2-5 vs. Table 2-6 and Fig. 2-1). Thus, low birth weight was a substantial cause of mortality in this data set and confounded the original relative risk. The crude estimate of the relative risk of mortality with healthcare-associated infection of 2.46 was 30% too high—it represented the added effect of low birth weight that was mixed in with the effect of healthcare-associated infection in causing death (Fig. 2-1). After adjustment to remove the confounding effect of low birth weight, the relative risk was lower, the *p* value was larger, and the lower bound for the relative risk was closer to 1.0

There might also have been a slight trend of increasing relative risks (from 1.44 to 2.65) as birth weight category increased. If the relative risk were significantly

TABLE 2-5

Crude Association Between Healthcare-Associated Infections and Death

Death	*Exposed*	*Unexposed*	*Totals*
Outcome (+)	46	104	150
Outcome (–)	92	662	754
Totals	138	766	904

$$\text{Relative risk} = \frac{\text{Probability of outcome (+) among exposed}}{\text{Probability of outcome (+) among unexposed}} = \frac{a/(a+c)}{b/(b+d)}$$

Crude relative risk of mortality with infection: risk ratio = 2.46.
95% confidence intervals for crude risk ratio: (1.83–3.30).
Chi = 5.7; $p < 10^{-8}$.

different in the different strata, this would represent effect modification. However, statistical testing did not show that the relative risk differed significantly among the strata, and instead the relative risks from the various strata appear to represent random variation from a true underlying relative risk. Therefore, effect modification was not present and the reporting of the RR_{MH} was appropriate.

Example of Confounding and Effect Modification In another study of mortality with healthcare-associated infections from a different neonatal intensive care unit, data were available on underlying disease as well as birth weight *(25)*. Infants in neonatal intensive care units have only a few different diagnoses, and of these underlying diseases, only the persistence of a patent ductus arteriosus (PDA) appeared to have any influence on the outcome

TABLE 2-6

Association of Healthcare-Associated Infection With Death Stratified by Birth Weight

		Healthcare-Associated Infection		
Birth weight (g)		*Exposed*	*Unexposed*	*Relative Risk*
<1,000	Died	12	10	
	Total	25	30	1.44
1,000–1,499	Died	12	24	
	Total	42	107	1.27
1,500–1,999	Died	7	18	
	Total	18	142	3.07
2,000+	Died	15	52	
	Total	53	487	2.65

Note: Mantel–Haenszel adjusted relative risk of mortality with infection: risk ratio = 1.89; 95% confidence intervals for adjusted risk ratio (1.41–2.55).
Chi = 4.1; $p < 10^{-4}$.
(Adapted from Freeman J, Goldmann DA, McGowan JE Jr. Methodologic issues in hospital epidemiology. IV. Risk ratios, confounding, effect modification, and the analysis of multiple variables. *Rev Infect Dis* 1988;10:1118–1141.)

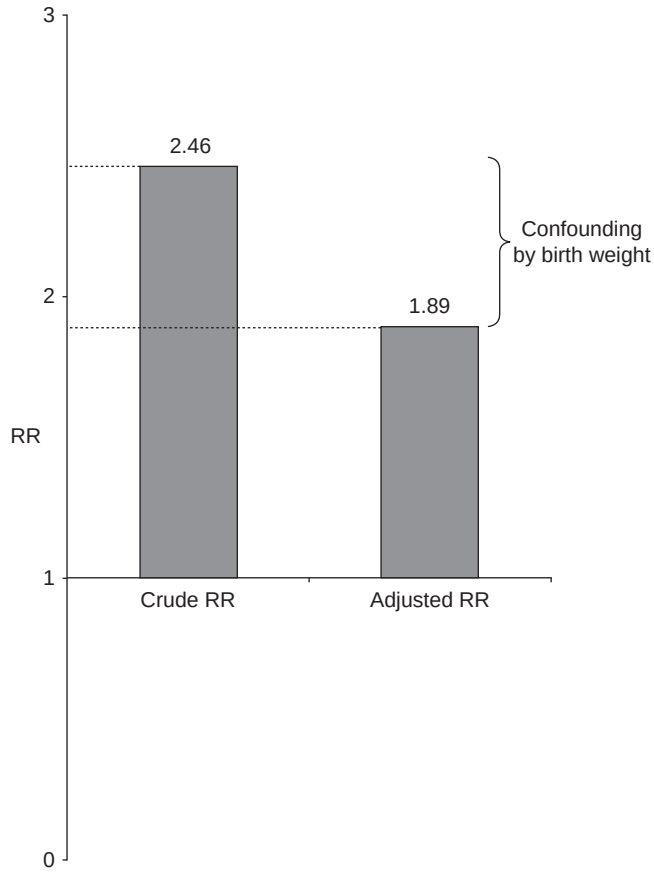

FIGURE 2-1 Crude and adjusted risk ratios for the association of healthcare-associated infection with death in neonates in Utah for Table 2-6, showing the effect of confounding by birth weight.

(survived vs. died). The data, stratified on birth weight and PDA, are presented in Table 2-7. Again, the interest is in the effect of healthcare-associated infection (exposure) as a cause of mortality (outcome), but here we can also consider effect modification and confounding by the two extraneous variables, birth weight and the presence of a PDA. If we combine all of the data from this study into a single table (Table 2-7) and look at the crude effect of healthcare-associated infection on mortality, without stratifying by birth weight or PDA, this crude relative risk is 3.20. If we adjust for birth weight, the relative risk is 2.16, indicating confounding.

We can now investigate whether PDA modified the effect of healthcare-associated infection as a cause of death among these neonates. The relative risk of healthcare-associated infection on mortality was 0.88 for infants with PDA versus 5.01 for those without PDA (Table 2-7). This heterogeneity of the effect of infection on mortality according to PDA status was highly significant (chi-square value = 7.3, $p = .007$), indicating that effect modification was present. Because the effect of healthcare-associated infection is so obviously different for neonates with and without PDA, it makes no biologic or statistical sense to combine these two groups. Thus, the crude and adjusted relative risks of mortality with healthcare-associated infection are presented separately for those with and without PDA. The crude and adjusted relative risks and the effect modification by

TABLE 2-7

Association of Nosocomial Infection with Death, Stratified by Birth Weight and PDA Status

		Nosocomial Infection			
		PDA Absent		*PDA Present*	
Birth Weight (g)		*Exposed*	*Unexposed*	*Exposed*	*Unexposed*
<1,000	Died	2	7	2	3
	Total	4	38	4	17
1,000–1,499	Died	2	12	0	6
	Total	6	107	11	27
1,500–1,999	Died	2	10	1	0
	Total	6	136	3	12
2,000+	Died	1	27	0	3
	Total	4	520	2	14
Grand total	Died	7	56	3	12
	Total	20	801	20	70

PDA, patent ductus arteriosus.
Crude relative risk[a] = 3.20.
Relative risk adjusted for birth weight[b] = 2.16.
Stratified by PDA:
With PDA, relative risk = 0.88.
Without PDA, relative risk = 5.01.
Breslow-Day test for effect modification, chi-square = 7.3, $p = .007$.
Stratified by PDA and adjusted for birth weight:
With PDA, relative risk[b] = 0.90.
Without PDA, relative risk[b] = 3.42.
[a]All relative risks are the relative risk of death (outcome) for infants with nosocomial infection (exposure).
[b]Mantel–Haenszel relative risk.

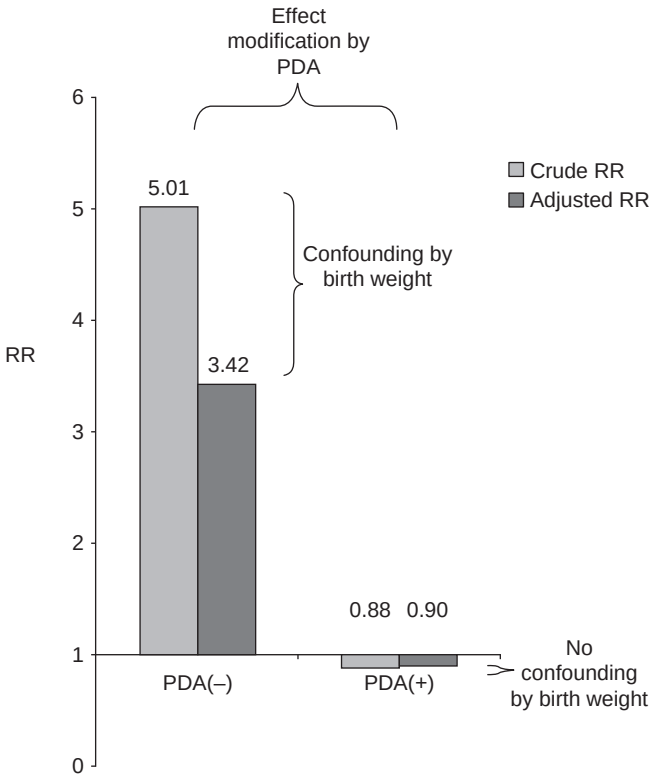

FIGURE 2-2 Crude and adjusted risk ratios for the association of healthcare-associated infection with death in neonates for Table 2-7, showing the effects of confounding by birth weight and effect modification by patent ductus arteriosus (PDA) status.

PDA are presented visually in Figure 2-2. Investigation of effect modification provides more biologic information concerning which patients (those without PDA) will be affected and also shows how much greater the effect will be for that group.

Finally, we both stratify by PDA and adjust for birth weight. Birth weight was not a confounder among those with PDA (crude relative risk = 0.88, $RH_{MH} = 0.90$; Table 2-7), but was a strong confounder among those without PDA (crude relative risk = 5.01, $RH_{MH} = 3.42$). Similar results are obtained when these data are analyzed by logistic regression later in this chapter (see Example of Logistic Regression Model: Healthcare-Associated Infection and Neonatal Mortality, below, and Table 2-12).

Example of Confounding When Incidence Density Is the Outcome Measure One frequently needs to correct for differing durations of exposure while investigating the effect of a specific exposure on an outcome. Incidence density data taken from an investigation of an apparent outbreak of healthcare-associated bacteremia with coagulase-negative staphylococci in a neonatal intensive care unit are presented in Table 2-8 (32). Neonatologists were convinced that an epidemic of bacteremia had occurred in 1982, so the number of individuals with first positive blood cultures for coagulase-negative staphylococci were enumerated for that year and for 1975. The numbers of patient-days at risk for a first positive blood culture were also accumulated for these neonates. On a simple level, the neonatologists were

TABLE 2-8

Longitudinal Comparison of Incidence Densities of Blood Cultures Positive for Coagulase-Negative Staphylococci in a Neonatal Intensive Care Unit

	Positive Cultures/Days at Risk		
Birth Weight (g)	*1982*	*1975*	*Incidence Density Ratio*
500–749	3/535	0/10	Unbounded
750–999	8/1,034	2/358	1.4
1,000–1,249	1/424	2/821	1.0
1,250–1,499	1/213	1/567	2.7
1,500–1,749	0/179	1/233	0.0
1,750–1,999	0/455	0/351	Undetermined
2,000+	3/1,880	2/1,289	1.0
Totals	16/4,720	8/3,629	

Ratio of numbers of cases 2.0.
Risk ratio crude for birth weight = 1.54, indicating an apparent 54% increase in 1982.
Mantel–Haenszel adjusted risk ratio = 1.13 (95% confidence interval 0.44–2.86).
There was no significant heterogeneity by birth weight, $p > .05$.
(Adapted from Freeman J, Goldmann DA, McGowan JE Jr. Methodologic issues in hospital epidemiology. IV. Risk ratios, confounding, effect modification, and the analysis of multiple variables. *Rev Infect Dis* 1988;10:1118–1141.)

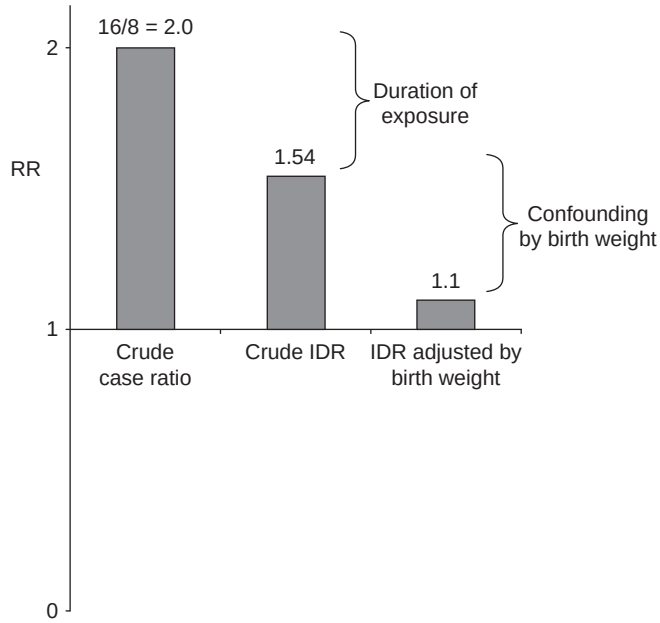

FIGURE 2-3 Crude, partially adjusted, and completely adjusted incidence density ratios for the longitudinal comparison of bacteremias in neonates in Table 2-8, showing the confounding effects of time at risk and of birth weight.

correct, because the number of bacteremias had doubled from 8 to 16, a relative risk of 2.0. Accounting for patient-days at risk led to a crude incidence density ratio of 1.54 (16/4,720 vs. 8/3,629). This incidence density ratio corrects for the much longer exposures to hospital experienced by the smallest neonates in 1982, and reduces the apparent relative risk from 2.0 to 1.54. This example used patient days for the incidence density denominator, whereas central or umbilical line-days are typically used for surveillance (20).

Finally, we can also adjust for birth weight in this analysis, and the adjusted incidence density ratio is approximately 1.1, indicating no real change in the bacteremia rate (Fig. 2-3). Note that different statistical programs and methods may produce slightly different results. In the original article, the authors combined the two strata containing infants with birth weights from 1,500 to 1,999 g to avoid a table with a zero marginal total, and calculated an adjusted relative risk of 1.13. Using OpenEpi, the Mantel–Haenszel adjusted relative risk is 1.16 if all seven strata are used and 1.14 if the 1,500 to 1,999 g birth weights are combined.

Inspection of the data shows many more patient days contributed by the lowest birth weight infants (those under 1,000 g) during 1982 than in 1975. What occurred was not an epidemic of bacteremia but *an epidemic of survival among the smallest neonates*. Important insights are thus gained through simple inspection of the stratified data.

Summary: Confounding and Effect Modification

To reiterate, several factors or determinants, acting jointly, are almost invariably responsible for a single outcome in healthcare epidemiology. Confounding is the case-mix–induced distortion of the relative risk for one exposure by the effects of other exposures. Effect modification is the biologic interaction of two exposures to produce an unexpectedly high or low relative risk. Confounding and effect modification are compared in Table 2-9. A general scheme for collection and analysis of data for epidemiologic comparisons is presented in Table 2-10.

To detect confounding and effect modification, first calculate a crude relative risk; then perform a stratified analysis, calculating RR_1 and RR_2 separately and an RR_{MH}. If the crude relative risk and the RR_{MH} differ to a meaningful extent, then confounding is present; report the RR_{MH}. If RR_1 and RR_2 are statistically significantly different, effect modification is present; report RR_1 and RR_2 separately and do not report the RR_{MH}.

CONTINUOUS VARIABLES

Epidemiologists most commonly deal with dichotomous (e.g., exposed yes or no, infected yes or no) categorical variables. However, continuous variables that can take on an infinite number of values, such as age, height, and weight, are also seen. Continuous variables can be plotted to form a frequency distribution. These data may be approached differently depending on whether they form a normal (bell-shaped) distribution. If the data are not normally distributed, transforming the data, as by taking the logarithm, may result in a normal distribution.

If data are normally distributed, the central tendency is described by the mean and the spread (how closely the values cluster around the mean) by the standard deviation; parametric methods (i.e., *t*-test, analysis of variance) are used to calculate *p* values that test whether the mean values in two or more groups are significantly different. If data are not normally distributed, the central tendency is best

TABLE 2-9

Comparison of Confounding and Effect Modification by a Third, Extraneous Variable, Which is Neither the Exposure nor the Outcome Under Study, in a Specific Epidemiologic Comparison[a]

	Confounding	*Effect Modification*
Comparison of attributes		
Effect on comparison	Always distorting: distorting effect may be positive or negative; not itself informative (see Tables 2.5–2.8)	Not distorting (unless also a confounder); provides additional information (see Table 2.7)
Source and generalizability	One specific data set; not a feature of biology; will differ among data sets containing same comparison	Biology/the real world; likely to be similar in most data sets containing same comparison; probably a real attribute of the biology of a disease
Analytic strategies:		
Observe effect in analysis by	Comparison of crude and adjusted measures	Comparison of effect across strata
Determine quantitative importance in analysis by	Subjective observation of magnitude of distorting effect in context of a specific study (see Tables 2.5–2.8)	Objective tests for heterogeneity of effect across strata of effect modifier: subjective inspection for effects in opposite directions

Note: In an epidemiologic comparison, a single extraneous variable may be a confounder, an effect modifier, neither, or both.
[a]Suggested methods refer to epidemiologic comparisons with discrete outcomes and utilize stratification as the primary analytic strategy. Reference is made to one or more of the studies reanalyzed in this chapter by table number.
(Adapted from Freeman J, Goldmann DA, McGowan JE Jr. Methodologic issues in hospital epidemiology. IV. Risk ratios, confounding, effect modification, and the analysis of multiple variables. *Rev infect Dis* 1988;10:1118–1141.)

described by the median and spread by the interquartile range (the 25th–75th percentile); nonparametric methods (i.e., Mann–Whitney *U* test, Wilcoxon test) are used to calculate *p* values for differences among groups.

In the following example, we determine whether maternal age was significantly related to disease in a neonatal intensive care unit outbreak. There were nine cases and 173 noncases. The simplest approach is to dichotomize age at its median (26.5 years) and analyze the data in the familiar 2×2 table. This yields a relative risk = 3.5 and *p* value = .17.

		Disease		
		Yes	No	
Exposure	Age ≤26.5	7	84	91
	Age >26.5	2	89	91
		9	173	182

To analyze age as a continuous variable, we used the freeware program EpiInfo. The mean ± standard deviation maternal age was 21.9 ± 5.3 years for cases versus 26.95 ± 6.2 for noncases. EpiInfo produces two *p* values, one parametric *p* value = .018 and a nonparametric *p* value = .0226. In this package, parametric *p* values are calculated assuming the variances are equal in the two groups; other statistical packages compute an additional parametric *p* value that assumes the variances are different in the two groups. Parametric *p* values are based on calculating the variances and are valid only if the data are normally distributed, whereas nonparametric *p* values are valid regardless of the distribution. For simplicity, nonparametric *p* values are often used in epidemiology. As in this instance, the nonparametric *p* value is usually marginally higher, that is, less likely to be statistically significant, than the parametric value. Note that the *p* values obtained by treating maternal age as a continuous variable ($p = .02$) are lower than the value obtained in the 2×2 table above after converting to a dichotomous variable ($p = .17$).

The above example was for analysis of unpaired continuous variable data. Alternate methods are used for analyzing paired values, for example, scores on a test before versus after an educational program. Rather than just averaging the mean of all scores before and comparing it with the mean of all scores after, we can take advantage of some additional available information, that is, that we know each score before corresponds to a score after. In brief, the method is to compute the difference between the before versus after scores for each subject, so that one value per subject is obtained, and then to statistically test the null hypothesis that the difference equals zero. This provides a more precise answer and can be done by either parametric or nonparametric methods.

ADDITIONAL TOPICS IN HEALTHCARE EPIDEMIOLOGY

Hypothesis-Generating Versus Hypothesis-Testing Studies

The classic hypothesis testing approach is to state a hypothesis, for example, postulate an association between one or a few exposure(s) and disease(s), and then deliberately collect data to verify or refute the hypothesis. Most explanations of how to conduct and analyze epidemiologic studies refer to this approach, that is, focusing on an exposure of primary interest and checking for confounding or effect modification from secondary exposure variables. However, in practice many modern epidemiologic studies take an alternate approach, namely, to evaluate a number of exposure variables and report whether any are significantly associated with disease. Using this approach, which is one type of

TABLE 2-10

General Approach to the Collection and Analysis of Data for Epidemiologic Comparisons With Discrete Outcomes[a]

Action	*Details of Method*
Collection and preliminary inspection of data	
Anticipate confounding and effect modification	Collect data on multiple variables associated with exposure or outcome; include data on severity of underlying illness and indications for therapy (if therapy was used)
Preliminary stratification for inspection of data	Stratify data repeatedly over a number of extraneous variables that might confound comparisons or modify the effect of an exposure on an outcome; experiment with alternative categorizations; determine workable sizes for strata
Preliminary inspection for presence of confounding variables	Compare crude risk ratios with risk ratios adjusted for various extraneous variables; identify and retain variables for which adjustment alters the risk ratio in an epidemiologically meaningful way
Preliminary inspection for presence of effect modification	Compute stratum-specific risk ratios for different categories of various extraneous variables; identify and retain variables for which the risk ratio appears to vary across strata: if different categories produce risk ratios in opposite directions, then any summary estimate will be misleading (see Table 2.7): plan to report stratum-specific values
Test for effect modification	If different categories produce risk ratios of varying magnitude in same direction, formally test for heterogeneity of effect over strata: if no significant heterogeneity is present, plan to use Mantel-Haenszel summary risk ratio (see Tables 2.6, 2.7, 2.8); if significant heterogeneity is present, look for pattern to heterogeneity; also, plan to use standardized summary risk ratio
Final analysis and presentation of data	
Select variables for inclusion in final analysis	Retain confounding variables and variables that modified the effect of the exposure on the outcome as stratification variables in the final analysis
Select categories for stratification of confounders and effect modifiers	Choose most efficient and informative categories for stratification; use multiway stratification if necessary to include multiple variables simultaneously (see Table 2.7)
Present data in stratified format so readers can observe confounding and effect modification	Give summary risk ratios with confidence intervals if appropriate; compute Mantel–Haenszel estimates if there is no significant effect modification; compute standardized estimates if effect modification is present and stratum-specific risk ratios in same directions; give standard and reason for choice

[a]Suggested methods utilize stratification over levels of variables that may confound a comparison and/or modify the effect of the exposure on the outcome under study.
(Adapted from Freeman J, Goldmann DA, McGowan JE Jr. Methodologic issues in hospital epidemiology. IV. Risk ratios, confounding, effect modification, and the analysis of multiple variables. *Rev Infect Dis* 1988;10:1118–1141.)

hypothesis-generating study, there is no exposure of primary interest—all are created equal.

Repetition of data analyses with varying assumptions or methods until a statistically significant result is obtained have been called "data dredging" or "data torturing." Any complex data set will contain many apparent associations. Some of these are real and causal, whereas others are the result of random processes and represent no true association. Therefore, associations are less likely to be valid and reproducible if found in a hypothesis-generating study and should be interpreted with the caveats regarding performance of multiple testing and attention to Hill's criteria for causality.

A valid approach is to use one data set for hypothesis generation and a second independent data set for hypothesis testing. If only one data set is available, this can be divided into two, with the first for hypothesis generation and the second for hypothesis testing.

Multiple Comparisons

Strictly speaking, our use of the *p* value assumes that only one potential exposure is being evaluated. If the variable is statistically significant at the .05 level, there is a 5% chance that this association occurred due to chance alone. We are willing to accept this chance of error. However, if a large number of potential exposure variables are evaluated, the probability that one or more will be significant by chance alone rises. To compensate, it has been proposed that the required level of significance be set to approximately .05 divided by the number of variables tested (Bonferroni correction). For example, if 10 variables were tested, then we would require a *p* value of approximately .005 for statistical significance. This approach or other more sophisticated methods to account for multiple hypothesis testing is increasingly used in the literature. However, many epidemiologists prefer not to use rigid formulae such as these, but to interpret findings by considering Hill's criteria for causation as well as the *p* value and the number of variables considered. For example, if 15 independent statistical tests are performed, we can calculate that there is a 54% chance, that is, $1 - (1 - 0.05)^{15}$, that at least one would be statistically significant at the .05 level *(33)* and interpret any statistically significant findings accordingly.

Subgroup Analyses

Classically, studies specify a primary hypothesis, for example, that a given exposure is a risk factor for disease. It is common to additionally report the results of the exposure in subgroups; for example, the exposure may be a significant risk factor in men but not in women or in older but not in younger subjects. Testing in a large number of subgroups is a form of "data-dredging" that will often produce at least one statistically significant result. Therefore, subgroup analysis should be supported by statistical tests for interaction and generally considered to be hypothesis generating rather than hypothesis testing. Other guidelines for reporting subgroup analysis include presentation of a subgroup analysis in the published abstract only if it was a primary study hypothesis, indication of the number of prespecified subgroup analysis performed and reported, indication of the number of post hoc subgroup analyses performed and reported, and indication of the potential effect of multiple testing on type I error *(34)*.

Stratifying Continuous Variables and Analyzing Multilevel Tables

In data analysis, it is often necessary to construct appropriate groups from a continuous variable. An example is the grouping of neonates by birth weight. The cutoff values used to divide the groups can be chosen by allocating the same number of subjects in each group (e.g., quartiles with 1/4 of the subjects in each group), dividing the group at even numbers (e.g., 750–1,000 g), or using cut points that are widely used and accepted. The method used should be nonbiased (i.e., the cutoff values should not be manipulated to produce a predetermined result), include an adequate number of subjects in each stratum, and include subjects with a similar risk of the outcome in individual strata. Multilevel categorical variables result from this grouping.

To analyze multilevel categorical variables, we use a variation of the 2×2 table methods previously presented for dichotomous or binary exposure variables. In an example of the effect of birth weight on neonatal mortality, the continuous exposure variable birth weight has been divided into four groups to form a categorical multilevel variable (Table 2-11). Note that as the birth weight increases, the percent of neonates who died decreases from 22.2% to 5.7%; this is an example of a dose–response relationship as mentioned in Hill's criteria for causality. These data are analyzed by forming multiple 2×2 tables with the lowest rate stratum (≥2,000 g) acting as the nonexposed group in each (Table 2-11a–c). The number of 2×2 tables will be one less than the number of strata of the multilevel variable. Compared with the reference category, birth weight ≥2,000 g, which is assigned relative risk = 1.0, the risk of death was 1.44 times higher for 1,500 to 1,999 g, 2.31 times higher for 1,000 to 1,499 g, and 3.87 times higher for <1,000 g. Individual *p* values for each 2×2 table may be reported along with the individual relative risks. However, it is well to also calculate a test for heterogeneity among the four categories; this tests the null hypothesis that the rates are the same in the four birth weights. In this example, the chi-square value of 24.8 with three degrees of freedom indicates a highly significant difference in mortality among the birth weight groups.

Epidemic versus Endemic Disease

The approach to data collection and analysis may differ for epidemic versus endemic diseases. An epidemic is simply an increase in the frequency of occurrence of events above the usual level, often due to a high relative risk operating over a short period of time. Simpler cumulative incidence methods may be adequate for investigation of epidemics, but incidence density methods are generally preferable for measuring more subtle effects in surveillance of endemic disease. Of note, up to 90% of healthcare-associated infections and other adverse events are endemic rather than epidemic (35).

The approach to data interpretation may also differ during an epidemic. An epidemiologist should be more concerned with the biologic import of observed events, the size of the effect, and potential future events than with statistical significance. Hospital epidemics tend to involve small numbers and an epidemiologist may have to act before a sample size large enough for a contrast to reach statistical significance can be collected. A single unexpected fatality should trigger the same investigation as do multiple, less serious events *(36)*.

Systematic Reviews and Meta-Analyses

A systematic review is a "review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review" *(37)*. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies *(37)*. Using meta-analysis, the results (e.g., estimates of the relative risk) of multiple studies may be pooled to produce a single estimate that may be more informative and precise than any of the individual estimates. Meta-analyses may resolve uncertainty when reports disagree and produce more objective summaries of the literature than might be possible with unaided intellectual interpretation. In addition, meta-analyses may answer new questions not posed at the start of individual trials.

Originally, *meta-analysis* had meaning only in terms of randomized trials *(38)*, but it is now commonly used for observational studies as well. The results of randomized trials are, on average, unconfounded because of the randomization process. A summary of unconfounded study results will itself be unconfounded. On the other hand, meta-analysis of confounded observational studies will produce a confounded summary result.

The simplest statistical method to perform meta-analysis is to perform a stratified analysis where each separate study forms one strata and an RR_{MH} is calculated. As in conventional stratified analyses, we would not want to calculate and report an RR_{MH} if the relative risks differed significantly among the strata, that is, if there was heterogeneity of the relative risks. This amounts to a form of effect modification where the variable causing the effect modification is the study itself. Probably the most important epidemiologic issue confronted in a meta-analysis is the determination of whether there is heterogeneity among studies *(4,38–43)*. This is the same heterogeneity issue described in Table 2-7.

TABLE 2-11

Analysis of a Multilevel Variable Created by Categorization of a Continuous Variable

				Indicator Variables[b]		
Birth Weight (g)	***Died, n(%)***	***Survived (n)***	***Relative Risk***[a]	***BW1***	***BW2***	***BW3***
<1,000	14 (22.2)	49	3.87	1	0	0
1,000–1,499	20 (13.2)	131	2.31	0	1	0
1,500–1,999	13 (8.3)	144	1.44	0	0	1
≥2,000	31 (5.7)	509	1.0	0	0	0

Note: Data collated from Table 2-7.
Test for heterogeneity, chi-square = 24.8, three degrees of freedom, $p < .001$.
[a]See Table 2-11 a–c for calculation of the relative risks.
[b]For use in logistic regression model (Table 2-12).

TABLE 2-11A

		Died		
		Yes	*No*	
Exposure	<1,000	14	49	63
	≥2,000	31	509	540

Relative risk = (14/63)/(31/540) = 3.87, $p < .0001$.

TABLE 2-11B

		Died		
		Yes	*No*	
Exposure	1,000–1,499	20	131	151
	≥2,000	31	509	540

Relative risk = (20/151)/(31/540) = 2.31, $p = .004$.

TABLE 2-11C

		Died		
		Yes	*No*	
Exposure	1,500–1,999	13	144	157
	≥2,000	31	509	540

Relative risk = (13/157)/(31/540) = 1.44, $p = .3$.

There are two additional threats to the validity of a meta-analysis. First, publication bias may mean that studies with a statistically significant effect were more likely to be published and therefore to be included in the meta-analysis. Publication bias can be assessed with a funnel plot, that is, a scatterplot with one dot for each study, sample size plotted on the vertical axis, and effect size on the horizontal axis. If there is no publication bias, the scatterplot will be symmetric; if publication bias is present, there will be more small-sample studies with a large effect size than those with a small or negative effects (44). Second, variations in the quality (generally forms of misclassification or confounding) of studies included may bias the result. Criteria for the quality of studies included should be set, and a detailed checklist of items should be reported (*45*,46) (see also Chapter 7).

Quasi-Experimental Studies

The prefix "quasi" means "having some resemblance usually by possession of certain attributes." Here, we are referring to studies that have some resemblance to a randomized controlled study, for example, observational studies that aim to evaluate an intervention. Such pre–post intervention studies are very common, in part because of the difficulty and expense of performing formal randomized trials (47). A recent example is the successful use of a package of proven infection control measures to reduce catheter-associated bloodstream infections in Michigan hospitals *(48)*. These studies have a number of potential limitations: (a) confounding; that is, patients in the pregroups and postgroups may differ in severity of illness or other ways difficult to measure and control

for; (b) regression to the mean; that is, if infection rates in the preintervention period are higher than the historical mean, they will tend to decrease toward the historical mean in the postintervention period regardless of an intervention *(49)*; (c) preexisting temporal trends; that is, the infection rate may be increasing or decreasing independent of the intervention; and (d) seasonal trends in certain (especially outpatient respiratory) diseases, which may coincide with premeasurement or postmeasurement periods (47,*50*).

Quasi-experimental studies can be strengthened by using more sophisticated designs. For example, a simple study might have only one group with infection rates measured before and after an intervention (47). A more robust design might have two groups followed over time, only one of which receives the intervention. Another way to improve validity is to use more sophisticated data analysis methods that account for confounding variables, temporal trends, changes in temporal trends, and autocorrelation among infection rates measured several times both before and after an intervention *(51)*.

Propensity Scores

A related problem is the use of observational data, rather than a randomized study, to assess the effect of a treatment on disease. In this case, treatment is the exposure variable in an observational epidemiology study. Often the analysis is confounded by the fact that patients who receive a given treatment differ from those who do not. For example, treated patients may be sicker than those not treated. A standard approach to this problem would be to use a multivariable model with disease as the outcome variable and controlling for as many confounders as possible. However, if disease is uncommon, the number of confounders that can be adjusted for is limited. An alternate approach is to control for the propensity to receive treatment *(17,52)*.

The steps in using a propensity score are (a) construct a logistic model where the outcome variable is receipt of treatment and all available factors influencing receipt of treatment are included as explanatory variables; (b) based on the model, assign each patient a probability of being treated; (c) group the patients into categories (e.g., quintiles) with similar probabilities of being treated; and (d) measure the effect of treatment on disease while controlling for these propensity categories *(53)*. Thus, patients with a ¼ chance of receiving treatment are compared with other patients having a ¼ chance of receiving treatment, and so on, improving the reliability of the result. Propensity scores are useful when there are few patients with disease, many patients receiving the treatment, and many measured factors that are associated with receipt of treatment. However, unlike randomization, analyses adjusted for propensity score cannot control for the effects of unmeasured confounding variables.

One example of the use of propensity scores was to investigate whether intensive care unit mortality was lower for patients cared for by critical care specialists versus other physicians *(54)*. Patients cared for by critical care specialists had substantially higher severity of illness than other patients and would be expected to have higher mortality, and so an analysis that stratified for propensity to receive treatment from an intensivist was used. In a second example, the authors determined the effect of candidemia on hospital mortality, length of stay, and cost *(55)*. Propensity scores were used to compare patients with candidemia to patients without candidemia but who had the same propensity for exposure to *Candida*.

Sensitivity, Specificity, and Predictive Values

Suppose that we have a recognized laboratory method that we consider the "gold standard" (referred to as the "standard") and a proposed newer method (referred to as the "test") that may be cheaper, faster, or have some other advantage. We want to see how the newer test compares with the recognized standard. We run many specimens by both methods and arrange the data in the same format as the 2 × 2 table ("Yes" indicates a positive test, and "No" indicates a negative test). This same format can be used to compare two case definitions, two methods of collecting data, etc., as long as one can be considered the accepted standard.

		Standard: Yes	Standard: No	
Test	Yes	a	b	$a + b$
	No	c	d	$c + d$
		$a + c$	$b + d$	

We can then define four performance characteristics of the new test:

- Sensitivity = $a/(a + c)$: Of all true positives, what proportion were identified by the test?
- Specificity = $d/(b + d)$: Of all true negatives, what proportion were identified by the test?
- Positive predictive value = $a/(a + b)$: Of those positive by the test, what proportion are true positive?
- Negative predictive value = $d/(c + d)$: Of those negative by the test, what proportion are true negative?

Sensitivity and specificity are biologic characteristics and are not influenced by the frequency of disease in the population. On the other hand, the predictive values are influenced by the frequency of disease in the population. Thus, if the disease is rare in a population, the positive predictive value will tend to be low even if specificity is high. Stated another way, if the test is applied in a population where there are few true positives, then a large number of false positives (cell b in the 2 × 2 table) will be found, and most of those found to be positive will in fact be false positives (cell b will be higher than cell a).

There is a trade-off between sensitivity and specificity. A change that makes the test more sensitive (more able to detect true disease) will usually make it less specific (less able to exclude nondisease). This relationship can be depicted graphically as a receiver operating curve plotting sensitivity versus 1–specificity (56).

Sample Size and Power

Assume that there is a true difference in rates of disease in the exposed versus nonexposed populations that would be found if a very large number of subjects were studied.

However, by chance alone, a study of a limited sample of these subjects might or might not find a statistically significant difference. Power is the probability of finding a significant difference between the exposed and nonexposed in your *sample* of study subjects if there really is a difference in the rates in the *populations* from which the samples were taken. Power = 1—the probability of type II error, where type II error is the probability of not finding a significant difference when there really is a difference between the rates in the two populations.

Calculations of sample size and power involve specifying the following *(1)*:

- The rate of illness in the nonexposed group
- The rate of illness in the exposed group (or the relative risk)
- The *p* value required for statistical significance (usually .05) and whether a one- or two-tailed test will be performed
- The ratio of the number of exposed to nonexposed subjects

If the above four are specified, then one can additionally specify the power desired and calculate the sample size required. Alternately, one can specify the sample size and calculate the power that will be achieved. These calculations can be made easily by shareware programs such as EpiInfo, OpenEpi, and WINPEPI. For example, assume that the rate of SSI last year (nonexposed) was 4%, and one wanted to have 80% power to detect an SSI rate of 8% this year (exposed; relative risk = 2.0) with $p < .05$; entering these assumptions into the computer program, we would find that we would need 1,202 subjects, 601 exposed and 601 nonexposed. These types of calculations should probably be used more frequently in planning hospital surveillance, so that surveillance efforts can be continued for a sufficient period of time to detect a predetermined rate of illness.

In a prospectively planned study, it is desirable to have ≥80% power to detect a difference between exposure groups. A hypothesis-testing study with marginal power to detect a true difference generally will not be worth conducting. On the other hand, power calculations may not be crucial in pilot studies or hypothesis-generating studies. Power calculations are at best only a crude estimate that cannot anticipate all the intricacies of the final data set; for example, the need to control for confounders may increase the sample size needed. Additionally, planning for sufficient power may not be possible during an outbreak investigation, where, in the interests of protecting patients, one should usually proceed even though the number of subjects involved may be too small to yield a desirable degree of power.

For studies showing a statistically nonsignificant effect, calculations are sometimes performed to show that the sample size was inadequate to detect statistical significance given the measured rates of disease. However, such post hoc power calculations are misleading and should not be performed or relied upon *(57)*. For example, consider a study showing 2/20 (10%) ill in the exposed and 1/20 (5%) ill in the nonexposed, relative risk = 2.0, 95% confidence interval = 0.2–20.3 (nonsignificant). A post hoc calculation shows that if the true population relative risk were 2.0, the total sample size of 40 has only 9% power to find a significant difference. This low power is predictable given the nonsignificant result. If the relative risk of 2 encouraged us to do a larger study with 874 total subjects, which we calculate has 80% power to detect a population relative risk of 2.0, we might be disappointed to find the rates of disease to be similar, say 7.5% in both the exposed and unexposed groups. The problem with the post hoc power calculation stems from assuming, based on the results of the smaller study, that the true population relative risk is 2.0, when in fact we are only 95% sure it is between 0.2 and 20.3.

Shareware Programs for Epidemiologic Analyses

EpiInfo, available from the Centers for Disease Control and Prevention, was originally developed in DOS format in the 1980s. The current windows version allows the user to create data entry screens, enter and manage data, sort and print data, and perform bivariate and multivariate regression analyses *(58)*. A "Utilities" tab provides access to DOS versions of Statcalc, which permits quick entry of the four elements of a 2×2 table and calculation of the relative risk, odds ratio, *p* values, and confidence intervals; and a sample size and power calculator (see Chapter 15). OpenEpi is an online program developed by the creators of EpiInfo that performs many of the same functions but does not have data entry and management capabilities (59).

WINPEPE, a freeware program that performs a wide variety of epidemiologic and statistical calculations, can be downloaded from www.brixtonhealth.com *(60)*. This software does not have data entry and management capabilities, but some modules can import and analyze data sets created by other programs. Chapter 3 of this textbook contains a number of examples of the use of WINPEPE.

R is an increasingly popular statistical freeware program written in a language similar to S-plus that provides a platform for development of data analysis packages *(61)*. A strength is its sophisticated graphics, mapping, and spatial analytic tools. Currently, R is not the most convenient option for performing the typical analyses used by epidemiologists and is more appropriate for sophisticated analyses performed by mathematicians and statisticians. However, as its development continues and documentation improves, R may be an increasingly viable freeware option.

SaTScan is a DOS-based program for detection of disease clusters across both time and space *(62)*. It was first developed to scan for clustering of chronic diseases, more recently has been used for analysis of syndromic surveillance data *(63)*, and currently is being adapted for use in defining clusters of antimicrobial resistance *(64)*.

MULTIVARIABLE REGRESSION ANALYSIS

As noted in the introduction, regression modeling is used increasingly in the medical literature despite the lack of training of most healthcare epidemiology personnel in its use. Published articles using regression models show numerous omissions, such as lack of documentation of identification, coding, and selection of potential confounders and effect modifiers, and no investigation of potential nonlinearity of response (65). Multivariable models can be validly produced only by those well trained and experienced. This section is merely an introduction and overview. Essential reading is a paper by Sander Greenland (66), which is a literate description of the use of multivariable

models in epidemiologic research. For most epidemiologists, it is more important to understand how to interpret results of regression models than to actually fit them. However, some insight into the regression "black box" will benefit everyone who either collects or interprets data.

Regression models are used to identify confounding and effect modification, calculate adjusted relative risks and *p* values that are free of confounding and reflect the independent effects of variables, find which of several potential variables are independently associated with disease, and make predictions. Regression analysis makes it much easier to sift through a large number of variables to find the few that are significant predictors. Additionally, regression models produce a more precise result (narrower confidence interval) than other multivariable methods such as stratification. However, with these advantages come the potential for abuse: fitting models has become easy enough that well-meaning but inadequately trained individuals may easily and efficiently produce incorrect results.

Automated Algorithms for Modeling

Many statistical packages provide the capability for automated model building. This may occur by forward selection, starting with the single most highly statistically significant variable and adding one variable at a time to the model, or by backward elimination, starting with all variables in the model and removing nonsignificant variables one by one. The backward elimination method may produce poor results if too many variables are under consideration. Automated methods typically use *p* values for selecting variables; human judgment and intervention are required to consider biologic plausibility, confounding, effect modification, and nonlinearity of response. Automated methods may sometimes be used by experienced personnel as a first step in producing a model, but should never be relied on by inexperienced personnel to produce a final model.

Practical Aspects of Model Building

Model building requires skill and experience and cannot be reduced to a cookbook approach. It is not too difficult to fit a model involving cumulative incidence data and only a few dichotomous (e.g., yes or no) exposure variables. For this simple case, a model that controls for potential confounding can be produced. Complexity is introduced by the presence of a large number of potential exposure variables, a small number of cases, multilevel exposure variables (i.e., ≥3 levels), continuous (e.g., age, weight) exposure variables, colinearity among exposure variables, and effect modification. Additional complications include the need to account for time at risk (as in incidence density or survival analyses) and study designs with nonindependent records (see below).

Two variables are collinear if they measure nearly the same biologic property. An example would be two severity-of-illness scores that include many of the same components. It is advisable to identify colinearity by exploration before multivariable analysis. If collinear variables are introduced into a model, large changes in the regression coefficients and *p* values may occur. It may be obvious that only one of these variables can be in the model, but there is no statistical test to indicate which to choose.

All variables should be examined by univariable (e.g., 2×2 tables) methods first, and some should be further explored in stratified analyses. Continuous variables should be explored by plotting; for the model, they should be divided into categories (e.g., quartiles) and represented by indicator variables (Table 2-11).

Criteria for inclusion of a variable in a model include:

- The variable is statistically significant (usually $p < .05$) when in the model.
- The variable is an exposure of primary interest.
- The variable is a confounder of an exposure of primary interest. An informal rule of thumb would be that the variable produces a change of ≥10% in the regression coefficient of the variable of primary interest.
- The variable is of special biologic interest, for example, has been found in previous studies to be an important predictor.

Variables are introduced into the model one at a time and retained in the model if they meet one of the criteria for inclusion listed above. Continuous variables should be examined in several ways: as a simple continuous variable, as the continuous variable plus its square, as a transform (e.g., logarithm, reciprocal) of the continuous variable, and (most importantly) as a series of indicator variables coding (Table 2-11) for discrete categories. If the squared value of a continuous variable is statistically significant, this suggests a curvilinear relationship between the continuous variable and the outcome variable.

The pool of variables to try in the model includes those of special biologic interest and those with less than a certain *p* value in univariable analysis. It may be advisable to set this *p* value at a relatively high level, say .2, since some such variables may prove to have lower *p* values in the model or to be important confounders. Remember that it is necessary that a confounder be associated with the outcome, and a very weak association as indicated by $p > .20$ cannot result in much confounding effect *(67,68)*. Thus, if the available automatic algorithms employing *p* values are to be used for screening for potential confounders, the selection criterion should be set at some much larger value than .05, for instance, $p < .20$.

Effect Modification

After variables have been selected for the model, effect modification should be tested for. Interaction terms can be created by multiplying the main effect variables by one another, two at a time. These terms are then introduced into the model and checked for statistical significance. A problem is that there may be many interaction terms. A model with five main effect variables will have nine potential interaction terms, one or more of which may be significant by chance alone. If an interaction term is found to be statistically significant, one must decide whether to retain it in the final model on much the same basis as other variables, for example, by considering factors such as the *p* value, size of effect, biologic plausibility, and whether it substantially changes the main effects. It may be reasonable to report models with and without interaction terms.

Additional Considerations

In evaluating the validity of a fitted model, a variety of regression diagnostic tools, including analysis of residuals, are available (65,66,*67–74*). These diagnostics are extremely useful when multiple variables appear to carry the same

basic information (colinearity). When the results of fitting a multivariable model to estimate relative risk differ substantively from the results of stratified analysis on the same data, the results of the multivariable analysis are wrong. Remember, again, that no analytic scheme can correct selection bias or misclassification.

Recall that two conditions must be present for an exposure (i.e., $exposure_1$) to be confounded by a second exposure ($exposure_2$): $exposure_1$ must be associated with $exposure_2$ and $exposure_2$ must be associated with disease. Retaining $exposure_2$ in a model when it is not a confounder will, by definition, not change the estimated effect of $exposure_1$ and therefore will not produce a wrong answer. However, there will be a statistical penalty in the sense of an increased *p* value and wider confidence interval for $exposure_1$. Deciding whether to retain a confounding variable may be subjective, and in borderline cases models with and without the confounder may be reported *(68)*.

Multiple Regression Models Commonly Used in Epidemiology

Many types of regression models have been developed, but the following four are most commonly used: multiple linear regression, when the outcome variable is continuous; logistic regression, when the outcome variable is dichotomous; Poisson regression for incidence density data; and the Cox model for survival analysis data.

Linear Regression Linear regression or ordinary least squares regression is used for continuous outcome variables such as length of hospital stay or cost. The regression coefficients obtained in the model may be simply interpreted as in the following example where days of hospital stay is the outcome variable: if the regression coefficient for male gender was 2.0, then males on average had a length of stay 2 days longer than females, and if the coefficient for age ≥60 was 3.0, then patients ≥60 had an average stay 3 days longer than younger patients. The effects of the regression coefficients are combined by addition.

A number of statistical assumptions underlie this model, and one of the most important is that the outcome must be approximately normally distributed. If the outcome is not normally distributed, then the *p* values that arise from fitting a multiple linear regression model are uninterpretable *(69–71)*. Confidence intervals for regression coefficients are easily calculated from standard errors and the distribution of Student's *t*-test. Another very useful quantity that arises from multiple linear regression is the square of the multiple correlation coefficient or the multiple R^2. The multiple R^2 represents the proportion of variation of the outcome variable that is explained by the model. In contrast to other common types of regression models, the regression coefficients in a linear model can be calculated by an exact mathematical formula.

Logistic Regression Logistic regression, the most common type of model used in healthcare epidemiology, is used when the outcome variable is dichotomous (e.g., disease yes or no). The regression coefficient obtained for a variable is the natural logarithm of the odds ratios for that variable. Therefore, to obtain the odds ratio, the regression coefficient is exponentiated. Even in a cohort study, the relative risk cannot be directly determined using logistic regression, and therefore the odds ratio is used where logistic regression modeling is required. However, if data from a cohort study are analyzed using logistic regression, a simple formula can be used to estimate the adjusted relative risk from the adjusted odds ratio obtained from logistic regression *(75)*. The effects of the regression coefficients are combined by adding the regression coefficients or multiplying the odds ratios (see Example of Logistic Regression Model: Healthcare-Associated Infection and Neonatal Mortality, below).

Logistic regression requires less stringent biostatistical assumptions than linear regression but does not inherently adjust for differences in duration of exposure. There is no exact analog for multiple R^2 in logistic regression, but the area under receiver operating curves yields similar information. Unlike linear regression models, logistic regression models do not have exact algebraic solutions, and computers fit them with iterative approximation procedures. Not all models converge to a solution. Iterative fits were practically impossible before the general availability of the computer and still may be difficult for large and complex data sets (see Chapter 3).

Try study questions 8 and 9 in Appendix 1 at the end of the chapter.

Poisson Regression Poisson regression uses incidence density data, that is, the number of cases of disease during a certain person-time of follow-up. Like the incidence density approach, Poisson regression does not account for possible differences in disease incidence during early versus late follow-up. The regression coefficients obtained are the natural logarithm of the incidence density rate ratio. Poisson regression is a valid method to determine the rate ratio for a variable while accounting for time at risk and adjusting for potential confounding from other variables. However, Poisson regression is mainly used when data on individual subjects are not available; that is, Poisson regression is used if we know the total number of cases and the total person-time but do not know the person-time contributed by individual subjects or whether individual subjects were cases. If data on individual patients are known, then survival analysis (Kaplan–Meier plot or the Cox model) is used preferentially. Analogous to logistic regression, the effects of two or more exposures are predicted by adding the regression coefficients or multiplying the rate ratios.

Cox Proportional Hazards Models Cox models were created for survival analysis and are used when the outcome variable is dichotomous and when it is desirable to account for time at risk *(76,77)*. The terminology and methods for survival analysis were presented in an earlier section of this chapter. There are other survival analysis regression methods available, but these depend on modeling the shape of the survival curve. The Cox model represented a breakthrough, because it is not necessary to model the shape of the survival curve. The regression coefficients from Cox models are the natural logarithms of what are called hazard ratios; hazard ratios may be

interpreted as incidence density rate ratios or relative risks. The effects of two or more exposures are predicted in a manner similar to that used in logistic regression. As with logistic regression models, the Cox model can be fit only by iterative processes.

The Cox model assumes that the hazard ratio for a given exposure is constant over time; this is the proportional hazards assumption *(76,77)*. This means that if the hazard ratio for male gender is 2.0, then throughout all times of follow-up males have twice the risk of disease as females. If the hazard ratio for males were 2.0 during early follow-up but 1.0 (or anything other than 2.0) during late follow-up, this data set would not fit the proportional hazard assumption and the Cox model would not be appropriate. If the hazard ratio for a variable changes over the time of follow-up, essentially time is an effect modifier for the variable. The proportional hazards assumption can be investigated graphically or by creating a time-dependent covariate with the logarithm of time and the independent variable *(76)*. If the hazard ratio varies significantly over time, then the proportional hazards assumption is violated. In the previous investigation of the use of multivariate models in the medical literature, checking of the proportional hazards assumption was not reported in more than 80% of publications that used Cox models (65).

Cox Regression With Time-Dependent Covariates An important variant is the Cox model with time-dependent covariates. Although some exposure variables (e.g., gender) are inherent characteristics of the subject, others may vary over a time of follow-up (e.g., neutropenia, Apache II score). Most analysis methods would require some type of compromise for variables that change value; for example, neutropenia could be coded as never, sometimes, or always present. However, the Cox model with time-dependent covariates allows us to actually use different values for exposure variables at different times of follow-up. For example, a study of bloodstream infections in home infusion therapy patients allowed the value of several variables, such as catheter type, to vary as appropriate over time for each patient followed *(78)*.

Example of Logistic Regression Model: Healthcare-Associated Infection and Neonatal Mortality

The data for this exercise are from Table 2-7. The outcome variable was dichotomous (died or survived), and so logistic regression was used. Recall that in logistic regression we always produce odds ratios, even if the data are from a cohort study. We found in stratified analysis that healthcare-associated infection was a risk factor for death, birth weight was a confounder of this relationship, and PDA was an effect modifier.

Our logistic regression starts with model 1 (Table 2-12), which has only healthcare-associated infection (odds ratio = 3.9). We next add three indicator variables for birth weight groups (model 2); Table 2-11 shows how these indicator variables were coded. These indicator variables show the expected increase in mortality as birth weight decreases, and also that the effect of healthcare-associated infection decreases when we control for birth weight (odds ratio decreases from 3.9 to 2.6, suggesting confounding). We can do a statistical test for heterogeneity of the birth weight categories by taking the difference in –2 × log likelihood between models 1 and 2. This difference is 15.6, which can be evaluated as a chi-square with three degrees of freedom, since three variables were added to model 1 to produce model 2. The resulting *p* value for heterogeneity of the birth weight groups = .0014. Next, we add PDA to produce model 3; we note that PDA has a minimal effect on mortality (odds ratio = 1.2, $p = .6$). Finally, we create model 4 by adding the interaction term between healthcare-associated infection and PDA. This interaction term is not highly significant ($p = .03$) but has a substantial effect (odds ratio = 0.16).

TABLE 2-12

Logistic Regression Model: Confounding and Effect Modification in a Study of Neonatal Mortality

Model	*–2 × Log Likelihood*	*Variable*	*Regression Coefficient*	*Odds Ratio*	*Wald p Value*
1	522.4	HAI	1.37	3.9	.0004
2	506.8	HAI	0.97	2.6	.02
		BW1	1.41	4.1	.0001
		BW2	0.79	2.2	.01
		BW3	0.33	1.4	.3
3	506.4	HAI	0.91	2.5	.03
		PDA	0.20	1.2	.6
		BW1	1.36	3.9	.0003
		BW2	0.75	2.1	.02
		BW3	0.32	1.4	.4
4	501.7	HAI	1.65	5.2	.001
		PDA	0.58	1.8	.12
		BW1	1.26	3.5	.001
		BW2	0.71	2.0	.03
		BW3	0.26	1.3	.5
		HAI_PDA	–1.85	0.16	.03

Note: BW1–BW3 are indicator variables for age group (see Table 2-11), and HAI_PDA denotes interaction term between healthcare-associated infections and patent ductus arteriosus.
HAI, healthcare-associated infection; PDA, patent ductus arteriosus.

Model 3 (Table 2-12), without an interaction term, would indicate that the odds ratio was 1.0 (reference group) for infants with no PDA and no healthcare-associated infection, 1.2 for infants with PDA but no healthcare-associated infection, 2.5 for those with healthcare-associated infection but no PDA, and 3.0 (the latter calculated by 1.2 × 2.5 = 3.0) for those with both PDA and healthcare-associated infection. Model 4 indicates that the risks are 1.0, 1.8, 5.2, and 1.5 (the latter calculated by 5.2 × 1.8 × 0.16 = 1.5) for these four possibilities, respectively. The interaction term leads to a markedly different (in this case, lower) estimate of the risk in neonates with both PDA and healthcare-associated infection (3.0 in model 3 vs. 1.5 in model 4) than one would have predicted based on the separate effects of these two variables.

Longitudinal Analysis and Repeated Measures

Standard statistical techniques assume that all observations in a data set are independent. This assumption may be violated in various ways. First, since some patients are more prone to disease than others, most healthcare studies include patients with more than one episode of the illness. One approach to this problem is to study only the first infection for each individual, but this wastes data and does not represent the reality that patients often have multiple events. Second, longitudinal follow-up studies with repeated measurements on individual patients over time are sometimes necessary.

A third issue involves studies carried out at a limited number of medical centers. For example, consider a study done at five hospitals with 100 patients studied at each. Individual hospitals vary greatly in patient populations and style of practice. The 500 records from five hospitals are not independent as would be the case if a random sample of 500 patients from all US hospitals were studied. Methods for adjustment for center in multicenter studies, including the problems of nonindependence, confounding by center, and effect modification by center, have been reviewed (79).

To use all the data available without violating statistical assumptions, we can use methods that were developed specifically for longitudinal or repeated measures studies. The most popular method is the use of generalized estimating equations (GEEs) *(80)*. GEE models can be fit by various statistical packages including SAS; PROC GENMOD uses GEE to fit linear, Poisson, or logistic regression models *(81)*. Fitting these models is more complicated than fitting the other models discussed above. For example, it is necessary to specify the form of the matrix describing the correlations to be accounted for. It is worthwhile to compare the results obtained by standard models including all repeated events, standard models including only first events in a given patient, and the robust estimates from GEE models using various correlation assumptions. If these methods produce similar results, one can feel confident in drawing conclusions, and if they produce different results, more insight into the data is obtained. Fitting models using GEE must be done iteratively for both continuous and discrete data, and the fitting process will not always converge to a solution.

ACKNOWLEDGMENT

The author acknowledges the substantial contributions of Jonathan Freeman, who authored the original version of this chapter, and much of whose wisdom is retained in the current version.

APPENDIX 1: STUDY QUESTIONS

Question 1

Reliable information on patient admissions and discharges is usually available from the hospital administration. From a list of discharges during a 6-month period, a healthcare epidemiologist selected all cases that suffered at least one healthcare-associated urinary tract infection during hospitalization and an equal number of reference patients who did not acquire such infection during hospitalization. If the healthcare epidemiologist compared the cases of healthcare-associated urinary tract infection with the reference subjects for mortality during hospitalization, would this be a case–control study or a cohort study? (Hint: Carefully identify the exposure and the outcome.) Suppose the noncases were matched to the cases by primary underlying illness, operation, and age. Would this change your answer?

Question 2

Consider again the situation described in question 1. Using the same cases of healthcare-associated urinary tract infection and the same uninfected reference patients, the healthcare epidemiologist then compared the cases with the comparison subjects for events that occurred in the first week of hospitalization prior to the onset of the healthcare-associated infections. Specifically, the epidemiologist compared placement of indwelling bladder catheters among cases and reference patients. (Again, carefully identify the exposure and the outcome.) Would this be a case–control study or a cohort study?

Question 3

Among the discharges for a 6-month period, the healthcare epidemiologist in the questions above found 200 patients who suffered first healthcare-associated urinary tract infections. Of these infected patients, 30 died. The next sequential uninfected patient discharged after each of these infected patients was selected as a comparison subject, and the administrative records indicated that 10 of the 200 comparison patients died. Fill in the table below and calculate the relative risk of mortality with healthcare-associated urinary tract infection (refer to Table 2-1).

		Disease: Yes	Disease: No
Exposure	Yes		
	No		

$$\text{Relative risk} = \frac{\%\ \text{ill exposed}}{\%\ \text{ill nonexposed}} = \frac{a/(a+b)}{c/(c+d)}$$

Optional: If you are interested, compute the value of chi-square. For a single fourfold table, the value of chi-square may be computed as:

$$\text{chi-square} = \frac{(ad-bc)^2(n-1)}{(a+b)(c+d)(a+c)(b+d)}$$

Question 4

If the sampling fraction were changed and 10 times as many unexposed enrolled, with the same probability of infection, what would happen to the estimate of the relative risk? Optional: What would happen to the confidence intervals?

Question 5

Having decided that healthcare-associated urinary tract infections were a problem, the healthcare epidemiologist made a first inquiry into the possible causes of these

infections. The medical records of the above 400 patients were read, and the frequency of use of indwelling bladder catheters in the first week of hospitalization, prior to the onset of urinary tract infections, was determined. One hundred of the 200 infected patients had experienced prior bladder catheterization, but only 10 of the noninfected patients had been catheterized. Fill in the table below and calculate the odds ratio of exposure to bladder catheterization among infected and noninfected patients (see Table 2-1).

		Disease: Yes	Disease: No
Exposure	Yes		
	No		

$$\text{Odds ratio} = \frac{ad}{bc}$$

Question 6

Suppose the sampling fraction among the noncases, that is, those who were outcome-negative, was changed in question 5, and 10 times as many noncases were enrolled, but the odds of having a catheter remained the same in this larger group of noncases. How would this new larger sample affect the estimate of the odds ratio in question 5? Optional: How would it affect the confidence intervals?

Question 7

Suppose you erroneously calculated the relative risk instead of the exposure odds ratio for the data in question 5. What would happen to the relative risk if the new larger sample of noncases were used in this erroneous calculation?

Introduction to Questions 8 and 9

These questions were prepared to entice you to evaluate your own assumptions. As with many things in life, these questions have no unique correct answers.

Question 8

This is a question to help you discover how your brainstem is calibrated with respect to the additive or the multiplicative models in causal inference in epidemiology. Suppose there are two independent determinants of infection, and the first has a relative risk of 3.0 and the second has a relative risk of 5.0. If you use the conceptual framework of relative risks, this means that the relative risk of infection in the absence of either determinant of infection is defined as 1.0; the relative risk of infection with just the first determinant is 3.0; and the relative risk of infection with just the second determinant is 5.0. Now, in your view, what should be the relative risk of infection in the presence of both determinants of infection? Can you defend your choice of a relative risk of either 8.0 or 15.0 on a biologic basis? Remember that your selection of regression models makes this choice for you.

Question 9

After you have decided what the value of the relative risk should be in the presence of both determinants, consider the implications if the actual measured value of the relative risk in the presence of both determinants turns out to be less than the level you predicted (antagonism) or more than the level you predicted (synergy). Note that there are five different values for the relative risk (RR) in the presence of both determinants on which you should comment:

RR < 8.0
RR = 8.0
RR > 8.0 but <15.0
RR = 15.0
RR > 15.0

APPENDIX 2: ANSWERS TO STUDY QUESTIONS

Question 1

The question is whether this is a case–control study or a cohort study. Here the outcome is survival status at discharge (lived or died), and the exposure is healthcare-associated urinary tract infection (or not) prior to discharge. Although individuals who acquired healthcare-associated urinary tract infections were called cases, infection is the exposure. Because subjects were enrolled in this study on the basis of their exposure status (infected or not) and then compared for subsequent mortality, this is an exposure-selective cohort study with count data (numbers of persons). Matching may increase statistical efficiency but has nothing to do with whether this is a case–control or cohort study.

Question 2

In this example, the situation has been reversed, and healthcare-associated urinary tract infection is now the outcome with prior bladder catheterization the exposure. Because subjects were enrolled in this study by their outcome status (infected or not) and then compared for prior exposure to catheters, this is a case–control study.

Question 3

		Disease: Yes	Disease: No	
Exposure	Yes	30	170	200
	No	10	190	200

$$\text{Relative risk} = \frac{30/200}{10/200} = \frac{15\%}{5\%} = 3.0$$

RR = 3.0; chi-square = 11.08; $p < 10^{-3}$

Note: The combination of the relative risk and its 95% confidence interval, 3.00 (1.57–5.73), is much more

informative than just having the relative risk and the *p* value separately.

Question 4

If the sample of the unexposed is increased to 2,000 from 200 but the probability of the outcome remains the same, the relative risk will remain unchanged, but the value of chi-square will increase and the confidence intervals will shrink. The relative risk is 3.00 (2.06–4.37).

Question 5

		Disease: Yes	Disease: No
Exposure	Yes	100	10
	No	100	190
		200	200

$$\text{Odds ratio} = \frac{(100)(190)}{(100)(10)} = 19.0$$

chi-square = 101.3; $p < 10^{-8}$

Question 6

If the sample of noncases is increased 10 times from 200 to 2,000 but the odds of exposure remain the same, the odds ratio will remain unchanged, but chi-square will again increase and the confidence interval will shrink. The odds ratio is 19.0 (14.5–24.9).

Question 7

If one erroneously computes the relative risk from the above case–control study with the original sample size, relative risk = 2.64. If one then erroneously computes the relative risk with the larger sample size, relative risk = 1.82. The sampling fractions do not change the estimates of relative risks when they are calculated correctly.

Question 8

If one believes that independent effects are additive, then the relative risk in the presence of both determinants would be 3.0 + 5.0 = 8.0. If one believes that independent effects are multiplicative, then the relative risk in the presence of both determinants would be 3.0 × 5.0 = 15.0. Which is applicable depends on your point of view and the underlying biology.

Question 9

Any value less than your projected estimate would indicate antagonism between the two determinants, and any value greater than your projected estimate would indicate synergy between the two determinants. In either model, a relative risk of 7.0 in the presence of both determinants would indicate antagonism, and a relative risk of 16.0 would indicate synergy. However, if you believe in the additive model, then a relative risk of 10.0 would represent synergy, but if you believe in the multiplicative model, then the same relative risk of 10.0 would indicate antagonism. Effect modification is the epidemiologic term for synergy or antagonism.

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CHAPTER 3

Biostatistics for Healthcare Epidemiology and Infection Control

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It is common knowledge that investigators face challenges during all phases of planning and implementing research protocols. Clinical and experimental researchers possess the necessary expertise for the medical and scientific aspects of their investigations. Moreover, researchers usually have some knowledge of elementary statistical methods. Some researchers find elementary statistics adequate for their purposes and need only an occasional consultation with a biostatistician. However, recent trends in clinical research, especially in healthcare epidemiology and infection control, indicate increasing complexity that demands a higher level of statistical expertise. These general trends are probably going to continue for the foreseeable future—a situation that may leave a researcher feeling somewhat overwhelmed by all of the tasks to be handled in addition to mastery of subject matter. This chapter discusses the challenges and dilemmas related to statistical issues faced by the researcher during the various phases of planning and implementing a research protocol.

Statistics is the science of collecting, analyzing, interpreting, and presenting data. Descriptive statistical methods involve data reduction and summarizing many observations in a few representative numbers. Biostatistics is the application of statistical methods to biologic, biomedical, or health science problems. Data are numeric observations or measurements that result from a random phenomenon or process *(1,2)*. A random process cannot be controlled, and the data collected can never be reproduced exactly. Data from a random process always contain some natural variation. To identify reasons for observed differences among groups of observations, the researcher must sort out the special causes that lead to systematic variation and separate these from the natural variation that is always present. Consequently, decisions will be uncertain. Before making a decision, the researcher uses statistical inference to objectively evaluate data and quantify the level of uncertainty. In addition, the researcher uses statistical models to represent data in terms of special causes and natural variation; these models aid the researcher in making inferences and decisions based on the data.

The numeric observations are in the form of variables, also called *random variables*. Certain statistical techniques apply to each type of random variable (*1*–4,5,*6*,*7*,8,*9*). Measurement variables may be continuous, if the number of values is very large, or discrete, if only few values (generally <10) are possible. Some measurement variables are actually computed variables, for example, Acute Physiology and Chronic Health Evaluation III (APACHE III) scores. A ranked variable is a measurement variable, the values of which have been placed in ascending or descending order and replaced by the ranks. Attributes must translate into numbers (e.g., frequencies of occurrence or number of infected patients). Attributes are sometimes called *categorical variables*. If an attribute can be only present or absent, the term *dichotomous variable* is frequently used.

In today's clinical studies, even the most focused research protocol can yield enormous amounts of information. The typical clinical setting contains a multitude of measuring devices that can provide exquisitely detailed measurements. Many measurements are collected because of availability rather than need. As a consequence, when a study is concluded, an investigator can be faced with the task of sorting through a huge amount of data. Certain measurements or variables are relevant to and necessary for carrying out the specific objectives of a study. An investigator determines what type of data to collect based primarily on specialized knowledge.

Two concepts have especially important implications for investigators. *Accuracy* is the closeness of the measure to the true value; lack of accuracy has to do with bias *(1–3,9,10)*. Before recommending a study or grant for approval and/or funding, most reviewers insist that an investigator show how the results will be unbiased. Thus, the investigator's responsibility includes demonstrating the experimental validity of the study. *Precision* is the closeness of repeated measurements to each other *(2,3,9)*. Importantly, precision has no bearing on closeness to the true value. In fact, precision without accuracy can be a problem when an investigator is trying to make statistical inferences.

Most clinical studies involve samples that are chosen from a population, instead of the entire population (*2–4*,8,11,*12*,*13*). The term *population* refers to the reference or study population. A random sample is a group chosen from a population such that each member of the sample has a nonzero probability of being chosen, independent of any other member being chosen. A simple random sample is the same as a random sample, except that each member of the population has the same nonzero probability of

being chosen. Parameters of the reference population are usually unknown and unknowable. The investigator uses statistics from samples to estimate the parameters of the reference population. Because the sample is smaller than the population, information obtained from the sample is partial, and the investigator uses this information to infer something about the population. Most statistics used in healthcare epidemiology and infection control require the investigator to make the assumptions that (a) the reference population is infinitely large and well defined and (b) the sample behaves like a simple random sample. In practice, the population may not be well defined or infinite. Likewise, the sample may not be random; for clinical studies, samples are often composed of those patients who have been admitted to a particular hospital over a specified period because of certain underlying diagnoses and who have undergone various medical and surgical procedures.

DESCRIPTIVE STATISTICS

In published reports, healthcare epidemiologists summarize patient characteristics with descriptive statistics (*1–4*,5,*6*,*7*,8,*9*,11,*12*,*13*). Typically, a list of patient characteristics includes measures of central tendency and dispersion for continuous variables.

During the research process, the clinical investigator may start exploratory data analysis by obtaining descriptive statistics of important variables. These descriptive statistics have a variety of other practical uses. For example, a potentially important determinant of disease, such as age, may vary only slightly for those patients included in the study; consequently, the clinical investigator may decide not to consider this variable as a potential risk factor in this study. In addition, the researcher may note which variables have highly skewed distributions and, thus, might yield spurious results during data analysis. Finally, unusually high or low values can be identified and verified, if necessary. The following sections describe descriptive statistics for continuous variables.

Measures of Location or Central Tendency

Location refers to where on an axis a particular group of data is located relative to a norm or another group. Measures of central tendency or central location are used to obtain a number that represents the middle of a group of data.

Mean Mean usually refers to the arithmetic mean or average. The mean is probably the most commonly used measure of location. However, the investigator should be aware that the mean is sensitive to extreme values—both very high and very low values. Other means exist but are used less frequently; the geometric mean is an example. An investigator computes a geometric mean by first taking the logarithm of a group of numbers, computing the mean of the transformed values, and then obtaining the antilog of the mean. Blood pH values are logarithms; however, in practice, after calculating the mean of pH values, no one takes the antilog to obtain the mean hydrogen ion concentration. The Greek letter μ is used to represent the population mean. The sample mean $\bar{X}$ is an unbiased estimator of μ regardless of the shape of the distribution. If the underlying distribution is normal, then the sample mean is the unbiased estimator with the smallest variance.

Median The median is the 50% point or 50th percentile and, as such, is insensitive to extreme values. If an odd number of observations is ranked from smallest to largest, the median is the middle observation. If an even number of observations is similarly ranked, the median is the average of the $n/2$ and $(n/2) + 1$ observations where n is the sample size. For example, if the sample size is 20, after ranking, the median is the average of the 10th and 11th observations. For symmetric distributions, the mean and the median coincide. There is no standard symbol for the median of a population or a sample; however, M can be used for connoting the population parameter or the sample statistic *(4)*.

Mode The mode, or the value with the highest frequency, is a measure of concentration. Distributions may have more than one mode. Distributions with two modes are called bimodal. Trimodal refers to distributions with three modes. For symmetric distributions, the mean, median, and mode have the same value. No standard symbol exists for the mode of a population or a sample.

Measures of Dispersion or Spread

Range The range is the distance between the highest (largest) and the lowest (smallest) value. In healthcare epidemiology, investigators often refer to the interquartile range, which is the distance between the 25th and 75th values. Researchers should report ranges with medians; in this way, information on both location and dispersion can be conveyed to others. For a sample, the range is symbolized by R.

Variance The variance is a measure of dispersion that is often used in calculations. Another name for the variance is the mean square. For populations, the variance is called sigma squared and symbolized with the Greek letter σ^2; for samples, the variance is represented by s^2. Because of the availability of inexpensive calculators and spreadsheets with statistical functions, only definitional formulas for the variance of a population and a sample are given, where n is the sample size from a population with N members, and N is much greater than n. For the population, the variance is computed as

$$\sigma_X^2 = \frac{\sum_{i=1}^{n}(X_i - \mu_X)^2}{N},$$

where X_i is the value of the random variable X, measured on each member of the population; i is a unique identifier of each member of the population; μ is the population mean for the variable X; Σ signifies summing the squared deviations of the individual values from the mean over all members; and N is the number of members in the population. For the sample, the variance is computed as

$$s^2 = \frac{\sum_{i=1}^{n}(X_i - \bar{X})^2}{n-1},$$

where X_i is the value of the random variable X, measured on each observation in the sample; i is a unique identifier of each observation in the sample; $\bar{X}$ is the sample mean for the variable X; $\sum$ signifies summing the squared deviations over all observations; and n is the number of observations in the sample.

Standard Deviation The standard deviation is the square root of the variance and is sometimes called the root mean square. The standard deviation is a measure of the average distance from the mean. If the standard deviation is small, the observations are crowded near the mean; if the standard deviation is large, there is substantial spread in the data. For populations, the standard deviation is symbolized with the Greek letter σ; for samples, the standard deviation is represented by s. Standard deviations correspond to means. Occasionally, an investigator must approximate the standard deviation of a future sample. The expected range (i.e., the largest value that one expects to record from a future sample minus the smallest value) divided by 4 provides an approximation when no other information is available.

Other Descriptive Measures

Measures of Skewness Measures of skewness and kurtosis may be computed to evaluate how a distribution deviates from a normal distribution. Most clinical investigators do not routinely need these measures. In practice, the investigator may plot the distribution of the data to evaluate the presence of outliers, those observations with values much larger or smaller than the rest of the sample. A distribution that has a few to a moderate number of high values and a mean that is greater than the median is generally referred to as right or positively skewed. Conversely, a distribution that has a few to a moderate number of low values and a mean that is smaller than the median is generally referred to as left or negatively skewed. In summary, the direction in which the tail of the distribution points characterizes the direction of skew.

Kurtosis Kurtosis refers to how flat or peaked the distribution is relative to the normal distribution. If a distribution is flatter than the normal distribution, it is called platykurtotic. On the other hand, if a distribution is more peaked than the normal distribution, it is called leptokurtotic. For kurtotic distributions, the mean and the median coincide, but the standard deviation is either larger or smaller, respectively, than it would have been if the observations were sampled from a normal distribution.

Coefficient of Variation The coefficient of variation allows the researcher to compare two or more standard deviations, because the standard deviation has been standardized by the mean. The population coefficient of variation is $(\sigma/\mu)100\%$, and the sample coefficient of variation is $(s/\bar{X})100\%$. For most biologic data, the standard deviation increases as the mean increases. Therefore, the coefficient of variation of a particular variable tends to be rather stable over a wide range of values. For experimental studies, the coefficient of variation is an indicator of the reproducibility of the observations. The clinical investigator may use the coefficient of variation to compare variables that may be potential confounders or effect modifiers. For one group of subjects, the spread of different variables may be compared using the coefficient of variation. For two or more groups of subjects, the coefficient of variation may be used to compare the groups with respect to the spread of a particular variable.

PROBABILITY

Many patient characteristics are dichotomous attributes, which are either present or absent, such as fever. Some characteristics have the form of categorical variables with only a few possible states. For example, the investigator may categorize patients according to the presence of a rapidly fatal disease, an ultimately fatal disease, or a nonfatal disease. In some statistical texts, authors apply the term *discrete variable* to a characteristic or attribute with two or more states. In published reports, healthcare epidemiologists summarize these types of patient characteristics by indicating the proportion of the total group with each characteristic of interest.

During the research process, the clinical investigator often begins exploratory data analysis by considering the relationships between pairs of categorical variables. The following sections contain important rules and definitions that the clinical investigator must master before undertaking a complex study. Dichotomous variables are emphasized, because many clinically important risk factors are dichotomous variables.

Definitions and Rules

Many problems in healthcare epidemiology and infection control involve analysis of frequencies for various attributes (e.g., numbers of patients with and without infections). When only two outcomes are possible, the variable is called a dichotomous variable. For this example, a patient either has an infection or does not and cannot be characterized as being in both states simultaneously. Thus, having an infection is a dichotomous variable that represents mutually exclusive states. The infected state is represented by I and the noninfected state by $\not{I}$ (i.e., I stricken through with a line connoting "not"). The probability that an infection is present is represented by p; the probability that an infection is not present is represented by $(1–p)$. Some authors of statistics texts represent $(1–p)$ as q. Mathematically, we express the probability that a patient has an infection by the expression, $\Pr(I) = p$. Because the states are mutually exclusive and only these two states can occur, p and q, or $(1–p)$, sum to 1.0.

Probability can be expressed as a fraction with a numerator and denominator, a decimal fraction or proportion, or a percentage. In this chapter, probability is always a proportion. Probabilities can have any value between 0 and 1.0, inclusive. For dichotomous variables, a probability of 0 implies that an event (i.e., one of the two possible states) cannot occur; a probability of 1.0 implies that the event will always occur.

Researchers in healthcare epidemiology need a basic understanding of some concepts related to probability. After mastering a few easily understood concepts (i.e., three rules and six definitions), the researcher can achieve

a deeper understanding of how and when important statistics, such as risk ratio (RR), are used.

Unconditional or Total Probability In healthcare epidemiology and infection control, researchers must assess total or unconditional probabilities (*1–4*,5,8,*12*,*13*). The definition of a total probability is illustrated in the following example. The probability that a patient chosen at random has an infection may be calculated as the relative frequency of patients with infections: the numerator is the number of patients with at least one infection, the denominator is the total number of patients in the study. If 15 of 45 patients in the medical intensive care unit (ICU) have at least one infection, the empirical probability of being infected is .33. This probability may be symbolized as $\Pr(I) = p = .33$. Thus, the total probability of an event occurring is the number of times the event occurs divided by the number of times that it could have occurred.

Empirical Versus Theoretical Probabilities A clinical investigator obtains empirical probabilities from the sample of patients in the particular study. A better method for estimating the true or theoretical probability of a future patient, π, having at least one infection would involve enumerating all infections in all the patients over a long period. The investigator could continue to expand the sample size by including other units and other hospitals and so on. Finally, after the investigator had gathered a very large group of patients from many locations, the empirical probability would approach the theoretical probability of an average hospitalized patient having an infection. Thus, the theoretical probability of infected patients is the relative frequency for cases of infection over an infinitely large sample. During an investigation of a possible outbreak of disease, infection control officers compare empirical probabilities, p, with theoretical probabilities, π.

Conditional Probability In healthcare epidemiology, researchers are also interested in conditional probabilities (*1*,*3*,*4*,5,8,*12*,*13*). An example of a conditional probability is the probability of pneumonia, given that the patient has been intubated. The condition states the circumstances restricting the type of patients of interest to the researcher. A researcher obtains a conditional probability of healthcare-associated pneumonia given intubation by (a) enumerating the number of patients with the two characteristics (i.e., intubated patients with pneumonia) and (b) dividing by the number of patients who are intubated (i.e., those at risk for ventilator-associated pneumonia). In this example, the conditional probability of having pneumonia given that the patient is intubated may be symbolized by $\Pr(P \mid V)$, where $\mid$ indicates given, P symbolizes a patient with pneumonia, and V symbolizes a patient who is intubated or on a ventilator. Therefore, if 25 patients are ventilated and have healthcare-associated pneumonia and 100 patients are ventilated, $\Pr(P \mid V) = 25/100 = .25$.

Joint Probability and the Product Rule The first rule of probability considered in this chapter is the product rule (*1*,*3*,*4*,5,8,*12*,*13*). The product rule states that for any two events A and B, the joint probability of events A and B occurring together is equal to the product of the conditional probability of A given B times the total probability of B. In this example, the probability of being intubated and having pneumonia is obtained by multiplying the conditional probability of having pneumonia given that the patient is intubated by the probability of the patient being intubated. In the ICU, the joint probability that a patient selected at random will be both intubated and have pneumonia may be symbolized mathematically by $\Pr(P \text{ and } V)$, where P indicates a patient with pneumonia and V indicates a patient who is intubated or on a ventilator. In this example, if $\Pr(V) = .40$ (i.e., 40% of the patients in the study are ventilated) and $\Pr(P \mid V) = .25$ (i.e., 25% of the intubated patients have pneumonia), then $\Pr(P \text{ and } V) = \Pr(P \mid V) \times \Pr(V) = .25 \times .40 = .10$. Thus, 10% of the patients in the study have both characteristics.

Independent and Dependent Events Often the healthcare epidemiologist will want to know if there is an association between two events (*1*,*3*,*4*,5,8,*12*). No causal relationship can be identified without substantially more evidence than that provided by one investigation. In this example, the researcher might be looking for an association between a patient being intubated and development of healthcare-associated pneumonia. Therefore, the epidemiologist wishes to know if the ventilated patients in the study are more likely to develop pneumonia than expected based on the theoretical probability of healthcare-associated pneumonia in the particular ICU. In making this decision, the epidemiologist determines the probability of an average patient developing pneumonia and being intubated under the assumption that these two events are independent (i.e., they have no association). Under independence, $\Pr(P \text{ and } V) = \Pr(P) \times \Pr(V)$. If 20% of the patients in the study have pneumonia, then $\Pr(P) = .20$. Thus, if there is no association between being on the ventilator and developing pneumonia, $\Pr(P \text{ and } V) = .20 \times .40 = .08$. This result implies that one would expect 8% of patients to be ventilated and to develop pneumonia if the assumption of independence is correct for this situation. Based on previous computations, the investigator knows that, in this study, 10% of the patients actually have both characteristics. Because the empirical probability is not the same as the theoretical probability, the conclusion is that there is evidence of an association between intubation and pneumonia. Determining whether this association is evidence of a special cause or merely a reflection of natural variability requires the researcher to use inferential statistics. Inferential methods appropriate for this example are presented in other sections.

In this example, the researcher could have reached the same conclusion by comparing total and conditional probabilities. Under independence, the probabilities are equal; therefore, $\Pr(P \mid V) = \Pr(P)$. For the healthcare epidemiologist, this statement implies that with respect to a patient developing pneumonia, the ventilator is neither a risk factor nor a protective factor; therefore, patients on the ventilator have the same risk of developing pneumonia as any other patient in the study. For this example, $\Pr(P \mid V)$ is .25, a value that is greater than $\Pr(P) = .20$. When these two probabilities are unequal, there is evidence of an association between the two variables of interest.

Addition or Total Probability Rule The second rule is called the addition or total probability rule (*1*,*3*,*4*,5,8,*13*). This rule states that for any two events A and B, the total probability of A equals the sum of the joint probability of A and B plus the joint probability of A and not B: $\Pr(A) = \Pr(A \text{ and } B) + \Pr(A \text{ and not } B)$. For convenience, these probabilities are often displayed in a 2×2 table. Accordingly, the term *marginal probability* is used interchangeably with *total probability*.

Before continuing the discussion of probability, the layout of a 2×2 table is considered. Statistically, no restriction exists that stipulates placement of exposure and disease on a particular margin or the order in which presence and absence are given on a particular margin. However, the interpretability of some measures of association, which specifically apply to epidemiology, depends on a particular arrangement. When an investigator devises a 2×2 table, the proportion of patients with the two attributes and those without the two attributes should be placed on the main diagonal (i.e., cells 1 and 4 of the following table). Epidemiologists have developed other conventions, the use of which has helped to standardize presentation of data. Furthermore, some statistical software products have specific requirements for placement of attributes.

	Exposed to Ventilator	*Not Exposed to Ventilator*	*Total or Marginal Probability of Disease*
Pneumonia present	p_1	p_2	$p_1 + p_2$
Pneumonia absent	p_3	p_4	$p_3 + p_4$
Total probability of exposure	$p_1 + p_3$	$p_2 + p_4$	

In the previous table, p_1, p_2, p_3, and p_4 are joint probabilities. For this example, p_1 is the joint probability of a patient having both exposure to the ventilator and pneumonia. Marginal probability of pneumonia can be calculated as the sum of the joint probabilities. In this example, the probability of having pneumonia, $\Pr(P)$, equals the sum of the joint probabilities, $\Pr(P \text{ and } V)$ and $\Pr(P \text{ and } \not V)$ (i.e., $p_1 + p_2$). The other total probabilities, $\Pr(\not P)$, $\Pr(V)$, and $\Pr(\not V)$, can be calculated by using the addition rule and are displayed in the following table.

	Exposed to Ventilator	*Not exposed to Ventilator*	*Total or Marginal Probability of Disease*
Pneumonia present	$\Pr(P \text{ and } V)$	$\Pr(P \text{ and } \not V)$	$\Pr(P)$
Pneumonia absent	$\Pr(\not P \text{ and } V)$	$\Pr(\not P \text{ and } \not V)$	$\Pr(\not P)$
Total probability of exposure	$\Pr(V)$	$\Pr(\not V)$	1.0

Alternatively, using the definition of joint probability, the healthcare epidemiologist can replace the joint probabilities p_1 and p_2 with the product of the conditional probability of disease multiplied by the respective probability of exposure. The same can be done with p_3 and p_4. Frequently, the healthcare epidemiologist uses this approach when the research question involves identifying risk factors. Typically, the healthcare epidemiologist asks that question before designing a prospective study.

	Exposed to Ventilator	*Not Exposed to Ventilator*	*Total or Marginal Probability of Disease*
Pneumonia present	$\Pr(V) \times \Pr(P \mid V)$	$\Pr(\not V) \times \Pr(P \mid \not V)$	$\Pr(P)$
Pneumonia absent	$\Pr(V) \times \Pr(\not P \mid V)$	$\Pr(\not V) \times \Pr(\not P \mid \not V)$	$\Pr(\not P)$
Probability of exposure	$\Pr(V)$	$\Pr(\not V)$	1.0

Finally, a healthcare epidemiologist may wish to study a particular exposure and describe the relationship of that exposure to the presence of a particular disease. In this example, the investigator would be interested in the probability of exposure to the ventilator given that a patient has pneumonia. Usually, the healthcare epidemiologist asks this question before designing a retrospective study, often a case–control study.

	Exposed to Ventilator	*Not Exposed to Ventilator*	*Total Probability of Disease*
Pneumonia present	$\Pr(P) \times \Pr(V \mid P)$	$\Pr(P) \times \Pr(\not V \mid P)$	$\Pr(P)$
Pneumonia absent	$\Pr(\not P) \times \Pr(V \mid \not P)$	$\Pr(\not P) \times \Pr(\not V \mid \not P)$	$\Pr(\not P)$
Probability of exposure	$\Pr(V)$	$\Pr(\not V)$	1.0

In the healthcare setting, patients are exposed simultaneously to several risk factors. By considering each exposure separately, the healthcare epidemiologist can use this approach to identify the most likely route of exposure given a particular disease.

In summary, when the healthcare epidemiologist investigates the relationship between two dichotomous events (e.g., exposure and disease), the 2×2 table provides a useful and flexible way of displaying the relative frequencies at which the four possible combinations of exposure and disease occur in the sample. Depending on the specific research question, the investigator chooses the most meaningful way to express p_1, p_2, p_3, and p_4.

Applications Relevant to Epidemiology

Epidemiologists measure morbidity in terms of prevalence and incidence. Several applications of probability to epidemiology require the investigator to recognize the distinction between these two measures. Prevalence is the proportion of individuals who have the disease. Stated another way, prevalence is the proportion of individuals who have the disease out of all individuals in the population

(i.e., those who are at risk for the disease). Prevalence can be defined as the probability that an individual has the disease regardless of the time elapsed since diagnosis. In contrast, incidence is the rate at which new cases occur among individuals who were disease free. Incidence is the number of new cases that have occurred over a specified time divided by the number of individuals who were disease free (i.e., at risk for the disease) at the beginning of the period. Therefore, incidence can be defined as the probability that a disease-free individual will develop the disease over a specified period.

Relative Risk or Risk Ratio RR is the ratio of the incidence of a disease among exposed persons to the incidence of a disease among unexposed persons (*1*,*3*,5,8,*12–14*, 15,*16*,17,*18*,*19*,20,*21*,22). Often, epidemiologists use the term *risk ratio* interchangeably with *relative risk*. Values for RR are positive and range theoretically from zero to infinity; however, in practice, the denominator probability (i.e., incidence of disease in the unexposed) determines the upper limit for RR. For example, if the incidence of disease in the unexposed is 0.4, then the upper limit for RR is 2.5. This restriction limits the direct comparability of RRs across locations or studies.

If the probability of disease is equally likely for those exposed and those not exposed, the RR equals 1.0. Whenever the RR equals 1.0, exposure and disease are independent. If the probability of disease is higher for those exposed than for those not exposed, RR is >1.0 and exposure is a risk factor. If the probability of disease is lower for those exposed than for those not exposed, RR is less than 1.0 and exposure is a protective factor. As the RR of disease increases or decreases from 1.0, there is evidence that the two events, exposure and disease, are associated or dependent. Using the information in a tabled display, the infection control officer can obtain two conditional probabilities: $\Pr(P|V) = .25$ and $\Pr(P|\not V) = .167$. Thus, the RR is 1.497. In this situation, the officer would conclude that according to these data, a patient on a ventilator is about 1.5 times as likely to develop pneumonia as a patient who is not on a ventilator.

Odds Ratio When incidence is not known, RR cannot be obtained. However, the RR can be approximated by the odds ratio (OR) (*1*,5,8,*12–14*,15,*16*,17,*19*,20,*21*,22). If the proportion of diseased persons (i.e., prevalence) is small (i.e., <0.1), then the OR is usually a reasonably good approximator of the RR. Therefore, the investigator is responsible for carefully evaluating the OR as an approximator of the RR. In making this evaluation, the investigator must consider whether the disease is chronic or acute. Approximation of the RR is biased when only prevalent cases are used in the analysis. When the duration is short (because of either rapid fatality or cure), the numbers of incident and prevalent cases are very nearly the same; very little bias in approximating RR based on prevalent cases is likely. However, when duration is long, bias can be a problem. For example, when serum cholesterol is used to predict death from heart disease, the OR from prevalent cases is lower than the RR from incident cases. This downward bias occurs, because the individuals with the highest cholesterol values are more likely to have a high fatality rate and thereby to escape detection as prevalent cases. In addition, the investigator should be aware that for a particular sample, the OR will have a more extreme value compared with the RR. If the estimates of the OR and RR based on the sample are >1.0, the estimated OR will be larger than the estimated RR. Conversely, if the estimates of the OR and RR based on the sample are <1.0, the estimated OR will have a value smaller than the estimated RR.

Both RRs and ORs are very useful statistics and have many applications for observational and quasi-experimental studies. Although the clinical investigator often makes the same inferences from an OR as from an RR, these statistics are not interchangeable. Therefore, investigators should be very strict in stipulating whether an estimate is an RR or an approximation based on an OR. Furthermore, it is incumbent on the investigator to demonstrate the validity of any implicit assumption that the approximation based on an OR is a good approximation of RR. Failure to do so can have dangerous consequences involving misinterpretation of published reports and erroneous clinical decisions about patient care.

From the first table, the RR may be computed as a ratio with $p_1/(p_1 + p_3)$ in the numerator and $p_2/(p_2 + p_4)$ in the denominator. If the number of patients with pneumonia is small, p_1 will contribute very little to the quantity $(p_1 + p_3)$; likewise, p_2 will contribute very little to the quantity $(p_2 + p_4)$. The OR equals a ratio with p_1/p_3 in the numerator and p_2/p_4 in the denominator. Statistically, the OR can always be used to approximate the RR. As p_1 and p_2 become smaller, the OR may become a better approximator of the RR. Like RR, the OR ranges theoretically from zero to infinity. However, the OR has a property that can make it a more useful statistic than the RR. The OR is independent of the denominator probability (i.e., an OR of 2.0 has the same meaning regardless of the population or sample on which it was based). The OR is considered the odds of having the disease with the factor present relative to the odds of having the disease with the factor absent. The OR may be calculated from a 2×2 table by calculating the ratio of cross-products (multiplying diagonally): $\text{OR} = (p_1p_4)/(p_2p_3)$.

Sensitivity, Specificity, and Predictive Value The healthcare epidemiologist can use joint, conditional, and total probabilities for quantifying commonly used laboratory tests (5,8,*12–14*,15,*16*,17,*18*,*19*,20,*21*,22,*23*,24,*25*,*26*). The total or marginal probability of disease may be represented as $\Pr(D)$; this probability is an estimate of disease state prevalence in a population. Prevalence can be thought of as the underlying probability of disease state in a particular population. Likewise, $\Pr(\not D)$ can be thought of as the underlying probability of not having the disease state; it is not necessarily the probability of wellness or health.

In terms of conditional probability, the probability of a positive test result given that a patient has the disease—that is, $\Pr(T|D)$—refers to test sensitivity. Similarly, the probability of a negative test result given that a patient does not have the disease—that is, $\Pr(\not T|\not D)$—refers to test specificity. The sensitivity and specificity of a test are independent of prevalence.

The healthcare epidemiologist can display the various possible combinations of disease states and test results in a 2×2 table.

	Positive Test Result	*Negative Test Result*	*Marginal Probability*
Disease present	$\Pr(D) \times \Pr(T \mid D)$	$\Pr(D) \times \Pr(\bar{T} \mid D)$	$\Pr(D)$
Disease absent	$\Pr(\bar{D}) \times \Pr(T \mid \bar{D})$	$\Pr(\bar{D}) \times \Pr(\bar{T} \mid \bar{D})$	$\Pr(\bar{D})$
Marginal probability	$\Pr(T)$	$\Pr(\bar{T})$	1.0

In contrast, the predictive values of a positive test result (PV+) and a negative test result (PV–) depend on prevalence. In terms of conditional probability, the probability of a patient having the disease given that the test result is positive—that is, $\Pr(D \mid T)$—refers to positive predictive value of the test (PV+). Similarly, the probability of a patient not having the disease given that the test result is negative—that is, $\Pr(\bar{D} \mid \bar{T})$—refers to negative predictive value of the test (PV–).

	Positive Test Result	*Negative Test Result*	*Marginal Probability*
Disease present	$\Pr(T) \times \Pr(D \mid T)$	$\Pr(\bar{T}) \times \Pr(D \mid \bar{T})$	$\Pr(D)$
Disease absent	$\Pr(T) \times \Pr(\bar{D} \mid T)$	$\Pr(\bar{T}) \times \Pr(\bar{D} \mid \bar{T})$	$\Pr(\bar{D})$
Marginal probability	$\Pr(T)$	$\Pr(\bar{T})$	1.0

Alternatively, the healthcare epidemiologist may interpret this table in terms of joint probabilities. From this perspective, the epidemiologist considers the probability of an average (or random) patient having a test result that is considered true positive (TP), true negative (TN), false positive (FP), or false negative (FN). Specifically, the probability of a TP test result is a joint probability—that is, $\Pr(T \text{ and } D)$. The other three outcomes may be expressed similarly as joint probabilities. The probability of obtaining a TN result is the joint probability of testing negative and not having the disease. The probability of obtaining an FP result is the probability that a patient selected at random will test positive but not have the disease. Finally, the probability of obtaining an FN result is the probability of a patient selected at random testing negative but having the disease. In practice, these probabilities are often expressed as percentages. These probabilities may be displayed as follows.

	Test Results		*Total Probability*
	Positive	*Negative*	
Disease present	$\Pr(TP) = \Pr(T \text{ and } D)$	$\Pr(FN) = \Pr(\bar{T} \text{ and } D)$	$\Pr(D)$
Disease absent	$\Pr(FP) = \Pr(T \text{ and } \bar{D})$	$\Pr(TN) = \Pr(\bar{T} \text{ and } \bar{D})$	$\Pr(\bar{D})$
Total probability	$\Pr(T)$	$\Pr(\bar{T})$	1.0

Prevalence is the sum of the probability of a TP result and the probability of an FN result. Similarly, the probability of testing positive is the sum of the probability of a TP result and the probability of an FP result. The other two marginal probabilities can be obtained in the same way.

Bayes' Theorem In more complex situations, the healthcare epidemiologist encounters more than two possible clinical signs or symptoms (symbolized as T_i, where i indicates the alternative clinical signs and symptoms) and more than two possible disease states (symbolized as D_j, where j indicates the alternative disease states). The 2×2 tables can be expanded into i columns and j rows, representing clinical findings and disease states, respectively. Bayes' theorem or rule allows the healthcare epidemiologist to obtain the conditional probability of a particular disease given a particular clinical finding (*1*,*3*,5,8,*12*,15,*16*,*18*,*25*). Bayes' theorem or rule states that the conditional probability of D_1 given T_1 equals the joint probability of T_1 and D_1 divided by the sum of the joint probabilities of T_1 and each D_j:

$$\Pr(D_1 \mid T_1) = \frac{\Pr(T_1 \text{ and } D_1)}{\sum_{j=1}^{k} \Pr(T_1 \text{ and } D_j)},$$

where (a) $\Pr(D_j)$ represents the known probabilities of disease states in a specified population and the sum of all $\Pr(D_j)$ values equals 1.0 and (b) the various D_j values are mutually exclusive (i.e., a patient cannot have more than one disease). When healthcare epidemiologists need to choose the most likely explanation for their clinical findings, they often use Bayes' rule to assess the conditional probabilities of several disease states in light of their particular clinical findings. In published literature, epidemiologists may use conditional probabilities to discuss the merits of several alternative explanations. Clinicians may use Bayes' rule to evaluate a number of diagnostic possibilities. They realize that although no test is absolutely accurate, positive test results do tend to increase the probability that a particular disease is present. The conditional probability of disease given certain clinical findings provides a number that quantifies the amount of confidence that can be placed in stating that a particular disease is present. Differential diagnosis, decision theory, and decision making involve applications of Bayes' rule.

HYPOTHESIS TESTING

Hypothesis testing does have a place in analysis of data related to healthcare epidemiology and infection control. One-sample tests can be used to determine whether the sample is different from the reference population. Clinical investigators often use two-sample tests during exploratory data analysis to identify potentially important risk factors. The following sections address general definitions and rules for hypothesis testing for one- and two-sample tests for categorical and continuous variables using parametric and nonparametric methods.

Definitions and Rules

The hypothesis is always formulated about parameters. H_0 designates the null hypothesis and H_1 the alternative hypothesis. Based on sample statistics, the healthcare epidemiologist chooses which is the true situation. For a

one-sample hypothesis test, the reasons for this choice are based on how likely it is that these data could have been obtained from a specified reference population. Similarly, for a two-sample hypothesis test, the reasons are based on how likely it is that the difference between the two groups obtained from these data could have occurred given that H_0 is true. In making this decision, the epidemiologist may make errors. Naturally, minimizing the probability of making an erroneous decision is a paramount concern of the epidemiologist, even though the truth remains unknown and unknowable. The decisions that an epidemiologist can make relative to the truth (*1*,*2*,*4*,5,8,*10*,*25*) are displayed in the following 2×2 table.

	Unknown But True State of Nature	
Decision in Favor of	***H_0 True***	***H_1 True***
H_0	Correct	Type II error
H_1	Type I error	Correct

Traditionally, scientific investigators have agreed on the principle of keeping the probability of a type I error as small as possible. Pr(type I error) is the conditional probability of rejecting H_0 when H_0 is correct. Stated another way, Pr(type I error) is the probability of rejecting H_0 given that H_0 is correct. Statisticians have symbolized Pr(type I error) as α. Another commonly used name for Pr(type I error) is the significance level. The interpretation of a p value is consistent with the definition of the probability of a type I error; a p value gives the probability of finding a result that is at least this extreme, assuming that the H_0 is true. Stated another way, the p value qualifies the rejection of H_0 with a level of significance. An investigator rejects H_0 when the p value is less than α. The p value tells others the statistical significance of the results. Statistical significance has absolutely nothing to do with the scientific or clinical importance of findings.

Another type of error is possible—type II error. Pr(type II error) is the conditional probability of not rejecting the H_0 when H_1 is true. Stated differently, Pr(type II error) is the probability of deciding in favor of H_0 given that H_1 is correct. Statisticians have symbolized Pr(type II error) as β. In practice, statisticians are more concerned with power, symbolized as $1-\beta$. Power is the probability of discriminating between H_0 and H_1, (a) given a specified sample size, a stipulated difference between the values of the parameter under H_0 and H_1, and a particular α; and (b) assuming H_1 is true. Thus, power is the probability of rejecting H_0 when H_1 is true. Power depends on α, H_0 and H_1, and sample size. As α decreases, β increases. As the difference between H_0 and H_1 decreases, power decreases. As sample size increases, power increases—power is very dependent on sample size. Investigators want power to be as large as practically possible, because power represents the probability of correctly rejecting H_0. Typical values for power are 0.80, 0.90, 0.95, and 0.99. Before recommending a clinical trial for approval and/or funding, most reviewers insist that the investigator show that the likelihood of getting conclusive results (i.e., statistical power) is high. In unplanned clinical studies, power may be as low as 0.20 or occasionally even lower. Sometimes, epidemiologists compute power after a study has been completed. Under these circumstances, power is the probability of discriminating between H_0 and H_1, given the findings of the study.

Hypothesis Tests for Categorical Data

A random variable is a numeric quantity that has different values, depending on natural variability. A discrete or categorical random variable is a variable for which there exists a discrete set of values, each having a nonzero probability. Many data from biologic and medical investigations have a common underlying structure.

Cumulative incidence and prevalence of a disease are distributed binomially (*1*,8,*12*). Variables that follow a binomial frequency distribution are characterized by the following criteria: (a) a sample is taken of n independent trials, (b) each trial may have two possible outcomes (e.g., success/failure, present/absent, alive/dead), and (c) the probabilities for the outcomes are a constant p for success and $(1-p) = q$ for each failure for every trial. Usually a healthcare epidemiologist is not concerned with the order in which the failures occurred; instead the epidemiologist is interested in the number of failures and the probability that a number as extreme or more extreme occurred given that H_0 is true.

Generally, an incidence density variable follows a binomial distribution. For variables such as incidence density, the Poisson distribution is often an accurate approximation of the binomial distribution. The Poisson distribution is a discrete frequency distribution of the number of occurrences of rare events (*1*,8,*12*). For the Poisson distribution, the theoretical number of trials is infinite and the number of possible events is also very large. Incidence density studies often involve one or more cohorts of disease-free individuals. A failure is defined as the occurrence of the disease of interest in a previously disease-free individual. The probability of k events (i.e., failures) occurring in a period of time T is defined for a Poisson random variable. Thus, the Poisson distribution depends on two parameters: the length of the interval, T, and the underlying λ, which represents the expected number of events per unit of time. Time may also be defined as a combination of time and level of exposure (e.g., pack-years of smoking or patient-days in the ICU). The mean and the variance of a Poisson distribution are the same. For variables that follow a binomial distribution, when n is large and p is small, the mean and variance will be similar; thus, the Poisson may be used as an approximation of the binomial.

The following two sections describe statistical methods for one- and two-sample tests on binomial proportions or rates (*1*,*3*,*4*,5,*6*,*7*,8,15,*18*,*25*,*27*). Throughout these sections, unless otherwise stated, the significance level is .05; power is 0.80; and all tests are two-sided. In power and sample size formulas, a z-score for the 97.5th percentile is used for a two-sided test with a significance level of .05: $z_{0.975}$ is 1.96. When power of 0.80 is used to determine sample size, a z-score for the 80th percentile is used: $z_{0.80}$ is 0.842.

These sections, describing one- and two-sample tests for binomial proportions or rates, are not designed as casual reading material; instead, they provide a concise reference of commonly used statistical methods. The only

formulas included are those for the test statistics. Most clinical investigators use statistical packages for obtaining sample size estimates or power calculations. For appropriate formulas, the reader is referred to various biostatistical textbooks, for example, Rosner (8) or Sokal and Rohlf *(2)*. For a binomial probability, π refers to the population parameter and p refers to the sample statistic, which approximates the parameter. Each section follows the same format, which is outlined in the following.

Step 1. Set up H_0 and H_1.

The investigator uses the research question to form H_0 and H_1. Generally, H_1 reflects the result that the investigator expects to find (i.e., that there is a special cause that differentiates the study group from the norm). For a one-sample hypothesis test, H_0 states that the proportion of events or rate of occurrence (π) in the study group is the same as some specified or norm value, π_0. The investigator obtains this value, π_0, from some source other than the current study. Typically, the investigator obtains π_0 from theoretically derived values or uses nationally or locally compiled values. In the one-sample situation, H_1 states that the proportion of events or rate of occurrence (π) in the group being studied differs from the specified value, π_0. The investigator estimates π from a sample as p. If the estimated value is sufficiently close to the specified value, π_0, the investigator decides in favor of H_0 (i.e., that the data are consistent with H_0 being true). If the data fail to support H_0, the conclusion is that the data are not consistent with H_0 being true; therefore, the investigator rejects the H_0, concluding that the rate or proportion must be some other value (i.e., higher or lower than π_0).

For a two-sample hypothesis test, H_0 states that the proportion of events or rate of occurrence (π_1) from the first group is the same as that (π_2) from the second group. For a clinical trial, the groups might reflect those receiving and not receiving the treatment. For an observational study, the groups might reflect those subjects with and without the attribute of interest. Interpretations of failing to reject and rejecting H_0 are similar to those described for the one-sample situation.

Step 2. Choose α, power, and the difference between π and π_0 (or π_1 and π_2) that is clinically meaningful. Another term for the difference between π and π_0 (or π_1 and π_2) is effect size. Frequently, investigators overlook this step. For example, the healthcare epidemiologist may not have the opportunity to conduct a formal power analysis before data collection begins. However, whenever the effect size estimated from the sample is clinically meaningful but the results are consistent with H_0, the investigator should determine power retrospectively. This analysis allows the investigator to determine how much larger the sample would have to be to reject H_0, given the results of the study. Even when statistical significance is achieved, a retrospective power analysis can indicate how cautiously the results should be interpreted.

Step 3. Using an available computer package, determine sample size, n. Sample size is extremely sensitive to the effect size chosen by the investigator.

Step 4. Obtain data.

Step 5. Compute test statistic in terms of parameters under H_0. Obtain the p value associated with the test statistic, assuming H_0 is correct. The interpretation of the p value is valid only in terms of H_0 and H_1. By choosing to make a hypothesis test, the investigator restates the research question and must decide between H_0 and H_1 based on how consistent or inconsistent the data are with H_0. The term *consistent* connotes having sufficient empirical support for the investigator to decide that the unknown true state of nature is likely to be H_0 instead of H_1. Conversely, the term *inconsistent* connotes having sufficient empirical support for the investigator to decide that the unknown true state of nature is likely not to be H_0 but rather H_1. Therefore, the p value is the probability of obtaining a result that is at least as extreme as this result, which the investigator has obtained from these data, given that H_0 is true. Stated another way, the investigator rejects H_0 when the results from the study could be called unusual if H_0 were correct. The consensus among statisticians and scientists is that, if the p value is .05 or smaller, the investigator should reject H_0 and decide that H_1 is correct. A p value of .05 indicates that this result would occur no more often than 1 in 20 times if H_0 were true.

Step 6. Decide whether to reject or fail to reject H_0. Compare the p value to α.

One-Sample Tests for a Binomial Proportion or Rate

Normal Approximation Method The normal approximation method based on a z-test was selected because the computation of this test statistic more closely parallels the estimation of confidence limits than any of the other methods. If the normal approximation to the binomial distribution is valid (i.e., $npq > 5$), a two-sided hypothesis test is conducted as follows:

Step 1. Set up H_0 and H_1.

$$H_0: \pi = \pi_0 \text{ versus } H_1: \pi = \pi_0$$

Step 2. Choose α, power, and the difference between π and π_0 that is clinically meaningful.

Step 3. Using an available computer package, determine sample size, n. Sample size is extremely sensitive to the difference between π and π_0 and to how close these are to 0 or 1.0. When no information is available, a pilot study can be conducted to get some idea of differences that can be obtained in a particular clinical situation.

Step 4. Obtain data.

Step 5. Compute test statistic z_s in terms of parameters under H_0, where z_s is a z-score from the standard normal distribution, and obtain the p value as twice the probability associated with the z_s assuming that H_0 is correct. If the significance level is .05, $z_{0.975}$ is 1.96. With the wide availability of computer-based packages that contain statistical functions, many clinical investigators can obtain the p value.

$$z_s = \frac{(p - \pi_0)}{\sqrt{[(\pi_0(1-\pi_0)/n)]}},$$

where p is the estimate from the sample of the parameter π_0. One should note that $z^2 = \chi^2_{[1]}$; the squared z-score, obtained from the data (i.e., z_s), equals a chi-square test statistic with 1 degree of freedom obtained from the same data (i.e., χ^2_s). Most computer packages report a chi-square test statistic with 1 degree of freedom (i.e., χ^2_s) along with the associated p value. If the significance level is .05, $\chi^2_{[0.95]}$ with 1 degree of freedom is 3.84,

which equals 1.96^2. If the normal approximation to the binomial is not valid, p values may be obtained by the exact method.

Step 6. Decide whether to reject or fail to reject H_0. Compare the p value to α.

One-Sided Hypothesis Tests If the hypothesis test is one-sided (i.e., $H_1: \pi > \pi_0$), calculate power and estimate sample size substituting $1-\alpha$ for $1-\alpha/2$ in the previous formulas (e.g., $z_{0.95}$ is 1.645). In addition, the p value is not multiplied by 2. It is always easier to reject a one-sided test than a similar two-sided test. In addition, an effectively larger α increases power by reducing β.

Two-Sample Tests for Binomial Proportions or Rates When the random variable under study is classified into discrete categories, hypothesis testing and methods of inference should reflect the data structure. For the two-sample situation, there are two typical study designs: independent and paired samples. Before formulating the hypothesis, the investigator must determine whether the samples are independent or not. Two samples are independent when the data points in one sample are unrelated to the data points in the second sample. Samples that are not independent are paired. Paired samples may represent two sets of measurements on the same individuals. Alternatively, paired samples may represent measurements on different individuals chosen or matched such that each member of the pair is very similar to the other. Statistical analysis of data from clinical studies is valid only in the context of the study design; inferences are only valid in the context of research questions.

When a healthcare epidemiologist investigates the relationship between two dichotomous variables, the observations are tabulated in 2×2 tables according to attributes. For example, suppose the epidemiologist classifies observations according to the following two attributes:

Attribute 1: A, $\not{A}$
Attribute 2: B, $\not{B}$

The results will be classified into four groups that include all possible combinations of attributes 1 and 2: (A and B), ($\not{A}$ and B), (A and $\not{B}$), and ($\not{A}$ and $\not{B}$). After tabulation, data can be presented in the following format, where a, b, c, and d are the frequencies at which the four groups occur in the sample.

	B	$\not{B}$	*Total*
A	a	b	$a+b$
$\not{A}$	c	d	$c+d$
Total	$a+c$	$b+d$	n

The results of studies with either independent or paired designs may be tabulated according to the frequencies into the same four groups. Thus, this table can be obtained in different ways.

Two-Sample Tests for Independent Samples Both the table and the test statistic are the same regardless of whether the data are obtained from an observational study or a clinical trial. However, the research questions, hypotheses, and statistical tests may be different depending on the type of study. Consequently, the analyses also depend on study design.

Step 1. Set up H_0 and H_1. In many observational studies, the investigator can only control the total number of subjects; the research question involves whether the two sets of attributes are independent of each other. The statistical test is called a test of independence or association. In observational studies, the concept of independent samples stems from the notion that for a given attribute, such as pneumonia, the patients with pneumonia are unrelated to those without pneumonia. The null and alternative hypotheses may be written as follows:

$$H_0: \pi = \pi_0 \text{ for all four groups versus } H_1: \pi \neq \pi_0 \text{ for at leasts one group,}$$

where the null and alternative hypotheses are stated in terms of joint probabilities, that is, the observed proportion equals the expected proportion. The general approach is discussed in the earlier section on probability. For example, the investigator may record the observed joint probabilities of (a) developing pneumonia and being on the ventilator, (b) not developing pneumonia and being on the ventilator, (c) developing pneumonia and not being on the ventilator, and (d) not developing pneumonia and not being on the ventilator. The expected joint probabilities are those that would have occurred under the assumption of independence. The statistical test for association involves determining the probability of finding the observed joint probabilities if the attributes were independent.

For clinical trials, the general research question for studies with independent samples is whether the proportion of B (and $\not{B}$) is the same for A and $\not{A}$ (i.e., the proportion of patients who die is the same for those with the drug [treated] as for those without the drug [control subjects]). Usually, the investigator determines not only the total number of subjects but also the number of subjects in each group. The statistical test is called a test of homogeneity of two proportions. For example, a clinical trial of a drug that may reduce the death rate associated with ventilator-associated pneumonia may be conducted. In this example, the investigator first estimates the observed conditional probabilities of death depending on whether the subject is in the treated or the control group. Next, the investigator estimates the observed marginal probabilities of death and survival using the addition rule. Using these observed marginal probabilities, the investigator then estimates the expected conditional probabilities of death independent of whether the subject is in the treated or the control group. These expected (or theoretical) conditional probabilities are based on the assumption that the death rate is the same in both groups (i.e., that H_0 is true). The statistical test involves determining the probability of finding the observed conditional probabilities if the probability of death were the same in both groups. The null and alternative hypotheses may be stated as follows:

$$H_0: \pi_{B|A} - \pi_{B|\not{A}} = 0 \text{ versus } H_1: \pi_{B|A} - \pi_{B|\not{A}} = 0,$$

Step 2. Choose α, power, and the difference between $\pi_{B|A}$ and $\pi_{B|\not{A}}$ that is clinically meaningful.

Step 3. For clinical trials using an available computer package, determine sample size for each group, n_1 and n_2. Sample size is very sensitive to the difference between $\pi_{B|A}$ and $\pi_{B|\bar{A}}$. This difference, also called the effect size, should be that difference which is biologically or clinically meaningful in the opinion of the researcher. When no information is available, a pilot study can be conducted to get some idea of differences that can be obtained in a particular clinical situation. Although the algebra is not difficult, the formula for determining the sample size is quite complex; the reader is referred to the formula in Sokal and Rohlf *(2)* or Fleiss et al. (15), which minimizes the chances of underestimating the sample size required to detect the absolute value of the difference of $|\pi_{B|A}-\pi_{B|\bar{A}}|$ at given levels of significance and power. The formula in Rosner (8) is used in most statistical packages and yields sample size estimates that are generally about 5% smaller than those based on the Sokal and Rohlf or Fleiss formula. Computation of sample size can be tedious. For step 3, the investigator may wish to consult a biostatistician. Computer software is available for making some computations; however, the investigator should review documentation to determine which formulas are used and choose a software package that does not typically underestimate sample size. This precaution is especially important if sample sizes are less than 50 per group.

Step 4. Obtain data.

Step 5. Compute test statistic in terms of parameters under H_0 and obtain the p value. If the sample size is larger than 20 and no more than 20% of the expected cell frequencies (i.e., the cell frequencies expected under the assumption of independence) are <5, using large sample theory and the normal approximation to the binomial distribution is valid. In this situation, the following test statistic is appropriate for both observational studies and clinical trials. The test statistic is z_s, where

$$z_s = \frac{(p_{B|A} - p_{B|\bar{A}})}{\sqrt{(p_B(1-p_B)/n_1 + p_B(1-p_B)/n_2)}},$$

where n_1 and n_2 are the numbers of observations in each group. The p value is twice the probability associated with the test statistic, z_s, assuming that H_0 is correct.

Step 6. Decide whether to reject or fail to reject H_0. Compare the p value to α. When the two attributes are not independent of each other, there exists some form of association between the attributes. Inspecting the data will reveal what the association might be. The investigator must look closely at each of the individual cell chi-square values before making inferential statements about the nature of the association. The investigator's interpretation is based on the fact that the cells with the largest chi-square values have contributed proportionately more to the total chi-square test statistic. Note that $z^2 = \chi^2$; the squared z-score, obtained from the data (i.e., z_s), equals a chi-square test statistic with 1 degree of freedom obtained from the same data (i.e., χ_s^2). Most computer packages report a chi-square test statistic with 1 degree of freedom (i.e., χ_s^2) along with the associated p value. If the significance level is .05, $\chi_{0.95}^2$ with 1 degree of freedom is 3.84, which equals 1.96^2.

Fisher's Exact Test If the normal approximation to the binomial is not valid, Fisher's exact test must be used to obtain the exact probability of obtaining a table with cells *a*, *b*, *c*, and *d*. This situation is described by the hypergeometric distribution. Fisher's exact test may be used to give the exact p value for any 2×2 table. Many computer packages for statistical analysis provide results based on Fisher's exact test. For a calculator-based method, the reader is referred to Rosner (8). The interpretation of the p value from Fisher's exact test is the probability of obtaining a table at least as extreme as the observed table, assuming the two attributes are independent.

Two-Sample Test for Paired Samples

Both the table and the test statistic are the same regardless of whether the data are obtained from an observational study or from a clinical trial. When matched pairs are the basic experimental unit for a clinical study, pairs are classified as to whether or not the treatment or placebo was effective for each member of the pair. Sometimes each subject is used as its own control, thereby yielding paired results. In observational studies, the pairs may be classified as to whether or not the outcome is the same for each member of the pair.

A matched pair in which the outcome is the same for both members of the pair is called a *concordant pair*—that is, (present, present) or (absent, absent). For example, one might consider a study in which the event of interest is death (as contrasted with survival). If both members of the pair die, this result might be symbolized as (Yes, Yes); conversely, if both members live, the result might be symbolized as (No, No). A matched pair in which the outcomes are different for the members of the pair is called a *discordant pair*—that is, (present, absent) or (absent, present). Rosner (8) describes a type A discordant pair is a pair in which the outcome for the member from the first group is the event and the outcome for the member from the second group is not. Using the previous example, a type A discordant pair would contain a member from the first group who died and a member from the second group who survived—that is, (present, absent). According to the same logic, Rosner describes a type B discordant pair as a pair in which the outcome for the member from the first group is not the event and the outcome of the member from the second group is. Again, using the previous example, a type B discordant pair would contain a member from the first group who survived and a member from the second group who died—that is, (absent, present). After tabulation, data can be presented in the following format, where *a*, *b*, *c*, and *d* are frequencies.

	Treatment or Group 2		
Treatment or Group 1	*Present*	*Absent*	*Total*
Present	*a*	*b*	*a* + *b*
Absent	*c*	*d*	*c* + *d*
Total	*a* + *c*	*b* + *d*	*n*

Step 1. Set up H_0 and H_1. The null and alternative hypotheses may be stated as follows:

$$H_0 : \pi_{\text{Present|Group 1}} = \pi_{\text{Present|Group 2}},$$

where the estimate of $\pi_{\text{Present|Group1}} = a/(a + b)$ and the estimate of $\pi_{\text{Present|Group2}} = a/(a + c)$. This test is called McNemar's test. The investigator tests whether the "present" proportions for the two treatments or groups are the same. Note that the only important differences between $p_{\text{Present|Group1}}$ and $p_{\text{Present|Group2}}$ are between b and c. Testing for differences between b and c is the same as testing that the "present" proportion for treatment or group 1 is the same as the "present" proportion for treatment or group 2. Thus, the null hypothesis could be restated as the frequency that the two types of discordant pairs are equal: H_0:$\pi_{\text{Present\&Absent}} = \pi_{\text{Absent\&Present}} = 0.5$ versus H_1: $\pi_{\text{Present\&Absent}} \neq \pi_{\text{Absent\&Present}} \neq 0.5$, where the estimated $\pi_{\text{Present\&Absent}}$ is $b/(b + c)$ and the estimated $\pi_{\text{Absent\&Present}}$ is $c/(b + c)$. If the investigator chooses to state H_0 in terms of either $\pi_{\text{Present\&Absent}}$ and $\pi_{\text{Absent\&Present}}$, this becomes a one-sample test with n equaling $(b + c)$, the total number of discordant pairs. For the remainder of the procedure (i.e., steps 2 through 6), the reader is referred to the normal approximation method for one-sample tests for a binomial rate or proportion.

Two-Sample Test for Incidence-Density Variables In many epidemiologic studies, the investigator follows subjects for varying lengths of time (e.g., length of stay in the ICU), and the outcome variable is dichotomous. For example, the variable of interest might be whether or not a healthcare-associated infection developed in a sample of patients. When a subject converts from a negative status to a positive status, the investigator records the time to failure. The term *failure* connotes the event, usually death or a disease state, that the investigator is studying. In the simplest situation, the subjects are divided into two groups according to a single exposure (e.g., receiving or not receiving parenteral nutritional support). For this simple situation, the investigator has a choice of several methods for analyzing this type of data. Three commonly used methods are presented in this chapter. Two methods are presented in the following, and the third is discussed later (see the section on survival analysis). If the situation is more complex, the investigator must use either survival analysis or stratified analysis.

Rosner (8) presents a method that is appropriate when the investigator wishes to compare the incidence density rates of two groups. The investigator must assume that the incidence remains constant over the assessment time. Although patients are followed for varying lengths of time, the investigator knows whether a particular patient has either failed or not failed. The investigator counts the number of failures in each group. Then, the investigator computes the total number of person-time units elapsed from enrollment to the assessment time. After tabulation, data can be presented in the following format.

	Exposed	*Not Exposed*	*Total*
Number of events	a	b	$a + b$
Person-time	t_E	$t_{\bar{E}}$	$t_E + t_{\bar{E}}$

Step 1. Set up H_0 and H_1. The investigator tests whether the incidence-density (ID) is the same for the two groups of subjects. Stated another way, the investigator is interested in whether the rates of healthcare-associated infection per patient-day in the ICU are the same in the two exposure groups. The null and alternative hypotheses may be stated as follows:

$$H_0 : \text{ID}_E = \text{ID}_{\bar{E}} \text{ versus } H_1 : \text{ID}_E \neq \text{ID}_{\bar{E}},$$

where E indicates the exposed group, $\bar{E}$ indicates the unexposed group, the estimated $\text{ID}_E = a/t_E$ and the estimated $\text{ID}_{\bar{E}} = b/t_{\bar{E}}$. The total number of events in the exposed group equals a. Similarly, the total number of events in the unexposed group equals b.

Step 2. Obtain data. Because most studies of incidence density are observational, power analyses and sample size computations are usually not completed.

Step 3. Compute test statistic in terms of parameters under H_0 and obtain the p value. If normal approximation of the binomial is valid (i.e., $V_E \geq 5$), the test statistic is a z-score:

$$z_s = \frac{a - ((a+b)t_E/(t_E + t_{\bar{E}}))}{\sqrt{[(a+b)t_E t_{\bar{E}}/(t_E + t_{\bar{E}})^2]}}$$

where the observed number of events in the exposed group is a; the expected number of events in the exposed group (given that H_0 is true) is $(a + b)t_E/(t_E + t_{\bar{E}})$; and the variance is $(a + b)t_E t_{\bar{E}}/(t_E + t_{\bar{E}})^2$. The p value is twice the probability associated with the test statistic z_s, assuming that H_0 is correct. If the normal approximation of the binomial is not valid, exact binomial probabilities must be obtained.

Step 4. Decide whether to reject or fail to reject H_0. Compare the p value to α.

The second method is probably the most commonly used test for comparing incidence rates. The Mantel–Haenszel test, also called the log rank test, does not require the assumption of a constant incidence rate over time. In this situation, the investigator may place as much importance on time to an event as on whether or not the event occurred. For example, suppose a healthcare epidemiologist has a statewide surveillance program designed to detect new cases of positive tuberculin test results among nursing personnel during their first year of employment.

Step 1. H_0 and H_1 are the same as those described for the first method.

Step 2. Obtain data.

Step 3. Divide the year into shorter periods (e.g., months). Construct a 2×2 table for each interval. Note that subjects who have not experienced an event during a preceding interval are at risk for experiencing an event during the current interval; therefore, only the number of subjects not having the event in the preceding interval will appear in a given 2×2 table. Once a subject has experienced an event during a given interval, data for that subject does not appear on any table representing a subsequent interval.

Using these rules, the healthcare epidemiologist constructs the table for the first time interval using the following format.

	Group		
Event	*1*	*2*	*Total$_1$*
Yes	a_1	b_1	$a_1 + b_1$
No	c_1	d_1	$c_1 + d_1$
	$a_1 + c_1$	$b_1 + d_1$	n_1

where a_1 is the number of subjects in the first group who experienced events in the first interval; c_1 is the number of subjects in the first group who did not experience events during the first interval; $(a_1 + c_1)$ is the total number of subjects in the first group; b_1 is the number of subjects in the second group who experienced events during the first interval; d_1 is the number of subjects in the second group who did not experience events during the first interval; $(b_1 + d_1)$ is the total number of subjects in the second group; and n_1 is the total number of subjects in the study. Next, the healthcare epidemiologist constructs the second table using the following format.

	Group		
Event	*1*	*2*	*Total$_2$*
Yes	a_2	b_2	$a_2 + b_2$
No	c_2	d_2	$c_2 + d_2$
	$a_2 + c_2$	$b_2 + d_2$	n_2

where a_2 is the number of subjects in the first group who experienced events during the second interval; c_2 is the number of subjects in the first group who did not experience events during the second interval; $(a_2 + c_2)$ equals c_1 and is the total number of subjects in the first group who were at risk during the second interval; b_2 is the number of subjects in the second group who experienced events during the second interval; d_2 is the number of subjects in the second group who did not experience events during the second interval; $(b_2 + d_2)$ equals d_1 and is the total number of subjects in the second group who were at risk during the second interval; and n_2 equals $(c_1 + d_1)$ and is the total number of subjects at risk during the second interval. Continue constructing tables using the same format.

Step 4. Compute the test statistic over all the 2×2 tables in terms of parameters under H_0 and obtain the p value. The test statistic is the Mantel–Haenszel statistic, which may be computed with the following formula:

$$\chi_s^2 = \frac{\left(\sum_{i=1}^{t} a_i - \sum_{i=1}^{t} (a_i + b_i)(a_i + c_i)/n_i\right)^2}{\sum_{i=1}^{t} (a_i + b_i)(c_i + d_i)(a_i + c_i)(b_i + d_i)/n_i^2(n_i - 1)},$$

where i indicates the individual 2×2 tables and the other values are defined in the discussion on construction of the various tables. Under H_0, the Mantel–Haenszel statistic χ^2_{MH} follows a chi-square distribution with 1 degree of freedom. Therefore, for a test of significance at the .05 significance level, H_0 is rejected if χ^2_{MH} is greater than 3.84. The p value is the probability associated with χ^2_{MH} assuming that the null hypothesis is true.

Hypothesis Tests for Continuous Data

Distribution of Sample Means The central limit theorem states that, for a large sample size regardless of the underlying distribution of the individual observations, the sample mean, $\bar{X}$, follows a normal distribution with mean μ and variance σ^2/n (*1–4*,5,8,*9*,*16*). The mean of sample means is the same as the mean of the original population of individual values. The variance of sample means is needed to indicate dispersion or spread among $\bar{X}$ values. The standard error is the standard deviation associated with the population of means (i.e., the standard deviation of the mean): $\sigma_{\bar{X}} = \sigma / \sqrt{n}$. If the sample size n gets very large, the standard error approaches zero. What about the estimate from the one sample an epidemiologist actually collects? The estimated standard error (usually called simply the standard error) is $s/\sqrt{n}$, which is the standard deviation of $\bar{X}$, regardless of whether original data follow a normal distribution.

Clinical researchers often find that hypothesis testing for continuous variables is helpful. One-sample tests can be used to determine whether the sample differs from the reference population with respect to continuous variables such as APACHE III scores. Clinical investigators often use two-sample tests during exploratory data analysis to identify potentially important continuous risk factors such as age and temperature at admission.

The following two sections describe statistical methods for one- and two-sample tests for continuous variables (*1–4*,5,*7*,8,*9*,*16*). These sections are not designed as casual reading material; instead, they provide a concise reference of commonly used statistical methods. Each section follows the same format as has been described for hypothesis tests for categorical variables.

One-Sample Tests for a Continuous Variable

One-Sample Test for a Mean Provided that the sample size is adequate (e.g., 20 or more) and the distribution is approximately normal, a two-sided hypothesis test is conducted as follows.

Step 1. Set up H_0 and H_1.

$$H_0: \mu = \mu_0 \text{ versus } H_1: \mu \neq \mu_0,$$

where μ is the mean of the population from which the sample is obtained and μ_0 is the mean of the norm group.

Step 2. Choose α, power, and the difference between μ and μ_0 that is clinically meaningful.

Step 3. Using an available computer package, determine sample size n. Sample size is very sensitive to the difference between means, μ–μ_0, where μ is the mean of the population from which the sample is obtained and μ_0 is the mean of the norm group. This difference, also called the effect size, should be the difference that is biologically or clinically meaningful in the opinion of the researcher. When no information is available, a pilot study can be conducted to get some idea of the difference that can be obtained in a particular clinical situation.

Computer packages provide easily used algorithms for obtaining sample size estimates. If the estimated sample size n is relatively small (i.e., less than 30), that value should be adjusted by multiplying by the correction

factor $(t_{[0.975,n-1]}/z_{0.975})^2$, where $t_{[0.975,n-1]}$ is the *t*-score from a *t* distribution with $(n-1)$ degrees of freedom and *n* is the estimated sample size obtained from a computer package.

Step 4. Obtain data.

Step 5. Compute test statistic in terms of parameters under H_0, which follows a *t* distribution with $(n-1)$ degrees of freedom, and obtain the *p* value as twice the probability associated with the t_s, assuming that H_0 is correct. Like the standard normal distribution, the *t* distribution is symmetric; however, for each different degree of freedom, there is a different distribution. If the sample size is 100 or more, the *t* distribution resembles the standard normal distribution.

$$t_s = \frac{(\bar{X} - \mu_0)}{s/\sqrt{n}},$$

where $\bar{X}$ is the estimate of the mean obtained from the sample; μ_0 is the mean if H_0 is true; and $s/\sqrt{n}$ is the standard deviation of the mean estimated from the sample. The *p* value is twice the probability associated with the test statistic t_s with $(n-1)$ degrees of freedom, assuming that H_0 is correct.

Step 6. Decide whether to reject or fail to reject H_0. Compare the *p* value to α.

If the hypothesis test is one-sided (e.g., $H_1: \mu > \mu_0$), calculate power and estimate sample size substituting α for $\alpha/2$ in the previous formulas. In addition, the *p* value is not multiplied by 2. It is always easier to reject a one-sided test than a similar two-sided test. Furthermore, an effectively larger α increases power by reducing β.

One-Sample Test for a Variance or Standard Deviation The most frequently used hypothesis test for variances or standard deviations is the two-sided test, which is conducted as follows.

Step 1. Set up H_0 and H_1 in terms of σ^2 and σ_0^2.

$$H_0: \sigma^2 = \sigma_0^2 \text{ versus } H_1: \sigma^2 \neq \sigma_0^2,$$

where σ^2 is the variance of the population from which the sample was chosen and σ_0^2 is the variance of the norm group.

Step 2. Compute test statistic in terms of parameters under H_0, which follows a χ^2 distribution with $(n-1)$ degrees of freedom, and obtain the *p* value as twice the probability associated with the χ_s^2, assuming that H_0 is correct. Unlike the standard normal distribution, the χ^2 distribution is not symmetric. For each different degree of freedom, there is a different distribution. If the sample size is 100 or more, the χ^2 distribution resembles the standard normal distribution.

$$\chi^2 = \frac{(n-1)s^2}{\sigma_0^2},$$

where s^2 is the sample variance for the variable of interest; *n* is the sample size; and σ_0^2 is the variance if H_0 is true. The *p* value is twice the probability associated with the test statistic χ_s^2 with $(n-1)$ degrees of freedom, assuming that H_0 is correct.

Step 3. Decide whether to reject or fail to reject H_0. Compare the *p* value to α.

If the hypothesis test is one-sided (e.g., $H_1: \sigma^2 > \sigma_0^2$), the *p* value is not multiplied by 2. Sample size and power are based on the ratio of the standard deviations that the healthcare epidemiologist chooses as clinically important.

Two-Sample Tests for a Continuous Variable When the random variable under study is a continuous variable, hypothesis testing and methods of inference should reflect the data structure. Before formulating the hypothesis, the investigator must determine whether the samples are independent or not.

Two-Sample Paired Test for Means Paired samples are frequently encountered in biologic and health science research. For paired samples, a paired *t*-test is used. In follow-up or longitudinal studies, paired samples may represent two sets of measurements on the same individuals. Alternatively, paired samples may represent measurements on different individuals, matched such that each member of the pair is very similar to the other. In analyzing data from paired samples, the clinical investigator assumes that for the variable of interest, the mean difference, Δ, between paired observations is the same for all pairs.

Step 1. Set up H_0 and H_1.

$$H_0: \Delta = 0 \text{ versus } H_1: \Delta \neq 0$$

Step 2. Choose α, power, and the difference, Δ, that is clinically meaningful.

Step 3. Using one of the available computer packages, determine sample size *n*. Sample size is very sensitive to the mean difference. This difference, also called the effect size, should be that difference which is biologically or clinically meaningful in the opinion of the researcher. When no information is available, a pilot study can be conducted to get some idea of the mean difference that can be obtained in a particular clinical situation.

Step 4. Obtain data.

Step 5. Compute test statistic in terms of parameters under H_0, which follows a *t* distribution with $(n-1)$ degrees of freedom where *n* is the number of pairs, and obtain the *p* value as twice the probability associated with the t_s.

$$t_s = \frac{(\bar{X}_D)}{s_D/\sqrt{n}},$$

where $\bar{X}_D$ is the mean of the differences between pairs in the sample; s_D is the standard deviation of the difference between pairs in the sample; and *n* is the number of pairs. The *p* value is twice the probability associated with the test statistic t_s (assuming that H_0 is correct) with $(n-1)$ degrees of freedom where *n* is the number of pairs.

Step 6. Decide whether to reject or fail to reject H_0. Compare the *p* value to α.

If the hypothesis test is one-sided (i.e., $H_1: \Delta > 0$), calculate power and estimate sample size substituting α for $\alpha/2$ in the previous formulas. In addition, the *p* value is not multiplied by 2. It is always easier to reject a one-sided test than a similar two-sided test. Furthermore, an effectively larger α increases power by reducing β.

Two-Sample (Independent) Test for Means Independent samples are frequently encountered in biologic and health

science research. For independent samples, a *t*-test for independent samples is used. Continuous variables from cross-sectional studies involving two groups are often analyzed with independent *t*-tests.

Step 1. Set up H_0 and H_1.

$$H_0 : \mu_1 = \mu_2 \text{ versus } H_1 : \mu_1 \neq \mu_2 \quad \text{and}$$
$$H_0' : \sigma_1^2 = \sigma_2^2 \text{ versus } H_1' : \sigma_1^2 \neq \sigma_2^2$$

where μ_1 and σ_1^2 are the mean and variance of the population from which the first sample was chosen and μ_2 and σ_2^2 are the mean and variance of the population from which the second sample was chosen.

Step 2. Choose α, power, and the difference between μ_1 and μ_2 that is clinically meaningful.

Step 3. Using an appropriate computer package, determine sample size for each group, n_1 and n_2. Sample size is very sensitive to the difference between group means. This difference, also called the effect size, should be that difference which is biologically or clinically meaningful in the opinion of the researcher. When no information is available, a pilot study can be conducted to get some idea of differences between μ_1 and μ_2 that can be obtained in a particular clinical situation.

If the variances in the two groups are the same, the smallest total sample size involves equal sample sizes in each group. Sometimes it is not possible or practical to have equal sample sizes and the clinical investigator will specify different numbers of subjects in each group, usually in multiples of the smaller group size.

Step 4. Obtain data.

Step 5a. Compute test statistic in terms of parameters under H_0'. If the assumption about equal variances for the two samples is doubted, the investigator can use an *F*-test, commonly called *F'*, to determine the validity of this assumption. Under $H_0', F_s' = s_1^2 / s_2^2$ where s_1^2 is the variance estimated from the first sample and s_2^2 is the variance estimated from the second sample; F_s' follows an *F*-distribution with $\upsilon_1 = (n_1 - 1)$ and $\upsilon_2 = (n_2 - 1)$ degrees of freedom. For practical purposes, most textbooks recommend the following: label the populations (and hence the samples) such that $s_1^2 > s_2^2$ (i.e., $F_s' > 1.0$). Then, reject H_0' if $F_s' > F_{0.95}$ with υ_1 and υ_2 degrees of freedom, or $F_{0.95[\upsilon 1, \upsilon 2]}$. This is still a test at the α level of significance, but the upper tail value is used in determining the *p* value. If $p < .05$, the investigator rejects the assumption of equal variances and uses the Behrens–Fisher *t*-test, also called Satterthwaite's method. If $p > .05$, the investigator maintains the assumption of equal variances and uses Student's *t*-test. With general use of computers, restricting F_s' to be larger than 1.0 is no longer necessary. Therefore, the α level of significance for a comparable two-sided test is 0.10. Computer packages vary in reporting one- or two-sided *p* values; the investigator should check documentation to verify the nature of the *p* values.

Step 5b. For Student's *t*-test, compute test statistic in terms of parameters under H_0.

$$t_s = \frac{(\bar{X}_1 - \bar{X}_2)}{s_p \times \sqrt{(1/n_1 + 1/n_2)}},$$

where $\bar{X}_1$ is the sample mean obtained from the first sample; $\bar{X}_2$ is the sample mean obtained from the second sample; and s_p is the pooled sample standard deviation. The investigator obtains s_p by taking the square root and of the pooled sample variance, s_p^2.

The difference between two means follows a *t* distribution with $(n_1 + n_2 - 2)$ degrees of freedom. The *p* value is twice the probability associated with the test statistic t_s with $(n_1 + n_2 - 2)$ degrees of freedom, assuming that H_0 is correct.

For the Behrens–Fisher *t*-test

$$t_s = \frac{\bar{X}_1 - \bar{X}_2}{\sqrt{(s_1/n_1 + s_2/n_2)}},$$

where $\bar{X}_1$ is the sample mean obtained from the first sample; $\bar{X}_2$ is the sample mean obtained from the second sample; s_1^2 is the sample variance from the first sample; s_2^2 is the sample variance from the second sample; n_1 is the number of observations in the first sample; and n_2 is the number of observations in the second sample. The appropriate degrees of freedom (d') must now be calculated based on s_1^2, s_2^2, n_1, and n_2.

The *p* value is twice the probability associated with the test statistic t_s (assuming that H_0 is correct) with (d') degrees of freedom.

Step 6. Decide whether to reject or fail to reject H_0. Compare the *p* value to α.

If the hypothesis test is one-sided (i.e., H_1: $\mu_1 > \mu_2$ or $\mu_1 < \mu_2$), calculate power and estimate sample size substituting α for $\alpha/2$ in the previous formulas. In addition, the *p* value is not multiplied by 2. It is always easier to reject a one-sided test than a similar two-sided test. Furthermore, an effectively larger α increases power by reducing β.

Hypothesis Tests for Ranked Data

If the central limit theorem is not applicable, the clinical investigator must use nonparametric statistical methods to analyze data and make inferences (*1–4*,5,7,8,*12*). A more descriptive term for these methods is *distribution-free methods*. In general, nonparametric methods are more flexible than parametric methods, because nonparametric methods require fewer or no assumptions about the shape of the underlying distribution.

Distribution-free methods are required when the data are ordinal. Ordinal data are data that can be ordered but do not have specific numeric values. Measurement data are data that lie on a scale wherein common arithmetic is meaningful. In contrast, ordinal variables cannot be given a numerical scale that makes sense biologically or clinically. Essentially, the ranks are arbitrarily assigned; these could be reversed and still retain the same meaning for the researcher. Therefore, computation of means and standard deviations is absurd, because there would be no universally accepted meaning (outside of a researcher's laboratory or clinic). Medians and ranges are used instead.

A clinical investigator can apply nonparametric tests to any measurement data. This application may be particularly appropriate when the assumption of normality appears to be grossly violated. If the actual underlying distribution is in fact normal, the clinical investigator will pay a penalty, because in this situation the nonparametric counterpart for a parametric test statistic has less power.

Often, data are not normally distributed, even though a reasonable assumption has been made that the underlying (i.e., theoretical) distribution is normal. Parametric methods are often robust enough to withstand certain departures from normality. Some statisticians recommend that investigators analyze continuous data by both parametric and nonparametric methods. If the results of both analyses are consistent, the researcher is assured that the result reported from the parametric test is probably not biased. However, results from these analyses may not be consistent (i.e., the result from one analysis may be significant and the result from the other be very far from significance). In this event, the result from the parametric test is probably biased. After reviewing the data carefully, the researcher should (a) consider options for transforming the data so that the parametric test is valid or (b) report the result from the nonparametric test. Whenever it is appropriate to use nonparametric methods, these are usually more powerful than their parametric counterparts, and the results of tests are unbiased.

The following section describes nonparametric statistical methods for two-sample tests on ordinal (i.e., ranked) and continuous variables (*1–4*,5,*7*,8,*12*). These sections are not designed as casual reading material; instead, they provide a concise reference of commonly used statistical methods.

Sign Test This test was named because it depends only on the sign of the differences in responses between matched subjects in the treatment and control groups (or, alternatively, exposed and unexposed; survivors and nonsurvivors) and not on the magnitude of the actual differences, Δ. This test can also be used for paired observations on the same individual (e.g., before and after treatment). Under some conditions, we cannot observe an actual difference, D, between two treatments but can only observe if the differences are negative or worse (i.e., $D < 0$), positive or better (i.e., $D > 0$), or not apparent or discernible (i.e., $D = 0$). The sign test is based on the number of positive (i.e., $D > 0$) differences out of the total number of nonzero differences; all differences with a zero outcome are excluded from analysis. The sign test is a two-sided test. If the number of nonzero responses is greater than or equal to 20, the normal approximation to the binomial applies and the sign test is the same as McNemar's test (see the section on two-sample test for paired samples). If the number of nonzero responses is <20, exact binomial probabilities must be obtained.

Wilcoxon Signed Rank Test The Wilcoxon sign rank test may be applied to ordinal or measurement data. This test is the nonparametric counterpart for the paired *t*-test. This test is based on the ranks of the observations rather than on their actual values. It is more powerful than the sign test, because both the sign and the magnitude of the differences, based on rank, are used in computing the test statistic. If the distribution is normal, this test has less power than the paired *t*-test; otherwise, it is the more powerful test. This test should be used only when the number of nonzero differences is ≥16. For computation of the test statistic, see Rosner (8).

Wilcoxon Rank Sum Test and the Mann–Whitney U-Test The Wilcoxon rank sum test was developed for ranked or ordinal data; the Mann–Whitney *U*-Test was developed for comparisons that come from underlying distributions that are continuous. These tests are the nonparametric counterparts of the *t*-test for two independent samples. These tests, based on the ranks of the individual observations rather than on the actual values, should be used only when n_1 and n_2 are both ≥10. For computation of the test statistic, see Rosner (8).

POINT AND INTERVAL ESTIMATION

In the epidemiologic literature, interval estimation is more common than hypothesis testing. Confidence intervals from a single sample can be used to determine estimated upper and lower limits for a parameter from the reference population. Often, clinical investigators divide the sample into two or more groups according to certain characteristics and estimate confidence intervals (CIs) for each group. Using the previous example, the epidemiologist may be comparing the incidence of healthcare-associated pneumonia among patients who were ventilated to the incidence of healthcare-associated pneumonia among patients who were not ventilated. The following sections address general definitions and rules for estimating CIs, one- and two-sided CIs for categorical and continuous variables, and CIs for statistics with special application to epidemiology (*1–4*,5,8,*9*,*12*,15,*16*,20).

Definition and Rules

First, an epidemiologist estimates parameters according to data obtained from the sample. These estimates are called *point estimates*. For estimating the CI, the epidemiologist uses the point estimate from the sample and the standard deviation of that point estimate to compute a lower confidence limit, L_L, and an upper confidence limit, L_U. The confidence limits are affected by the level of confidence that the epidemiologist wishes to place in the statement. Typically, epidemiologists report 95% CIs; 95%, called the coefficient of confidence, equals $(1-\alpha)100\%$. Other traditional levels of confidence are 90% and 99%. It is crucial that the investigator state what level of confidence has been chosen. Often, the clinical investigator has a conflicting problem between having a high level of confidence and a CI that is not too large. For a specified level of confidence, increasing the sample size is the only option available to the epidemiologist for reducing the length of a CI. If the sample size must remain reasonably small, the epidemiologist may have to choose a lower level of confidence (e.g., 90%). The meaning of a CI is as follows: with repeated experiments, for each sample a different lower limit, L_L, and an upper limit, L_U, will be computed, because both the point estimate and standard deviation of that point estimate will be different for each sample; $(1-\alpha)100\%$ of the CIs will include the parameter and $\alpha 100\%$ will not. Thus, an investigator can state with $(1-\alpha)100\%$ confidence that the interval based on the sample contains the parameter. How does an epidemiologist obtain confidence limits, L_L and L_U?

Point and Interval Estimation for a Continuous Variable

Point and Interval Estimation for Means The point estimate for μ is $\bar{X}$. A more informative way of writing this point estimate is $\bar{X} \pm s_{\bar{X}}$ where $ss_{\bar{X}} = s/\sqrt{n}$. The second expression tells something about the precision of the estimate of the mean—the standard error or standard deviation of $\bar{X}$. Thus, it is not sufficient to give only $\bar{X}$. A two-sided 95% CI for μ is calculated as follows:

$$\bar{X} \pm \left(t_{[.975,n-1]} s_{\bar{X}}\right)$$

μ is fixed; L_L and L_U are variable so that $(1-\alpha)100\%$ of the intervals will contain μ. $\bar{X}$ and s both change with each new sample—thus, both location and length of the CI will change from one sample to the next. Because the t distribution is symmetric, $t_{0.025[n-1]}$ equals $-t_{0.975[n-1]}$.

Because the length of the CI depends on the sample through s, the healthcare epidemiologist must know something about s before making any decisions about sample size. The length of a two-sided $(1-\alpha)\%$ CI, L, is $2 \times t_{1-\alpha/2[n-1]} \times s/\sqrt{n}$. If the future value of σ can be estimated, sample size can be determined using an appropriate statistical package as

$$n' = [2 \times t_{1-\alpha/2[n-1]} \times s/L]^2$$

This number, n', underestimates the required sample size, because $t_{0.975[n-1]}$ is always larger than $z_{0.975}$. Thus, by multiplying n' by the squared ratio of the t-score with $(n'-1)$ degrees of freedom to the z-score, the adjusted sample, n_{adj}, can be obtained.

For observational studies, sample size determination relies heavily on how well the actual sample reflects the assumptions used to obtain sample size. Although there are no guarantees, sample size determination gives the clinical investigator some general idea of how large a sample may be needed.

Point and Interval Estimation for Variances and Standard Deviations The unbiased estimator of σ^2 is the sample variance, s^2. If the underlying distribution of the variable is normal, reliable estimates of CIs can be obtained. If the underlying distribution of the variable is not normal, the following methods may not be reliable. Variances do not follow a symmetric distribution. The ratio of s^2 to σ^2 follows a chi-square distribution with $(n-1)$ degrees of freedom, $\chi^2_{[n-1]}$. Note that the χ^2 distribution is not symmetric; thus, a CI for a variance or a standard deviation is not symmetric. A CI for a variance can be estimated using the following formula:

$$L_L = \frac{(n-1)s^2}{\chi^2_{[0.975,n-1]}} \quad \text{and} \quad L_U = \frac{(n-1)s^2}{\chi^2_{[0.025,n-1]}},$$

where L_L and L_U are always positive. A CI for σ is obtained by taking the square root of L_L and L_U. As the confidence increases, the length will increase. Reducing the length requires a reduction in confidence or an increase in sample size. As the sample size increases, the CI will become less skewed. These limits are independent of the estimated mean.

Point and Interval Estimation for a Binomial Proportion or Rate

The point estimate of π is p, estimated from the sample. When there is only one group with two outcome possibilities (i.e., survival and nonsurvival), the unbiased estimator of p is the proportion of the sample with the characteristic. The standard deviation of p is estimated by $\sqrt{pq/n}$. For a large sample, p is distributed normally with mean p and variance pq/n. Generally, the assumption of normality is valid when npq is >5.

Under the assumption of normality, approximate CIs for π can be obtained as follows:

$$p \pm \left(z_{1-\alpha/2} \times \sqrt{pq/n}\right)$$

The length of a two-sided $(1-\alpha)\%$ CI, L, is $2 \times z_{1-\alpha/2} \times \sqrt{pq/n}$. Sample size can be determined as follows: $n = [(2 \times 1.96pq)/L]^2$. Because the standard normal distribution is symmetric, $z_{0.025}$ equals $-z_{0.975}$. There are many other formulas for computing CIs for proportions and rates; the reader is referred to Rosner (8) and Fleiss et al. (15).

Point and Interval Estimation for Risk Ratios and Odds Ratios

For independent samples, a clinical investigator uses data displayed in 2 × 2 tables to estimate the RR or the OR. Whether the data reflect incidence or prevalence determines which statistic is estimated. Throughout this section, it is assumed that the clinical investigator has displayed the data such that exposure to the ventilator is the first column and presence of pneumonia is the first row.

When incidence of disease for the sample is known, the epidemiologist is interested in estimating the RR of disease, which is the ratio of two conditional probabilities. In the previous example, the RR of pneumonia is $\Pr(P|V)/\Pr(P|\not V)$.

	Exposed to Ventilator	*Not Exposed to Ventilator*	*Total or Marginal Probability of Disease*
Pneumonia present	$\Pr(V) \times \Pr(P\|V)$	$\Pr(\not V) \times \Pr(P\|\not V)$	$\Pr(P)$
Pneumonia absent	$\Pr(V) \times \Pr(\not P\|V)$	$\Pr(\not V) \times \Pr(\not P\|\not V)$	$\Pr(\not P)$
Probability of exposure	$\Pr(V)$	$\Pr(\not V)$	1.0

Conditional probabilities may be obtained as column probabilities by dividing the joint probability in each cell by the respective total probability of exposure. For the a-cell, $\Pr(V) \times \Pr(P|V)/\Pr(V) = \Pr(P|V)$.

After completing the process for each of the four cells, the clinical investigator obtains the following 2 × 2 table containing only conditional probabilities, that is, probabilities conditioned on exposure:

	Exposed to Ventilator	*Not Exposed to Ventilator*
Pneumonia present	$\Pr(P \mid V)$	$\Pr(P \mid \not V)$
Pneumonia absent	$\Pr(\not P \mid V)$	$\Pr(\not P \mid \not V)$
Probability of exposure	1.0	1.0

From this table, the RR can easily be obtained by dividing the conditional probability of developing pneumonia for those exposed to the ventilator by the conditional probability of developing pneumonia of those who were not so exposed: $\Pr(P \mid V)/\Pr(P \mid \not V)$. If $\Pr(P \mid V) = 0.25$ and $\Pr(P \mid \not V) = .167$, RR equals 1.497. The interpretation of the RR is as follows: patients who are ventilated are 1.497 times as likely to have pneumonia as those who are not ventilated.

Under the assumption of normality, approximate CIs for RR can be obtained as follows:

$$L_L = \mathrm{RR}(\exp[-z_{0.975}/s_{\mathrm{RR}}])$$
$$L_U = \mathrm{RR}(\exp[z_{0.975}/s_{\mathrm{RR}}])$$

where RR is estimated from the sample; $z_{0.975} = 1.96$; $\exp(x) = e^x$; and

$$s_{\mathrm{RR}} = \sqrt{[(1-\Pr(P \mid V))/n_{11} + (1-\Pr(P \mid \not V))/n_{12}]},$$

where n_{11} is the number of patients with pneumonia and exposure to the ventilator and n_{12} is the number of patients with pneumonia and no exposure to the ventilator.

When prevalence of disease for the sample is known, the epidemiologist estimates the odds in favor of disease based on joint probabilities. In the following table, p_1, p_2, p_3, and p_4 are joint probabilities. For example, p_1 is the joint probability of a patient having both exposure to the ventilator and presence of pneumonia. The OR equals a ratio with p_1/p_3 in the numerator and p_2/p_4 in the denominator. This expression can be simplified as follows: $\mathrm{OR} = (p_1p_4)/(p_2p_3)$.

	Exposed to Ventilator	*Not Exposed to Ventilator*	*Total or Marginal Probability of Disease*
Pneumonia present	p_1	p_2	$p_1 + p_2$
Pneumonia absent	p_3	p_4	$p_3 + p_4$
Total or marginal probability of exposure	$p_1 + p_3$	$p_2 + p_4$	1.0

Under the assumption of normality, approximate CIs for OR can be obtained as follows:

$$L_L = \mathrm{OR}[\exp(-z_{0.975}/s_{\mathrm{OR}})]$$
$$L_U = \mathrm{OR}[\exp(z_{0.975}/s_{\mathrm{OR}})]$$

where OR is the OR estimated from the sample; $z_{0.975}$ is 1.96; $\exp(x) = e^x$; and

$$s_{\mathrm{OR}} = \sqrt{[(1/n_{11} + 1/n_{12} + 1/n_{21} + 1/n_{22})]},$$

where n_{11} is the number of patients with pneumonia and with exposure to the ventilator; n_{12} is the number of patients with pneumonia and without exposure to the ventilator; n_{21} is the number of patients without pneumonia and with exposure to the ventilator; and n_{22} is the number of patients without pneumonia and without exposure to the ventilator.

For matched pairs, the clinical investigator can estimate RRs and ORs from stratified analyses. Methods for point and interval estimation are covered in that section.

Relationship Between CIs and Hypothesis Testing

CIs give a range of values within which the parameter (e.g., μ, σ, σ^2, π, RR, or OR) is likely to fall. When reporting CIs, the clinical investigator does not use a *p* value; however, the parameter estimate, the level of confidence, and the standard deviation of the estimate (i.e., the standard error) are reported. Conversely, when a hypothesis has been tested, the investigator should report the *p* value, the parameter estimate, and the standard deviation of the estimate (i.e., standard error). Sample size is as important for estimation of CIs as it is for testing hypotheses. In general, if H_0 is rejected, the corresponding CI does not contain the parameter under H_0. The one-to-one relationship between a CI and the corresponding hypothesis test is easiest to represent with the two-sided case. For completeness, it is a good practice for clinical investigators to provide enough information that both CIs and *p* values are obvious to anyone reading the report. In practice, editorial policies of various journals may restrict an investigator's report to either CIs or *p* values.

REGRESSION AND CORRELATION COEFFICIENTS

A clinical investigator uses regression or correlation analysis when the objective of the study is determining the functional relationship between two or more variables measured on the same individual. There are comparable regression and correlation methods for continuous and discrete variables.

Uses of Regression Analysis

Regression analysis has several applications that are relevant to epidemiologic studies (*1*,*2*,28). The first application is the study of causation. When looking for causal relationships, an epidemiologist must be aware that, although a cause-and-effect relationship may exist between two variables of interest, regression analysis cannot establish that the relationship is actually causal. Often, the study of causation will involve the second application of regression analysis for health science research—prediction. Nomograms, widely used in the clinical setting, have usually been developed from regression analysis. Third, the epidemiologist can use regression analysis to identify easily measured variables that can be substituted reliably for

others that may be difficult, expensive, or hazardous to collect. Substituting one variable for another does require a previous experimental study to establish the relationship between the variable of interest and the surrogate variable. A fourth commonly used application is controlling for one or more extraneous or confounding variables. After controlling statistically for a variable that cannot be controlled by experimental design, the clinical investigator can make more precise inferences about the relationship between the two variables of primary interest, usually exposure and outcome (or disease). Age, sex, weight, severity of illness, and type of infection are examples of common confounding variables. In a purely experimental setting, confounding variables can often be controlled or eliminated. However, in a naturalistic setting, the investigator must rely on statistical control. Finally, inverse regression or calibration is used for obtaining many assay results.

Regression Coefficients

In the simplest situation, the clinical investigator wishes to quantify the relationship between two variables, X and Y. For regression analysis, the convention is to call X the independent variable and Y the dependent variable. Another term for X is *explanatory variable*. Clinical investigators often call Y the *response variable*. Generally, the investigator is trying to predict Y from X (i.e., $Y|X$, read Y given X).

In regression analysis, the clinical investigator must describe the functional relationship between X and Y in terms of an ideal mathematical relationship or model, symbolized as $Y = F(X)$, which states that Y is a function (i.e., F) of X. The experienced investigator understands that the relationship between X and Y can take many forms. If the relationship is linear, the functional relationship can be symbolized as $F(X) = \alpha + \beta X$. Some relationships are curvilinear, requiring the addition of a quadratic term to the mathematical model: $F(X) = \alpha + \beta X + \gamma X^2$. Some curvilinear relationships vary episodically over a day or month and can be described reasonably well with sinusoidal functions: $F(X) = \alpha + \beta \sin X$. Some relationships are not linear; two examples are $F(X) = \alpha + \beta\sqrt{X}$ and $F(X) = \alpha + \beta/X$.

For the models presented in the preceding paragraph, the investigator can make these relationships linear by using transformations of X, Y, or both. Therefore, statisticians call these relationships intrinsically linear. The term *intrinsically linear* means that the parameters, such as α and β, are linearly related to X and Y. Some relationships are intrinsically nonlinear, meaning that the relationship of X and Y to the parameters is not linear: $F(X) = \alpha + \beta e^{-\gamma X}$. Special methods are needed for estimating regression coefficients when the relationship has a nonlinear functional form.

In nature, the observed relationship is never exact; because of natural variability, there is always some deviation from the ideal mathematical relationship or model. Thus, the clinical investigator describes the functional relationship in terms of a statistical relationship: $Y = F(X) + \varepsilon$, where ε is distributed normally with mean 0 and variance σ_ε^2. Conceptually, ε is an error term and σ_ε^2 represents the variance of Y for a given X. The investigator assumes that X is measured or controlled perfectly, thereby not contributing to the natural variability of Y. Collectively, the error terms are called the residuals, which are random deviations in Y from the ideal relationship. Thus, ε is a random variable that measures the deviation of each individual observation, Y_i, from $\mu_{Y|X}$ (i.e., the expected value of Y_i on the regression line). Furthermore, σ_ε^2 is independent of X. For example, σ_ε^2 is the same for both small and large values of X. The clinical investigator uses the residuals to determine if there is a linear relationship based on the data.

Simple Linear Regression Coefficients

Simple linear regression is the term for linear regression with only one independent variable (*1–4*,5,*6*,*7*,8,*9*,*10*,*12*,*16*, 28,*29*,30,*31*). For a simple linear regression, $Y = \alpha + \beta X + \varepsilon$, the parameters α and β are unknown and must be estimated from the data with statistics. The line $Y = \alpha + \beta X$ is defined as the regression line, where α is the intercept (i.e., the value on the Y-axis that corresponds to $X = 0$), and β is the slope. The regression line describes the regression of Y on X. The slope may be positive, indicating that as X increases, the expected value of Y increases. Similarly, the slope may be negative, indicating that as X increases, the expected value of Y decreases. Finally, the slope may be zero, depicting a horizontal line and indicating that there is no relationship between X and Y. By accounting for the systematic relationship between X and Y, the investigator reduces the total variability of Y. Even if a linear relationship exists, all observations could be displayed on one axis (i.e., the Y-axis) only; however, the variation in Y would be much larger (s_Y^2) , because no attempt has been made to account or adjust for the variability in the X values that contributes to the variability of Y.

Estimating the Intercept and Slope Plotting the data is an important step, because the graph is useful for suggesting whether there is a linear relationship. The difference between Y_i, the actual observation, and the corresponding expected value on the line, $\mu_{Y|X}$, reflects ε_i, the deviation for the particular observation. Some of these differences are positive and others are negative. The sum of the deviations (vertical deviations) is zero (i.e., $\sum_{i=1}^{n} \varepsilon_i = 0$). The investigator uses the method of least squares to minimize the squared deviation between the line and the observations.

Estimate of the Slope The investigator estimates β from the data, using the following formula:

$$b = \frac{s_{XY}}{s_X^2},$$

where the numerator is the sample covariance between X and Y, and the denominator is the sample variance of X. The covariance can be either negative or positive; the variance is always positive. One should note that a small value of β does not necessarily imply that the relationship is not strong between X and Y. By itself, b (as an estimate of β) does not tell whether there is any relationship between X and Y. An experienced investigator realizes that a change of units usually makes the size of the regression coefficient change. To determine whether the relationship is strong, the investigator has to know b relative to s_ε^2, the estimated variance of the residuals.

Estimate of the Intercept The estimate of α is a function of b: $\hat{\alpha} = \bar{Y} - b\bar{X}$, where $\bar{Y}$ is the estimated mean of Y and $\bar{X}$ is the estimated mean of X. Estimation of α is based on the premise that two points are necessary to determine a line. Thus, every regression line goes through the point $(\bar{X}, \bar{Y})$ and the Y-intercept. If the point $(\bar{X}, \bar{Y})$ and the estimated slope b are known, then the estimate of α is based on simple algebra.

Simple Linear Regression Analysis

Interpreting Residuals The assumptions on which linear regression is based are that the residuals are independently and identically distributed normally with mean 0 and variance σ_ε^2. One or more of these assumptions may be violated. In practice, a clinical investigator detects any violation of these assumptions by plotting the residuals and conducting certain hypothesis tests (*1*,*2*,28,*29*,30,*31*,32). The investigator applies diagnostic procedures to various plots of residuals and determines how the assumptions may be violated. Generally, lack of randomness in the residuals has some implications about possible violations. First, randomness or lack of randomness can be determined by examining a graph of the residuals plotted against the values of X. For example, plotting the residuals may reveal evidence of heteroscedasticity, which means unequal variances. In the clinical setting, heteroscedasticity is often characterized by increasing residuals as X increases. Second, systematic differences or deviations from the regression line are often revealed in a graph with actual values plotted on the X and Y axes and the predicted values superimposed on the same graph. Systematic deviations of the actual values from predicted values may indicate that a straight-line relationship is not the best fit. Third, plotting of actual values may reveal one or more points that are outliers and, as such, are influential points. Influential points often cause spurious results by drastically changing the estimated slope and intercept from what would have been expected had the influential points not been included in the analysis. Finally, the investigator chooses appropriate ways of dealing with the problem or problems. Typically, the investigator can make transformations or adjust the data in other appropriate ways so that the residuals will meet these assumptions. After the investigator has taken remedial action, the resulting graphs should reveal that the residuals meet the assumptions.

Prediction or Estimation of $\mu_{Y|X} = a + bX$ For a given value of X, $\hat{Y}$ is the estimation of $\mu_{Y|X}$ and is the corresponding point on the estimated regression line. Thus, the estimated regression line is composed of $\hat{Y}$s or expected values of Y across all values of X included in the study. Hence, $\hat{Y}$ is the estimate of the average response for a given X and is regarded as the predicted value of Y for a particular value of X. Interpolation within the range of the data is acceptable. Extrapolation is dangerous. Caution is needed when we are using any prediction equation outside the range covered by the X values in the study. Beyond these values, the relationship may no longer be linear.

Method of Least Squares The numerator of the sample variance for Y is $\sum_{i=1}^{n}(Y_i - \bar{Y})^2$. Another name for this expression is the total corrected sum of squares where *corrected* refers to the deviation of each observation from the mean (i.e., corrected for the mean). In some statistics texts, the total corrected sum of squares is abbreviated as CSS. Frequently, clinical investigators use the method of least squares to partition the total CSS for Y into two parts: (a) the sum of squares due to regression (i.e., regression SS or model SS) and (b) the residual or error sum of squares (i.e., residual SS or error SS).

As stated previously, the point $(\bar{X}, \bar{Y})$ always lies on the regression line. For any sample point, the total vertical deviation of each point (X_i, Y_i) from $(\bar{X}, \bar{Y})$ is the vertical distance that Y_i lies from the mean $\bar{Y}$; thus, measured on the Y-axis, the total deviation is $(Y_i - \bar{Y})$ (Fig. 3-1). The regression component of that point (X_i, Y_i) is the vertical distance from $(\bar{X}, \bar{Y})$ to the predicted value on the regression line $(X_i, \hat{Y}_i)$ measured on the Y-axis; thus, on the Y-axis, the regression component is the quantity $(\hat{Y}_i - \bar{Y})$ (Fig. 3-1). Now, for any sample point, the residual component

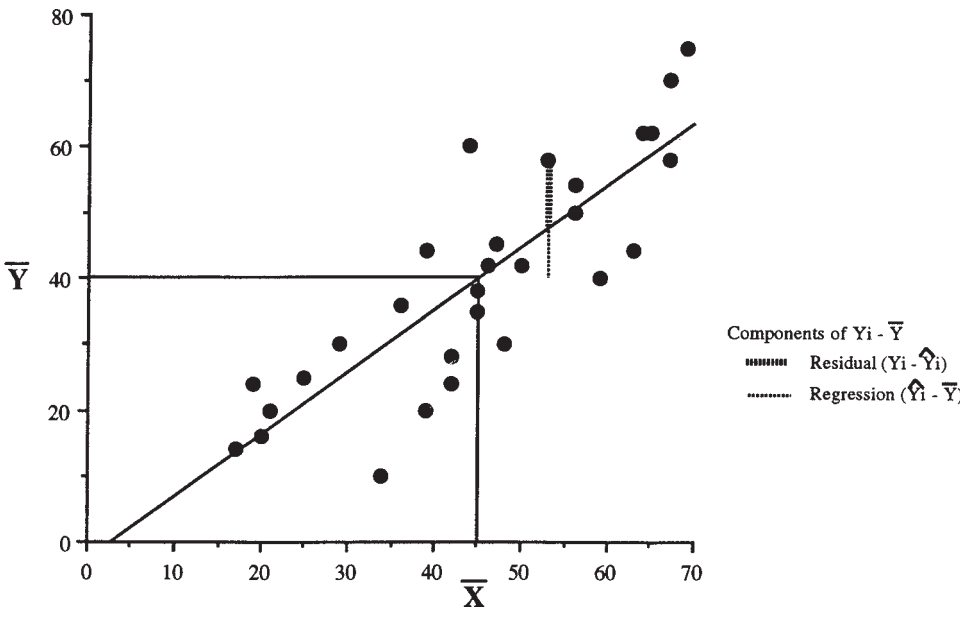

FIGURE 3-1 The total vertical deviation of each sample point (X_i, Y_i) from $(\bar{X}, \bar{Y})$ is divided into two components: the residual component $(Y_i - \hat{Y}_i)$ and the regression component $(\hat{Y}_i - \bar{Y})$. All three distances are measured on the Y-axis.

(i.e., residual) of that point about the regression line is the vertical distance from the actual observation (X_i, Y_i) to the predicted value on the regression line $(X_i, \hat{Y}_i)$; thus, on the *Y*-axis, the residual component is the quantity $(Y_i - \hat{Y}_i)$ (Fig. 3-1). Therefore, the total deviation $(Y_i - \bar{Y})$ of each point from the regression line can be separated into residual and regression components.

In using the least squares method, the investigator squares and sums the total deviations, the regression components, and the residuals: $\sum(Y_i - \bar{Y})^2 = \sum(\hat{Y}_i - \bar{Y})^2 + \sum(Y_i - \hat{Y}_i)^2$. The residual sum of squares (SS) tells the investigator how well the regression line fits the data. However, the investigator needs a formal goodness-of-fit test to assess whether this value is large or small. Partitioning the total corrected SS allows the investigator to construct an analysis of variance (ANOVA) table. The total deviations, the regression components, and the residuals correspond to three sources of variation. These sources of variation are similarly named: regression (also called model), error (also called residual), and total. The degrees of freedom for the total variation is the denominator of the sample variance of *Y*: $(n-1)$. The regression SS has 1 degree of freedom for each regression coefficient estimated; for simple linear regression, the degree of freedom is 1. The residual degrees of freedom are obtained by subtracting the regression degrees of freedom from the total degrees of freedom: for simple linear regression, $(n-1)-1 = (n-2)$. The mean squares (MSs) are the values of SS divided by the respective degrees of freedom. The regression MS has a special interpretation as the variance attributable to linear regression, $s^2_{\hat{Y}}$; conceptually, the regression MS is the explained variation of *Y* attributable to variation in *X*. The residual MS also has a special interpretation as the variance attributable to *Y* after adjusting for *X*, $s^2_{Y|X}$; conceptually, the residual MS is the unexplained variation of *Y*.

The formal goodness-of-fit test is an *F*-test with the model MS in the numerator and the error MS in the denominator: $MS_{Model}/MS_{Error} = F_s$. F_s follows an *F* distribution with numerator degrees of freedom equaling 1 and denominator degrees of freedom equaling $(n-2)$. The *p* value is the probability of obtaining a result this extreme, or more so, assuming that only natural or unexplained variability in *Y* exists. If the *p* value is <0.05, the investigator concludes that, according to these data, the model does account for a sufficient amount of the variation in *Y* to say that the model has adequate goodness of fit. Conversely, if the *p* value is >0.05, the investigator concludes that, according to these data, the evidence is insufficient to say that the model has adequate goodness of fit.

ANOVA TABLE

Source of variation	*Degrees of freedom*	*SS*	*MS*	F_s
Regression (or model)	1	$\sum(\hat{Y}_i - \bar{Y})^2$	$\sum(\hat{Y}_i - \bar{Y})^2$	MS_{Model}/MS_{Error}
Residual (or error)	$n-2$	$\sum(Y_i - \hat{Y}_i)^2$	$\sum(Y_i - \hat{Y}_i)^2/(n-2)$	
Total	$n-1$	$\sum(Y_i - \bar{Y})^2$		

Tests of Hypotheses The clinical investigator may wish to determine if there is a linear relationship between *X* and *Y*. If the slope β equals zero, there is no relationship between *X* and *Y*. Note that the magnitude of β does not tell the investigator whether the slope is different from zero. Therefore, the investigator forms the null hypothesis as H_0: $\beta = 0$ and the alternative hypothesis as H_1: $\beta \neq 0$. Single-sided alternative hypotheses (i.e., $\beta > 0$; $\beta < 0$) are allowed if there is previous knowledge that the relationship can only be either positive or negative or if a biologic phenomenon, such as growth, excludes one direction. Statistically, a one-sided test is superior to a two-sided test, because the probability of rejecting the null hypothesis is greater at the same level of significance.

Because the assumptions for regression analysis state that the residuals are normally distributed, the estimate of β (i.e., *b*) is also normally distributed with mean β and variance σ_b^2. The clinical investigator estimates the variance of *b*, s_b^2, from the data. The numerator of s_b^2 is the variation around the regression line (s_ε^2), and the denominator is the total variation of *X*.

One should note that the numerator, the variation around the regression line (s_ε^2), is interpreted as the amount of variation in *Y* remaining after taking into account or adjusting for the variation in *X*. Then, to test H_0: $\beta = 0$, the investigator computes the test statistic:

$$t_s = \frac{b}{s_b},$$

which follows a *t* distribution with $(n-2)$ degrees of freedom. Like all *t* statistics, the degrees of freedom for this test statistic are the degrees of freedom associated with the denominator, in this situation s_b^2. Because s_ε^2 is contained in s_b^2, the degrees of freedom equal the degrees of freedom for the residual SS, that is, $(n-2)$. The *p* value is twice the probability associated with t_s, assuming that the null hypothesis is true. For one-sided tests, the investigator uses the same t_s but does not multiply the probability associated with t_s by 2. Rejecting H_0 implies that the data show evidence of a linear relationship between *X* and *Y*. If the investigator does not reject H_0, this conclusion implies that the data show no linear relationship between *X* and *Y*.

Confidence Intervals for β The $(1-\alpha)100\%$ CI for β is computed in the usual way:

$$b \pm t_{[0.975,n-2]}s_b.$$

Conceptually, this CI is the same as the CI for μ. Whenever the CI does not include zero, the investigator rejects H_0. If the $(1-\alpha)100\%$ CI includes the hypothesized value, the results of the study, according to these data, are consistent with H_0. The interpretation of the CI is the following: the estimate of β is a random variable; for each sample, there will be a different estimate β and a different s_b. The slope can fluctuate within these bounds with 95% confidence that the true slope lies there.

R^2 for Simple Linear Regression R^2 measures the proportion of the variance or variation of *Y* that can be explained by the variance or variation in *X*. Stated another way, R^2 is the proportion of the total variation in *Y* explained

by regression. Mathematically, R^2 equals the regression SS divided by the total corrected SS: $R^2 = SS_{Reg}/CSS$. Therefore, R^2 is a summary measure of goodness of fit for simple linear regression.

For simple linear regression, the proportion of explained variance is usually expressed as r^2, instead of R^2. If the amount of explained variance is small, r^2 is small and a large proportion of the variation is unexplained by regression. Conversely, if the amount of explained variance is large, r^2 is large and a small proportion of the variation in Y is unexplained by regression. For this reason, r^2 is referred to as the coefficient of determination. Similarly, $(1–r^2)$ is called the coefficient of nondetermination.

This concept of r^2 extends to multiple linear regression, except that r^2 is replaced by R^2, which is called the sample multiple correlation coefficient. This concept can be easily demonstrated if multiple regression is addressed from the path coefficient perspective. For an excellent explanation, see Sokal and Rohlf *(2)*. No single quantity is the counterpart of r^2 or R^2 when the healthcare epidemiologist uses logistic regression analysis or survival analysis.

Correlation Coefficients

A correlation coefficient measures the degree (in terms of both closeness and direction) of association (or relationship) between two random variables that vary together. Usually, both variables are measured on the same subject. Unlike a regression coefficient, no distinction is made between the independent and the dependent variables; generally, any distinction would be arbitrary or meaningless. Furthermore, the correlation coefficient does quantify how strong the linear relationship is between the two variables of interest. Thus, a clinical investigator reports a correlation coefficient when there is no obvious outcome or response variable. Typically, the investigator intends to describe and quantify the relationship but does not wish to use one variable to predict another.

The correlation coefficient is a dimensionless value that ranges between –1.0 and +1.0, inclusive. Therefore, the investigator may compare correlation coefficients obtained from different studies. Unlike the regression coefficient, the correlation coefficient is unaffected by changes in scale.

If the correlation coefficient is –1.0, there is a perfect negative correlation between the two variables; all the points lie on a straight line. If the correlation coefficient is +1.0, there is a perfect positive correlation between the two variables; all the points lie on a straight line. A correlation coefficient between zero and –1.0 implies that there is a negative relationship; as one variable increases, the other decreases. Similarly, a correlation coefficient between zero and +1.0 implies that there is a positive relationship between the two variables; as one variable increases, the other also increases. Finally, if the correlation coefficient is zero, there is no relationship between the two variables; a graph of the data reveals that the points are randomly distributed within a circle or a horizontal rectangle.

Linear Correlation Coefficient

Estimate of ρ The linear correlation coefficient, ρ, is also called the Pearson product moment correlation coefficient (*1–4*,5,*7*,8,*9*,*12*,*16*). The sample Pearson correlation coefficient is used to estimate ρ when both variables are continuous variables that are both normally distributed. The investigator estimates ρ from the data using the following formula:

$$r = \frac{s_{Y1Y2}}{s_{Y1}s_{Y2}},$$

where the numerator is the covariance between the two random variables Y_1 and Y_2, and the denominator is the square root of the product of the variances of Y_1 and Y_2. The covariance can be either positive or negative. In the clinical setting, many more than two variables are measured on each patient. If more than one correlation coefficient is estimated, the clinical investigator should indicate which one is being discussed.

Because the assumptions for correlation analysis state that both variables are normally distributed, the estimate of ρ (i.e., r) follows a t distribution with $(n–2)$ degrees of freedom with mean ρ and variance σ^2_r. Therefore, the clinical investigator estimates the variance of r from the data: $s^2_r = (1–r^2)/(n–2)$.

Hypothesis Tests Most often, the clinical epidemiologist is interested in the question of whether or not Y_1 and Y_2 are correlated (*1–4*,5,8,*9*). Therefore, depending on how much information is known in advance, the epidemiologist forms the following hypotheses:

$$H_0: \rho = 0 \text{ versus } H_1: \rho \neq 0.$$

One-sided alternative hypotheses are allowed if there is previous knowledge that the relationship can only be either positive or negative or if a biologic phenomenon, such as growth, excludes one direction. Testing these hypotheses requires the assumption that both variables are continuous and distributed normally. The epidemiologist tests H_0 according to the following test statistic:

$$t_s = \frac{r}{s_r},$$

where s_r is $\sqrt{(1-r^2)/(n-2)}$. The test statistic follows a t distribution with $(n–2)$ degrees of freedom. The p value is twice the probability associated with the test statistic, assuming that H_0 is true. For one-sided hypothesis tests, the probability is not multiplied by 2.

Confidence Intervals for ρ The healthcare epidemiologist cannot use r directly for estimating CIs (*1–4*,5,8,*9*). First, r is transformed with Fisher's z-transformation. Then, the $(1–\alpha)100\%$ CI for z_F .is computed in the usual way. Finally, the epidemiologist transforms L_L and L_U back to the original correlation scale. Conceptually, this CI is the same as the CI for μ. Whenever the CI does not include zero, the investigator rejects H_0. If the $(1–\alpha)100\%$ CI includes the hypothesized value, the results of the study according to these data are consistent with H_0. The CI is interpreted as follows: the estimate of ρ is a random variable; for each sample, there will be a different estimate r and a different s_r. The linear correlation coefficient can fluctuate within these bounds with 95% confidence that the true value lies there.

Relationship Between the Linear Regression Coefficient and the Linear Correlation Coefficient For simple linear regression, there is a relationship among the regression coefficient, the correlation coefficient, and R^2. These relationships do not hold for multiple linear regression or other forms of regression. Conceptually, two simple linear regression coefficients exist. Usually, the investigator regresses Y on X: $Y = \alpha + \beta_{Y|X} X + \varepsilon$. However, the investigator could regress X on Y: $X = \alpha' + \beta'_{X|Y} Y + \varepsilon'$. The two estimated regression coefficients, $b_{Y|X}$ and $b'_{X|Y}$, always have the same sign. The estimated Pearson product moment correlation coefficient, r_{XY}, is the square root of R^2; the correlation coefficient also equals the geometric mean of two estimated regression coefficients (i.e., the square root of the product of slope from the regression of X on Y and the slope from the regression of Y on X), where the sign of the covariance between X and Y determines the sign of r. Thus, there is a relationship between correlation and regression. The closer the data points lie to a straight line, the stronger the relationship becomes and the larger the correlation coefficient is. The slope of the line has no bearing on the correlation. However, whenever there is a significant correlation, there will be a significant regression and vice versa. The clinical investigator can depict this relationship graphically by plotting the two estimated regression lines (i.e., $Y = a + b_{Y|X}X$ and $X = a' + b'_{X|Y}Y$) on one set of axes; the correlation coefficient is a measure of the angle between the two regression lines. As the angle becomes larger, the correlation coefficient decreases toward zero. When the angle is 90 degrees, the lines are perpendicular, the correlation coefficient is zero, and the scatter of data is circular or rectangular. As the angle between the regression lines becomes smaller, the correlation coefficient increases toward −1.0 or +1.0. When the angle is 0 degrees, the lines coincide, the correlation coefficient is either −1.0 or + 1.0, and the scatter of the data is a perfectly straight line.

The regression coefficient can also be interpreted as a rescaled version of the correlation coefficient where the scale factor is the ratio of the standard deviation of Y to that of X:

$$r = \frac{b_{Y|X}}{(s_Y / s_X)}.$$

Thus, the correlation coefficient can be regarded as a standardized regression coefficient (2). The standardized regression coefficient is a dimensionless value that represents the predicted change in Y, expressed in the number of standard deviation units that would be expected for each change in X by one standard deviation unit. The clinical investigator can use standardized regression coefficients to compare regression coefficients obtained from several studies on a variety of patient groups.

Nonparametric Correlation Coefficients The primary assumption for estimating linear correlation coefficients is that both variables are distributed normally. Sometimes the healthcare epidemiologist finds that one or more of the variables of interest is not distributed normally. In this circumstance, the epidemiologist can choose to estimate a nonparametric correlation coefficient (*1–4*,5,*7*,8,*9*,15,*16*,*33*).

Rank Correlation The Kendall coefficient of rank correlation, the Greek letter tau (τ), and the Spearman rank correlation coefficient, ρ_s, are nonparametric coefficients. When these are reported, the clinical investigator makes no assumptions about the distributions of the variables.

Spearman's rank correlation coefficient (also called Spearman's rho) is a sample correlation coefficient based on ranks. First, the investigator ranks the values of each variable from largest to smallest (or vice versa) and then estimates ρ_s using the Pearson product moment formula, substituting ranks for the actual values. The rationale for this estimator is that if there were a perfect correlation between the two variables, the ranks for each subject on each variable would be the same. Thus, the change in rank (i.e., the rank of the first variable minus the rank of the second variable) would be zero for every subject. Spearman's rank correlation coefficient can also be used for estimating the correlation between ordinal (i.e., rank) variables.

Kendall's τ provides a measure of reranking. Estimation of Kendall's τ is slightly more difficult than estimation of Spearman's rank correlation coefficient. For the method, see Sokal and Rohlf *(2)*. Usually, if both Kendall's τ and Spearman's rank correlation coefficient are estimated from the same data, the estimate of Kendall's τ is smaller than that of Spearman's rank correlation coefficient. However, the p values are usually very close to the same value. When an investigator estimates Kendall's τ, the Greek letter is used for the statistic. Kendall's τ is one of few examples of Greek letters being used for both the parameter and the statistic.

Point Biserial Correlation Coefficient The point biserial correlation coefficient, ρ_{pb}, is used when one random variable is dichotomous and the other is continuous. Asymptotically, the point biserial correlation coefficient is the same as a Pearson product moment correlation coefficient estimated for one dichotomous variable and one continuous variable.

Biserial Correlation Coefficient The biserial correlation coefficient, ρ_b, is used when one random variable has been forced to be dichotomous (e.g., by dividing a measurement into upper and lower halves) and the other random variable is continuous. Asymptotically, the biserial correlation coefficient is the same as a Pearson product moment correlation coefficient estimated for one dichotomous variable and one continuous variable.

Phi Fourfold Coefficient The phi (φ) fourfold coefficient is the special name given to the measure of concordance for 2×2 tables (*7*,15). Asymptotically, the phi coefficient is the same as a Pearson product moment correlation coefficient estimated for two dichotomous variables. Thus, this statistic gives a measure of correlation or concordance for dichotomous variables. When an investigator estimates φ, the Greek letter is used for the statistic; φ is another one of few examples of Greek letters being used for both the parameter and the statistic.

Contingency Coefficient The contingency coefficient is used to measure concordance between categorical variables depicted in $r \times c$ tables (i.e., tables in which

the numbers of rows and columns are not necessarily the same) *(7,33)*. Thus, when one or both of the categorical variables has three or more levels, the investigator would choose the contingency coefficient (*C*) as an estimate of the correlation coefficient.

The Kappa Statistic

The kappa statistic, κ, is used to measure concordance for 2×2 and square $r \times c$ tables (i.e., tables in which the numbers of rows and columns are the same) (8,*33*). Often, these tables reflect paired data. When an investigator estimates κ, the Greek letter is used for the statistic; κ is another one of few examples of Greek letters being used for both the parameter and the statistic.

The healthcare epidemiologist may find many uses for the kappa statistic. For example, two radiologists may read radiographs of patients in a particular ICU. On a given day, which radiologist reviews radiographs often depends on a staffing schedule. In actuality, each radiograph is reviewed by only one radiologist. Therefore, one radiologist may review the radiographs for a particular patient taken on admission. The next radiograph taken on the same patient 3 days later may be read by the other radiologist. Naturally, the healthcare epidemiologist would like to know whether the radiologists are likely to give the same diagnosis to the same patient based on the same radiograph. Analyzing data from patients in this ICU may require the epidemiologist to make the assumption that the diagnoses from the two radiologists are the same. Rather than making this assumption, the epidemiologist can design a study to measure the agreement (or concordance) between the two radiologists when they review the same radiographs. In a hypothetical study, one might suppose that the various diagnoses available to the radiologists are (a) definitely not interstitial disease, (b) probably not interstitial disease, (c) possibly not interstitial disease, (d) possibly interstitial disease, (e) probably interstitial disease, and (f) definitely interstitial disease. Therefore, the epidemiologist needs a measure of concordance. The epidemiologist forms the hypotheses for the kappa statistic:

$$H_0 : \kappa = 0 \text{ versus } H_1 : \kappa \neq 0.$$

First, the epidemiologist asks the radiologists each to review a number of radiographs. For this particular study, the epidemiologist is not as concerned about the radiologists agreeing with a gold standard as with their agreement with each other. After collecting the data, the epidemiologist tabulates the results in a 6×6 table.

Concordance is measured by the proportion of observations in the cells along the main diagonal. The healthcare epidemiologist compares the observed concordance rate with that which would be expected if there were no concordance among the two radiologists. The epidemiologist estimates κ and the variance of κ; for specific formulas, the reader should see Rosner (8). Then, to test H_0, the epidemiologist computes the test statistic, which is a *z*-score and follows the standard normal distribution. The *p* value is the probability associated with z_s, assuming that the null hypothesis is true. Rejecting H_0 implies that the data show evidence of concordance between the two radiologists. Finally, the epidemiologist uses the following guidelines for evaluation of the estimated κ statistic: (a) an estimated $\kappa > 0.75$ denotes excellent reproducibility; (b) an estimated κ between 0.40 and 0.75, inclusive, denotes good reproducibility; and (c) an estimated $\kappa < 0.40$ denotes marginal reproducibility (8).

The $(1-\alpha)100\%$ CI for κ is computed in the usual way. Conceptually, this CI is the same as the CI for μ. Whenever the CI does not include zero, the investigator rejects H_0. If the $(1-\alpha)100\%$ CI includes the hypothesized value, the results of the study, according to these data, are consistent with H_0. The CI is interpreted as follows: the estimate of κ is a random variable; for each sample, there will be a different estimate κ and a different s_κ. The concordance can fluctuate within these bounds with 95% confidence that the true concordance lies there.

MULTIVARIABLE ANALYSIS

Most epidemiologic investigations involve more than one or two variables of interest. Therefore, clinically based studies of disease determinants often yield data sets that require complicated analytic methods. Generally, the healthcare epidemiologist identifies an outcome variable (e.g., death, infection, or time to an event). In addition, there are other selected variables, including the particular exposure, that are relevant to the investigation. The primary focus of the study is the relationship between the particular exposure and the specified outcome; complexities arise, because the epidemiologist must sort out interrelationships among other variables that affect (confound) the relationship between the outcome and exposure (see Chapter 2).

Although the epidemiologist has specialized knowledge about the disease process under investigation, usually a complete theoretical framework describing the true relationship between the exposure and the outcome variables is lacking. Furthermore, the epidemiologist cannot control or manipulate through experiments the process linking exposure to outcome in ways that may reveal the true relationship. Fortunately, statisticians have developed a variety of multivariable analytic methods that address many problems encountered in clinically based research.

What does the term *multivariable analysis* mean? Many investigators refer to the statistical analysis of one dependent variable and several descriptive or explanatory variables (i.e., several independent variables) as multivariate analysis. However, this practice reflects a misuse of a statistical term that refers to the analysis of more than one dependent variable. For this reason, I have chosen to use the term *multivariable analysis* to encompass the following statistical methods: stratified analysis, multiple linear regression, multiple logistic regression, and survival analysis.

Model Selection Process

General Problems Dealing with more than one explanatory variable is a challenge for many clinical investigators. Kleinbaum et al. (28) suggest the following four ways in which multivariable analysis is more difficult than simple univariate analysis (i.e., one explanatory variable). First, usually more than one statistical model can be developed

for the same data set to adequately describe the relationship between the exposure and outcome variable. Choice of which model is the best is generally somewhat subjective and often sample dependent. Second, on any one graph, an investigator can depict at most three dimensions. Usually, an investigator considers more than three variables. In this situation, the investigator must limit each graphic depiction to two or three variables. Third, when the model includes more than one or two explanatory variables, most clinical investigators have difficulty translating the statistical model into a clinically meaningful explanation. Finally, analysis requires the investigator to use a computer software package for statistical analysis. When the number of independent variables is large, the model selection process can be very time-consuming. Many computer algorithms do not have built-in limits for the number of dependent or independent variables; the investigator has the responsibility of setting reasonable limits. The following discussion suggests some reasonable limits. Thus, in addition to specialized knowledge about the disease process, the epidemiologist must develop some expertise in multivariable analysis and acquire related computer skills.

Model Selection Whenever the research problem involves determining which explanatory variables should be included in the analysis, a clinical investigator needs a model selection strategy. Because some relationships among variables are specific to a particular sample (i.e., they are sample dependent), many investigators find that adhering to a formal strategy is especially helpful during exploratory data analysis. In a very real sense, each data set has new information that can provide the investigator with insight into the exposure–disease relationship. If some of the intricacies of this relationship, especially those that are unique to the current study, can be dissected early in the model selection process, the investigator is more likely to understand the clinical implications of the final model.

The goal of the model selection process is to identify a statistical model that reflects important aspects of the exposure–disease relationship. Therefore, before the process begins, the investigator must perceive a theoretical framework firmly based on considerations of subject matter. The statistical methods are the mathematical tools that the investigator uses to derive empirical support for the framework and discover new aspects of the relationship that can be used to modify the framework. Both biostatisticians and epidemiologists warn against relying exclusively on any statistical package to determine the best model for a data set. Except for pharmacokinetic, pharmacodynamic, and growth models, almost all statistical models commonly used in healthcare epidemiology are empirical rather than mechanistic. This distinction implies that even though a functional relationship may exist between the exposure and disease, limited information is available on the role that other variables have in influencing how the exposure–disease process is manifested in a given patient sample. Both biostatisticians and epidemiologists also caution investigators about literally interpreting the model as an accurate reflection of the true exposure–disease process. Finally, they are adamant in stating that any type of model selection technique can be abused.

After gaining experience with multivariable analysis, a clinical investigator may develop a unique style of model selection. However, until that experience has been gained, the cautious investigator should strictly adhere to guidelines provided by a biostatistician or epidemiologist who has extensive experience in model selection. Draper and Smith *(29)* have summarized, in a very readable chapter, the process of planning, developing, and validating a statistical model. In their text, Rothman et al. (34) devoted several chapters to the modeling process. Other authors have discussed the process and provided the reader with annotated examples: Kleinbaum et al. (20,28), Myers (30), and Myers and Milton *(31)*.

The Planning Stage The model selection process actually begins with the statement of the problem and identification of the research question. During the planning stage, the clinical investigator selects the response variable. If there is more than one response variable of interest, the investigator should limit the number to a few—no more than five is best. For each response variable, the clinical investigator lists all variables that could possibly be related to the outcome. This list is usually very long and may include almost every variable on a patient's chart. From this extensive list, the investigator identifies those variables that can be collected and groups these collectible variables into broad categories. For example, one category might contain all demographics, another could include severity of illness indices or perhaps comorbidities, and so on. Finally, by the end of the planning stage, the investigator should have a reasonable list of variables that merit inclusion in the study.

Are there resources available that can help the investigator in selecting variables for serious consideration? Resources include (a) reports of similar investigations published in the peer-reviewed literature and (b) discussions with experts in the disease of interest. During the initial planning stages, the clinical investigator bases decisions on subject matter expertise not statistics! However, some statistical considerations become important near the end of the planning stage.

Toward the end of the planning stage, the investigator studies the feasibility of the project. Specific items that require the attention of the investigator include the number of patients required to address the problem, the number of patients available, the time needed to accrue the minimum number of patients necessary for the investigation, the costs for data collection, other budget-related issues, and the availability of skilled ancillary personnel to ensure collection of high-quality data.

Data Collection and Quality Control Once the investigator has decided that the project is feasible, patient enrollment and data collection begin. Quality control of the data is vital to the success of the entire project. Remarkably, this is a step that some investigators overlook completely. Planning what quality control measures are needed for a clinical investigation may require advice from a biostatistician or epidemiologist. Unfortunately, despite precautions and the highest level of quality control, most data sets will contain some errors that escape detection. Reasonable goals for quality control include eliminating systematic errors,

especially misclassification, and minimizing the impact of random data entry errors. Therefore, the safeguards are directed at detecting influential errors, those errors that can bias results and threaten the validity of statistical inferences. Remember that a single error, such as a 50-lb newborn human infant, can have a disastrous impact on the findings of a study.

Model Selection—Univariate Analyses The first exploratory step in actual model selection involves obtaining descriptive statistics for the variables of interest. For continuous variables, testing for goodness of fit to the normal distribution may be important. In addition, for continuous explanatory variables, the range (or some other measure of variability) is usually an important consideration. For example, if the ages of the patients are very similar, age is not likely to influence the relationship between exposure and disease regardless of whether other studies have found that age is an important determinant of the disease of interest. Including variables with limited variability can compromise the model because of overparameterization.

The next steps in actual model selection are (a) plotting relationships between continuous variables, (b) using 2×2 and $r \times c$ tables to study relationships between discrete variables (i.e., attributes), and (c) estimation of Pearson and Spearman correlation coefficients for all pairs of variables. During this phase, the investigator is gaining an appreciation of which variables are associated with other variables and to what degree. The investigator should be careful about including explanatory variables in the multivariable model that are more highly correlated with each other than with the response variable. Including highly correlated independent variables in a model can lead to problems of multicollinearity. Other terms for the same phenomenon are collinearity and multiple collinearity. Multicollinearity in a statistical model occurs when two or more independent variables are strongly correlated with each other. When the explanatory variables are highly correlated with each other, the estimated coefficients are also highly correlated, thereby yielding unreasonable regression coefficients and an implausible and unusable statistical model.

At the end of the exploratory step, the investigator should have narrowed the list of potential explanatory variables to about 20 or fewer. Final models with more than five or six explanatory variables are difficult to explain. In narrowing the list, the investigator should be aware of the following rule: no fewer than 5 to 10 observations are needed for each potentially important explanatory variable that will be included in the final model. Having at least 30 observations for each variable included in the final model is a reasonable target.

Model Selection—Multivariable Analyses Style and philosophy influence the investigator's choice of which analytic procedures to use in developing multivariable models. Every procedure has strengths and weaknesses; all can be abused. Initially, most biostatisticians recommend using a rather liberal entrance or deletion criterion for variable selection (e.g., $p < .20$ or $p < .25$). As the final model emerges, traditional levels of significance for selected explanatory variables can be imposed. Regardless of what statistical procedure was used for model selection, most biostatisticians recommend that the investigator use appropriate diagnostic procedures to assess various aspects of the emerging statistical models and subject the results to the scrutiny of other clinical specialists with expertise in the exposure–disease process of interest. Regression diagnostics include examining the residuals and checking for systematic lack of fit.

Because more than one statistical model can provide a valid representation of the exposure–disease relationship, the investigator should select the best model and several competing models. Assessing the best model in light of competing models is a type of sensitivity analysis. The objective of this sensitivity analysis is to reveal which variables are stable in the model, reflecting the average patient, and which are seemingly sample specific (i.e., sample sensitive), reflecting small groups of patients with distinct characteristics.

Problems with Confounding Epidemiologists apply the term *confounder variables* to variables that are partially related to both the exposure and the outcome variables (20,34). In the statistical sense, a confounder is only partially confounded (i.e., associated or correlated) with both the exposure and the outcome variables; if a confounder were completely confounded with either variable, the confounder would be completely inseparable from that variable.

Confounders create problems for the investigator. The investigator's objective is to show whether a particular exposure and the outcome are related. If the investigator ignores an important and influential confounder, the estimates of RRs, ORs, or regression coefficients are biased. Consequently, the investigator does not know whether the relationship (or lack of one) is attributable to the confounder or to the exposure (see Chapter 2).

Indications of Multicollinearity Sometimes an explanatory variable will seem to have an important effect on a response when the variable is considered by itself with simple linear regression or correlation analysis. However, after adjusting for another explanatory variable, no significant relationship may remain. This apparent contradiction is an indication of multicollinearity. Inclusion of both variables in the statistical model may or may not be appropriate. There are rules for inclusion and exclusion, but their interpretation is subjective. Thus, the investigator must carefully assess any problems related to multicollinearity.

An investigator can learn to recognize some indications of multicollinearity. As variables are selected for inclusion or exclusion from the model, coefficients affected by multicollinearity will appear to be unstable in that their values will change dramatically. Sometimes multicollinearity can be severe enough to change the sign of an estimate. Another concomitant indication of multicollinearity is that affected coefficient estimates will often have large standard errors; sometimes the standard errors are several times larger than the estimates. Statisticians have developed several methods for detecting multicollinearity (*29*,30,*31*,32,35,36). Condition indices, variance inflation factors, and tolerance values can be used to determine which variables in the current model are affecting the estimates of regression

coefficients. Whenever multicollinearity appears to be an important problem, the clinical investigator should seek advice from a biostatistician experienced with model selection.

Indications of an Overparameterized Model Including explanatory variables that are not statistically significant can be considered overparameterizing the model. Subjective interpretation plays a role in the distinction between overparameterization and appropriate inclusion of a variable that is not statistically significant at traditional levels. Overparameterization and multicollinearity often occur simultaneously. One serious problem with highly correlated explanatory variables is that the model becomes very difficult to interpret in terms of actual clinical applications. After all, one of the reasons for using multiple linear regression is to allow the investigator to identify which explanatory variables have a significant relationship with the response after adjusting for other significant explanatory variables. Therefore, the investigator has to carefully evaluate problems associated with overparameterizing the model.

Detection of Influential Observations An influential observation is one that has an unusually large influence on the estimate of one or more regression coefficients. In general, influential observations are unique to a specific sample. By carefully examining the plots of each explanatory variable against the response, the investigator can identify many influential observations during exploratory analysis. However, in most large data sets, a few influential observations may emerge during model selection. In addition to examining plots of residuals, statisticians have developed several other methods for detecting influential observations (*18*,*29*,30,*31*,32,35,36). An investigator uses influence diagnostics for revealing which observations reflect the average patient and which are seemingly from patients with distinct characteristics. If possible, the investigator should determine why an observation has been identified as influential. Often, this process of examining influential observations reveals biologically and clinically important reasons for exclusion. After one or more influential observations have been identified, biostatisticians usually advise fitting the model after leaving out the suspect influential observations. Alternatively, inclusion of a dummy variable in the model (to designate the main group, $X = 0$, and set of influential observations, $X = 1$) may allow for including all observations in the final model.

Stratified Analysis

As discussed previously, cumulative incidence and prevalence of a disease are distributed binomially. An important assumption is that the probabilities for the outcomes are a constant p for success and $(1–p) = q$ for each failure for every trial. Often, in clinical studies, data from samples of patients fail to meet this assumption; other variables in addition to exposure influence the probability of the outcomes. One of the statistical methods for addressing confounders is stratified analysis (*1*,5,*6*,8,15,20,*21*,34). The investigator uses stratified analysis for controlling or adjusting for the confounder and estimates an adjusted RR or OR.

Mantel–Haenszel Test Two-way tables can be extended to multiway tables to accommodate several attributes. Typically, the Mantel–Haenszel test is used for situations in which (a) both the exposure and the outcome are dichotomous variables and (b) one or more other attributes are partially confounded with the relationship between exposure and outcome. The investigator forms a number of strata based on levels of one or more confounding variables; the confounding variables must be categorical, discrete, or continuous variables that have been forced to be categorical (e.g., by dividing into quintiles). The strata are chosen so that the data within each stratum are as homogeneous as possible. Typically, strata reflect patient characteristics (e.g., age category) or institutional characteristics (e.g., medical and surgical ICUs). The investigator assumes that the strata are independent. The Mantel–Haenszel test requires a reasonably large total sample size; however, this test was developed to accommodate sparse data within strata. The Mantel–Haenszel test for 2×2 tables can be generalized to $r \times c$ tables, but that application is beyond the scope of this chapter.

Within each stratum, the investigator constructs a 2×2 table relating the exposure and outcome variables. The test statistic does not depend on a particular arrangement of the 2×2 tables as long as the arrangement is the same for all strata. Choice of which variable is designated as the rows and which is designated as the columns is arbitrary. Similarly, the order in which the data for the rows and columns are coded is arbitrary. However, certain statistical software packages may require a particular arrangement, particularly when the investigator is estimating ORs or RRs.

H_0 states that there is no association between exposure and outcome after controlling for variables that create strata; H_1 states that there is an association after controlling for the strata. Under H_0, the Mantel–Haenszel statistic, χ^2_{MH}, follows a chi-square distribution with 1 degree of freedom. Thus, for a test of significance at the .05 significance level, H_0 is rejected if χ^2_{MH} is >3.84. The p value is the probability associated with χ^2_{MH}, assuming that the null hypothesis is true.

The investigator should report results based on the Mantel–Haenszel test only when there is no evidence of statistical interaction involving the strata. The Mantel–Haenszel test is still valid statistically; however, the interpretability of the results may be in question. Therefore, the investigator should not rely exclusively on the p value associated with the test statistic but should carefully study the patterns of association displayed in the various strata with a particular interest in detecting evidence of a statistical interaction involving the strata or test for homogeneity of strata using the Breslow–Day test. For example, if the Mantel– Haenszel test statistic is not significant, (a) there may be no association between the exposure and the outcome (i.e., H_0 is correct) or (b) there may be opposing or inconsistent patterns among the strata. An obvious interaction is present when the pattern exhibited by some strata is in the opposite direction from the pattern of other strata. In contrast, even without the presence of opposing patterns, interaction may be present when Fisher's exact test indicates significance for some strata and lack of significance for others; in this situation, determining what constitutes

an interaction is somewhat subjective. Finally, even if the Mantel–Haenszel test statistic reaches significance, there may be evidence of an interaction. In this circumstance, the issue of interpretability is addressed subjectively, according to subject matter considerations. For example, significance could be attributable to one or more dominant strata that have a strong pattern of association in one direction and overwhelm the lack of association or an opposing pattern in the remaining strata. Regardless of the significance of the test statistic, evidence of an interaction indicates that analysis of data over all strata may be inappropriate. If an investigator encounters evidence of an interaction involving the strata, he or she should seek the advice of an experienced biostatistician or epidemiologist (see also Chapter 2).

Estimates of Adjusted ORs and RRs The Mantel–Haenszel method can be used to estimate strata-adjusted ORs and RRs along with respective 95% CIs. The reader should review the previous discussion of unadjusted ORs and RRs estimated from 2×2 tables. Unlike the RR, the OR is not constrained by the denominator. This property is particularly advantageous when estimated ORs are combined over strata.

Strata-adjusted estimation is based on the assumption that the parameter is the same for each stratum and that the values of estimates differ because of sampling. When estimating adjusted measures of association, the investigator should carefully study the pattern of association displayed by the various strata. The same problems of interpretability discussed for the Mantel–Haenszel test apply to estimation. However, unlike the test statistic, estimates are not valid unless the assumption of homogeneity is met. Criteria for what constitutes a violation of this assumption are somewhat subjective.

Either test-based or precision-based CIs can be estimated. For a discussion of the advantages and disadvantages of these intervals, the reader is referred to Kleinbaum et al. (20). Sometimes, extreme estimates or confidence limits are obtained because of very small observed frequencies in some cells (often as few as only one or two events).

A Special Case—Matched Pairs For matched pairs, the clinical investigator can estimate RRs and ORs from stratified analyses with the strata representing the pairs. Methods for point and interval estimates are the same as those described previously. Usually, the investigator does not study the pattern of association for the various strata.

Breslow–Day Test The Breslow–Day test for homogeneity tests the null hypothesis that the ORs for all strata are equal versus the alternative that the OR for at least one of the strata is different *(37)*. The test statistic is valid only when every stratum has a large number of observations (generally more than 20). Under H_0, the test statistic follows a chi-square distribution with degrees of freedom equal to one less than the number of strata included in the test statistic. Strata with a zero column or row total are excluded from computation of the test statistic. Regardless of whether the investigator uses the Breslow–Day test, it is incumbent on the investigator to carefully study the pattern of association displayed by the various strata. When the estimates of ORs have opposing patterns, there is usually no question about the inequality of ORs over strata. However, evidence of other patterns of interaction is more subjectively determined.

Multiple Linear Regression

Multiple Linear Regression Analysis A clinical investigator uses multiple linear regression analysis when the objective involves studying the relationship between more than two variables at the same time (*1*,*2*,4, 5,*6*,*7*,8,*9*,*18*,*21*,28,*29*,30,*31*). There is a single continuous dependent or response variable, but there are several independent, descriptive, or explanatory variables. The explanatory variables may be continuous or dichotomous; in addition, categorical explanatory variables can be recoded for inclusion in a multiple regression model.

The statistical model is $Y_i = \alpha + \beta_1 X_{1i} + \beta_2 X_{2i} + \ldots + \beta_k X_{ki} + \varepsilon_i$, where i is the indicator for each subject and ranges from 1 to n. The data set contains n sets of $(k + 1)$ measurements where n indicates the number of subjects in the sample; a complete set of measurements is taken on every patient. Of these measurements, k values are X values, and one is a Y value. The β values are partial regression coefficients with the intercept, α, corresponding to the intercept in simple linear regression. A partial regression coefficient quantifies the relationship between a particular explanatory variable and the response after adjusting or controlling for all other effects in the model.

The same assumptions that were necessary for simple linear regression also apply to multiple linear regression. Multiple linear regression merely reflects an expansion of the simple case to p-dimensions, each representing a different independent variable. Regardless of form, the explanatory variables are assumed to function independently. Most often, the independent variables have the form of main or direct effects (e.g., age, days on mechanical ventilation, or APACHE III score). However, some of the independent variables may represent interactions of two other independent variables, X_1X_2. As a standard practice, the investigator should include the direct effects of X_1 and X_2 in a model in which the interaction is included. An example of an interaction is the joint effect of age and APACHE III score on a particular response variable. Independent variables may represent higher powers of other independent variables, X_1^2 or X_1^3. Generally, when higher powers, such as X_1^3, are included in the model, the lower powers (X_1 and X_1^2) are also included. For example, the relationship between the response and age may not be completely linear but may increase at an increasing rate, thereby requiring the inclusion of age and age-squared.

An investigator should always be conservative in interpreting a multiple regression model. Other variables, not included in the model, may actually be the cause of differences in the response.

Polynomial or Curvilinear Regression Models Polynomial regression is a special case of multiple linear regression for one independent variable, X, and one continuous dependent variable, Y. The highest degree polynomial that may be fit to the data is one less than the number of observations. For most biologic phenomena, biostatisticians

recommend limiting the model to a cubic regression. The general rule for using polynomial regression analysis is that the investigator use as simple a model as possible but one that explains as much of the variation of Y as possible. The investigator should be aware that as the degree of the polynomial becomes higher, the interpretation of the curve becomes more difficult. The model for a quadratic regression is

$$Y_i = \alpha + \beta X_i + \gamma X_i^2 + \varepsilon_i$$

where i is the indicator for each subject and ranges from 1 to n. Both β and γ are partial regression coefficients.

Tests of Hypotheses Methods for regression analysis and hypothesis testing are similar to those described for simple linear regression. The same principle of least squares is used to estimate the regression coefficients by minimizing the residual sum of squares over all data points. The clinical investigator tests the overall null hypothesis that all β values equal zero versus the alternative hypothesis that at least one β value does not equal zero. Under the null hypothesis, the F_s, which is the ratio of the model or regression MS divided by the residual or error MS, follows an F distribution with p and (n–k–1) degrees of freedom. The p value is the probability associated with F_s, assuming that the null hypothesis is true.

The overall F-test will not identify which specific explanatory variables are associated with the response. The clinical investigator must perform t-tests to investigate the specific association of each independent variable with the response. For one- or two-sided t-tests on individual partial regression coefficients, the investigator uses a t statistic with (n–k–1) degrees of freedom. The p value is twice the probability associated with t_s, assuming that the null hypothesis is true.

Interval Estimation Generally, the investigator wishes to estimate partial regression coefficients. The printed results from most computer software packages include estimates and standard deviations of the estimates. The standard deviations of the estimates may be called standard errors. The clinical investigator obtains the 95% CIs for each partial regression coefficient in the usual way:

$$b \pm t_{[0.975,n-k-2]} s_b$$

Conceptually, this CI is the same as the CI for μ. Whenever the CI does not include zero, the investigator rejects H_0. If the (1–α)100% CI includes the hypothesized value, the results of the study according to these data are consistent with H_0. The CI is interpreted as follows: the estimate of β is a random variable; for each sample, there will be a different estimate b and a different s_b. As the variable X changes by one unit, the expected response changes by b units after controlling for all other variables in the model. Controlling for all other variables implies that the value of each of the other explanatory variables in the model has been set to the respective mean value. An investigator should always be conservative in interpreting a multiple regression coefficient. Other variables, not included in the model, may actually cause the variability of response.

Standardized Partial Regression Coefficients The concept of standardized regression coefficients can be extended to multiple linear regression; these are called standardized partial regression coefficients. By using standardized partial regression coefficients, the clinical investigator can express relative changes that are independent of any units of measurement. In addition, the investigator can use standardized partial regression coefficients for ranking the effects of the explanatory variables in order of importance.

Partial regression coefficients are standardized by dividing the estimated partial regression coefficient by the ratio of the standard deviation of the response variable to the standard deviation of the respective explanatory variable:

Thus, the standardized regression coefficient is a dimensionless value that represents the predicted change in Y, expressed in standard deviation units that would be expected for each change in X of one standard deviation unit after adjusting for all other variables in the model.

Partial Correlation Coefficients The healthcare epidemiologist obtains estimates of partial correlation coefficients following analyzing data by multiple regression methods. Partial correlation coefficients provide an estimate of the remaining correlation after one or more other variables are held constant (i.e., after adjusting for the other variables) *(2,4,9)*. Partial correlation coefficients are used when there are correlations among the explanatory variables. In practice, the epidemiologist examines both the total (or unadjusted) correlation coefficients and the partial (adjusted) correlation coefficients.

Multiple Logistic Regression

A clinical investigator uses multiple logistic regression analysis when the outcome or response variable follows a binomial distribution (*1*,5,*6*,8,*18*,20,*21*,34). Generally, the objective is similar to that for multiple linear regression and involves studying the relationship between more than two variables at the same time. There is a single dichotomous dependent or response variable and several independent or explanatory variables. Typically, the investigator refers to any explanatory variables, other than the specified exposure, as confounding variables. The investigator wishes to examine the relationship between the exposure and the outcome after controlling for the confounding variables. These confounding variables may be continuous, dichotomous, or categorical variables. When the strata used in stratified analysis and the confounding variables used in logistic regression are defined similarly, the results from the two methods are identical. By permitting continuous variables and interactions to be included in the model as explanatory variables, logistic regression is more flexible than stratified analysis. However, logistic regression does have one potentially serious limitation—only ORs can be estimated from logistic regression. However, these ORs can be used as approximators of RRs if the study design permits.

In logistic regression, the response variable is expressed as p and is the probability that the response, Y, is an event—that is, $p = \Pr(Y = 1)$. For logistic regression analysis, the presence of the event is almost always coded as one. Given

that a subject has certain values for X_1 to X_k, the expected or average probability of an event is $p = \Pr(Y = 1)$. The event or outcome of interest may be a particular disease or death. For this discussion, the event is disease.

The statistical model is

$$p_i = \frac{e^{\alpha+\beta_1 X_{1i}+\beta_2 X_{2i}+\cdots+\beta_k X_{ki}+\varepsilon_i}}{(1+e^{\alpha+\beta_1 X_{1i}+\beta_2 X_{2i}+\cdots+\beta_k X_{ki}+\varepsilon_i})},$$

where i is the indicator for each subject and ranges from 1 to n; $\exp(x) = e^x$;

Using the logit transformation, this model becomes

$$\ln(p_i / (1 - p_i) = \alpha + \beta_1 X_{1i} + \beta_2 X_{2i} + \cdots + \beta_k X_{ki} + \varepsilon_i.$$

Note that the logit transformation yields a model that is linear in its parameters, thus incorporating certain properties of multiple linear regression. The data set contains sets of $(k + 1)$ measurements on each subject. Of these measurements, k values are X values, and one is the event, Y. The β values are partial regression coefficients with the intercept, α, corresponding to the intercept in simple linear regression. In a logistic regression model, the explanatory variables are related multiplicatively to each other rather than additively as they would be in a linear model. Unlike the errors from the multiple linear regression model that are distributed normally, the errors of the multiple logistic model are distributed according to a binomial distribution. Furthermore, the expected value of Y for a given X lies between zero and 1.0. Because of complexities that involve fitting the parameters of this model, clinical investigators rely on a computer-based iterative algorithm.

Throughout this discussion, note that the natural logarithm of the odds of disease is $\ln[p/(1–p)]$. The intercept, α, represents the natural logarithm of the baseline odds of disease (i.e., the event). The baseline odds correspond to the odds of disease among the unexposed—that is, when all X values are set to zero. The partial regression coefficients quantify the relationships between a particular explanatory variable and the response after adjusting or controlling for all other effects in the model. When a partial regression coefficient quantifies the relationship between a dichotomous variable and the response, β represents the natural logarithm of the additional odds of disease among those with the attribute after controlling for all other variables in the model. For a categorical or continuous variable, the multiplicative relationship between the explanatory and outcome variables becomes apparent. β represents the change in the natural logarithm of additional odds of disease per unit change in X. Controlling for all other variables in the model implies that all other attributes occur at equal frequencies. The reader is referred to Rothman et al. (34), Kleinbaum et al. (20), and Hosmer and Lemeshow (35) for additional information on implications for epidemiologic models.

The same assumptions that were necessary for analysis of data in 2×2 tables and stratified analysis also apply to multiple logistic regression. In addition, logistic regression shares many similarities with multiple linear regression. Multiple logistic regression reflects k-dimensions, each representing a different independent variable. Regardless of form, the independent variables are assumed to function independently. Independent variables usually have the form of main or direct effects (e.g., presence of a healthcare-associated infection, age, days on mechanical ventilation, or APACHE III score). However, some independent variables may represent interactions of two other independent variables that should also be included in the model as direct effects, X_1 and X_2.

An investigator should always be conservative in interpreting a multiple logistic regression model. Other variables, not included in the model, may actually be the cause of differences in the probability of an event.

Tests of Hypotheses Tests of hypotheses, interval estimation, and interpretation of the results are counterparts of those for multiple linear regression.

Generally, the clinical investigator does not test an overall null hypothesis that all of the explanatory variables in the model are zero. However, this test is usually available. If competing models for the same data are being compared, there are test statistics available for assessing the joint or combined significance of all explanatory variables included in the model. The Score, Akaike Information Criterion, and the Schwartz Criterion statistics are used for this purpose.

The clinical investigator can perform z-tests to investigate the specific association of each independent variable with the response. Alternatively, for two-sided hypothesis tests on individual partial regression coefficients, the investigator can use a Wald chi-square statistic, which follows a chi-square distribution with 1 degree of freedom under the null hypothesis. The p value is the probability associated with χ^2_s, assuming that the null hypothesis is true. For more information on hypothesis testing, see Lawless (36).

Interval Estimation Generally, the investigator wishes to estimate partial regression coefficients and adjusted ORs. The printed results from most computer software packages include estimates and standard deviations of the estimates. The estimates of regression parameters are maximum likelihood estimates. Standard deviations of these estimates may be called standard errors. Sometimes the printed results also contain estimated adjusted ORs and asymptotic 95% CIs. The clinical investigator obtains the asymptotic 95% CIs for each partial regression coefficient in the usual way.

Whenever the CI does not include zero, the investigator rejects H_0. If the asymptotic $(1–\alpha)100\%$ CI includes the hypothesized value, the results of the study, according to these data, are consistent with H_0. The CI is interpreted as follows: the estimate of β is a random variable; for each sample, there will be a different estimate b and a different s_b. As the variable X changes by one unit, the expected natural logarithm of additional odds of disease changes by b units after controlling for all other variables in the model.

The interpretation of the OR is illustrated in the following example: after controlling for all other variables in the model, patients who are ventilated are 1.497 times as likely to have pneumonia as those who are not ventilated. Controlling for all other variables implies that the value of each of the continuous explanatory variables in the model has been set to the respective mean value and that each of the dichotomous variables occurs at equal frequencies. An investigator should always be conservative in interpreting

an OR estimated from multiple logistic regression analysis. Other variables, not included in the model, may actually cause the variability of response.

Matched Case–Control Studies For matched case–control studies, the investigator can use conditional logistic regression to study the effects of confounders (20). The reason for matching is that the investigator knows that certain factors are partially confounded with the relationship between exposure and outcome. However, there may be other potential confounders that the investigator wishes to consider in a multiple regression model. Because of complexities involved in fitting the parameters of this model, clinical investigators rely on a computer-based iterative algorithm.

Survival Analysis

A clinical investigator uses survival analysis when the outcome or response variable is time to an event (*1*,*3*,5,*6*, 8,*18*,20,*25*,34,38,*39*,*40*). The event is often considered a failure. Survival analysis is a form of conditional logistic regression analysis that allows for censored observations. Some survival analysis is based on parametric models that allow for left-, right-, or interval-censored observations. In clinical investigations, the most commonly used models for survival analysis are nonparametric models that allow for right-censored observations. In the clinical setting, a common feature of lifetime or survival data is the presence of right-censored observations; censoring arises from either withdrawal of subjects or termination of the study. For censored observations, the lifetime is known to have exceeded the recorded value, but the exact lifetime remains unknown. Survival data should not be analyzed by ignoring the censored observations. Among other considerations, the longer lived units are generally more likely to be censored. Therefore, the analysis must correctly use the censored observations and the uncensored observations.

The investigator regresses the survival time variable on one or more independent variables. The survival curve gives the probability of survival up to time t for each time. The hazard function is the instantaneous probability of having an event at time t given that the subject has survived up to time t. Under Cox's proportional hazards model, the hazard is modeled as $H(t) = h_0(t)e^{(\beta_1 X_1 + \cdots + \beta_k X_k)}$, where X values are independent variables and $h_0(t)$ is the baseline hazard at time t. Cox's proportional hazards model has become the method of choice for multivariable analysis of incidence density variables. By taking logarithmic transformations, the investigator can interpret the regression coefficients in a way similar to multiple logistic regression. The investigator uses similar methods for hypothesis tests and point and interval estimation of regression coefficients and conditional RR approximations of RRs. Cox's proportional hazards model can be generalized to accommodate both time-dependent and constant explanatory variables. Because of complexities involved in fitting the parameters of survival models, clinical investigators rely on statistical software.

Usually, a first step in survival analysis is the estimation of the distribution of the failure times. The survival distribution function (SDF) is used to describe the lifetimes of the population of interest. The SDF evaluated at time t is the probability that a subject sampled from the population will have a lifetime exceeding t—that is, $S(t) = \Pr(T > t)$ where $S(t)$ denotes the survival function and t is the lifetime of a randomly selected subject. A likelihood ratio test may be used to test for equality of SDF between the strata. Estimates of some other functions closely related to the SDF may also be obtained. These related functions include the cumulative distribution function, the probability density function, and the hazard function. The hazard function indicates when the likelihood of failure is greatest.

Clinical investigators may select other variables for defining strata. Survival estimates within the strata can be computed and displayed using Kaplan–Meier plots for visual comparison of the results. The median survival time corresponds to that time when half the subjects have failed and half still survive. The investigator may also be interested in the times when 25% and 75% of the subjects in the sample have failed. In addition, rank tests for homogeneity can be used to indicate whether there are significant differences between strata at shorter and/or longer survival times. The Wilcoxon test places more weight on early (shorter) survival times. The log rank test places more weight on larger (longer) survival times.

Often there are additional variables, called covariates, that may be related to the failure time. These variables can be used to construct statistics that test for association between the covariate and the survival time. Two commonly used tests are the Wilcoxon and log rank tests. These tests on covariates are computed by pooling over any defined strata, thereby adjusting for the strata variables. These two tests are similar to those used to test for homogeneity.

Model Selection Techniques for Regression Analysis

Having selected a set of potential explanatory variables, the clinical investigator wishes to know which of these should be included in the final model. If there are only a few explanatory variables, the investigator can consider assessing all possible regression equations. With any more than three or four explanatory variables, the investigator should consider another technique. Statisticians have developed several techniques based on objective criteria for model selection. Before choosing one of these methods, a clinical investigator should review the section on model selection and consider consulting an experienced biostatistician or epidemiologist.

A forward inclusion procedure begins with no explanatory variables in the model. For each potential explanatory variable, the algorithm computes each variable's contribution to the model as if it alone were included in the model. Generally, for each potential explanatory variable, the p value associated with the test statistic is compared to a specified level of significance. That variable, which contributes the greatest amount of information and has a p value less than the specified value, is entered into the model. In the second step, the algorithm computes the contribution to the model (now containing one explanatory variable) for each remaining potential explanatory variable. That variable, which contributes the greatest amount of information and has a p value less than the specified value, is entered

into the model. If there is none that meets the entrance criteria, the process stops. If a variable does enter the model, this process continues until there are no variables remaining that meet the criteria for entrance. Once a variable has entered the model, it stays. Models selected with a forward selection technique should be scrutinized for multicollinearity and overparameterization.

A backward elimination procedure begins with a model that includes all potential explanatory variables in the model. For each variable included in the model, the algorithm computes the amount of information contributed by that variable and the *p* value associated with the test statistic. The variable that contributes the least amount of information and has a *p* value greater than a specified value is eliminated from the model. This process continues until all variables remaining in the model yield test statistics with associated *p* values that are smaller than the specified value. Once a variable has been eliminated, it is gone. Although this model selection was designed to address issues of multicollinearity and overparameterization, models selected with a backward elimination technique should be scrutinized for underparameterization.

A stepwise algorithm combines the techniques of forward inclusion and backward elimination. As with forward inclusion, potential explanatory variables are added one by one to the model. The technique begins with no variables in the model. The algorithm computes each potentially explanatory variable's contribution to the model as if it alone were included in the model. Generally, for each potential explanatory variable, the *p* value associated with the test statistic is compared to a specified level of significance. The variable that contributes the greatest amount of information and has a *p* value less than the specified value is entered into the model. However, a stepwise algorithm differs in that variables that are already in the model do not necessarily remain there. For each variable included in the model, the algorithm computes the amount of information contributed by that variable and the *p* value associated with the test statistic. The variable that contributes the least amount of information and has a *p* value greater than a specified value is eliminated from the model. This process continues until there are no variables remaining that meet the criteria for entrance or deletion. Even though this model selection technique was developed to minimize problems related to multicollinearity and overparameterization, models selected with a stepwise algorithm should be scrutinized.

ROLE OF A CONSULTING BIOSTATISTICIAN IN CLINICAL RESEARCH

In some situations, the statistical aspects of a study become so involved that consulting with a biostatistician is essential. Throughout this chapter, I have indicated when, in my opinion, an investigator with a moderate level of both research experience and analytic skills should consider seeking the assistance of a biostatistician. Those with a lower level of either experience or skills should seek advice earlier in the research process. For some projects, a healthcare epidemiologist should consider involving the biostatistician as a member of the research team. Ideally, this arrangement requires a high level of commitment on the parts of both the healthcare epidemiologist and the biostatistician. Most researchers lack the time and mathematical background required to master complex statistical issues and methods (e.g., multivariable model selection). Thus, a progressively more common practice is to include a biostatistician (or a scientist with specialized training in statistics) on research teams.

The research goals and objectives of a consulting biostatistician are similar to those of researchers in other scientific disciplines: to develop and disseminate high-quality science through research. However, the biostatistician focuses on the statistical aspects of research questions. These aspects include experimental design, statistical analysis, interpretation of results, and dissemination of results through publication. As a member of a research team, a biostatistician should be capable of serving all statistical needs of the project. Occasionally, a research project presents some unique feature that has not yet been considered in the field of applied statistics. Many biostatisticians will recognize that this feature provides a research topic in biostatistics and the opportunity for developing a new statistical technique.

Qualifications, abilities, and available time will limit a biostatistician's role on a research project. Obviously, technical skills and knowledge of statistical methods are essential. Most biostatisticians have a general knowledge of many statistical methodologies. However, like most professionals, biostatisticians have special interests and, thereby, acquire practical experience in specific types of analytic methods. For example, if the study involves complex multivariable model development and selection, the investigator should attempt to seek assistance from a biostatistician who has an interest in those analytic methods and is experienced in multivariable models and model selection.

Most research questions can be addressed several ways. Constraints that are independent of the question usually make one design more desirable than another. In addition to having the necessary practical experience, possessing problem-solving abilities allows a biostatistician to appreciate practical issues and to choose efficient experimental designs and appropriate statistical methods.

Good interpersonal skills are necessary for the biostatistician to communicate effectively with the principal investigator. If the biostatistician becomes a team member, these skills are needed for communication with coinvestigators, technicians, and other ancillary staff members. Oral and written communication abilities are important team traits. Tactfulness is an interpersonal skill that is especially needed by biostatisticians who interact with individuals who may feel uncomfortable and vulnerable when they discuss statistical issues.

Typically, biostatisticians work as consultants on a large number of projects. The demand for biostatisticians exceeds the supply. Therefore, researchers will need to make compromises with biostatisticians regarding their level of involvement as members of research teams. From the biostatistician's perspective, being a member of a research team represents a long-term investment of

time and effort. The biostatistician needs time to learn enough about the health science of the problem so that he or she can assist the investigator with the interpretation of results. The biostatistician needs time to complete the analyses. Because computers complete computations extremely quickly, investigators can forget that programming and exploratory data analyses can be extremely time-consuming for the biostatistician.

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CHAPTER 4

Principles of Healthcare Epidemiology

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Epidemiology is the study of the distribution and determinants of health and disease in populations. Healthcare epidemiology is the application of epidemiologic principles to the inpatient, long-term care, and outpatient environments. Healthcare epidemiology has its roots in infection control, and this activity remains central to most healthcare epidemiology programs. In the past two decades, however, the scope of the field has expanded to encompass control and prevention of both infectious and noninfectious adverse events. Concurrently, the reach of healthcare epidemiology has expanded to include events that are a result of hospital exposures that do not become evident until after discharge. The term *healthcare-associated* has come into common usage to encompass all healthcare-related events and is gradually replacing the more narrow term, *nosocomial*. This chapter examines the background and rationale for healthcare epidemiology and reviews the characteristics of an effective healthcare epidemiology program in the hospital.

HOSPITALS IN THE UNITED STATES

The hospital environment is highly complex and continuously presents new challenges to the epidemiology team. There are currently 5,815 hospitals in the United States, and this number has been relatively stable over the past decade *(1)*. Among hospitals, 86% are community based (including university hospitals), 8% are nonfederal psychiatric hospitals, and 4% are run by the federal government. US hospitals have 951,045 staffed beds and handle more than 37 million admissions each year. In 2006, there were 119 million visits to hospital emergency rooms and 102 million visits to hospital outpatient departments *(2)*.

Patients move through the hospital environment rapidly. In 2006, the average length of stay per inpatient was only 4.8 days, compared to 5.4 days in 1995 and 6.5 days in 1985 *(2)*. With this rapid turnover, it is easy for a patient to acquire an infection in the hospital and be discharged before the infection is diagnosed or becomes manifest. This creates a problem in case finding and thus affects the accuracy of attack rates.

Overall, 7.3% of the US population was hospitalized at least once in 2006, which is slightly less than the 7.7% figure for 1997. Although the major discharge diagnoses have remained relatively static over the past decade, the severity of illness has increased in many centers. In part, this is a reflection of advances in the outpatient environment, which can now handle mild or moderate illnesses without hospitalization. Third-party payers have also restricted or eliminated inpatient reimbursement for patients deemed to have milder illnesses, causing hospitals to try to limit admissions in this group. In addition, the inpatient population is influenced by population demographics. For example, as Americans have become more obese, type 2 diabetes has become more prevalent in the inpatient and outpatient settings *(3)*. Diabetes may increase the severity of many comorbid illnesses and the susceptibility to healthcare-acquired infections or surgical complications. Thus, although fewer patients are hospitalized and length of stay has decreased, severity of illness has increased in the inpatient population. The result is an increased susceptibility to adverse events and increased difficulty in detecting and preventing such events.

Healthcare is a major part of the US economy, and hospitals contribute a significant proportion of this cost. The total expenses for US hospitals exceed $690 billion per year *(1)*, accounting for 31% of all national health expenditures and rising steadily in the new millennium *(2)*. To the extent that adverse events are preventable, they represent an opportunity to reduce cost and improve quality.

The hospital environment includes healthcare workers as well as patients, and both groups have a right to be protected from harm. Almost six million workers are employed by hospitals in the United States *(2)*, and many of the nation's 1.7 million physicians work at least partially in an inpatient setting. Hospitals also provide a training site for the country's 71,000 medical students *(4)*, 145,000 nursing students in entry-level baccalaureate programs *(5)*, and 109,000 house staff *(6)*.

RATIONALE FOR HEALTHCARE EPIDEMIOLOGY

The practice and study of healthcare epidemiology is founded on the principle of nonmaleficence, as expressed in the phrase *primum non nocere*: "first do no harm." Unfortunately, the hospital environment has great potential to do harm. In the year 2000, the Institute of Medicine published

their seminal report *To Err is Human* (7), demonstrating that medical errors were a leading cause of death and injury in the United States. Based on data from previous studies, the report estimated that 44,000 to 98,000 Americans die annually in hospitals as a result of potentially preventable medical errors. As a result, medical errors have become at least the eighth most common cause of death in this country. In this context, medical errors are defined as potentially preventable adverse events, including medication errors *(8)*, accidental injuries, misdiagnoses, healthcare-associated infections, and others. Importantly, the goal of healthcare epidemiology is to improve patient outcomes and not all errors result in adverse outcomes.

Although the overarching goal of healthcare epidemiology is to improve health outcomes by reducing adverse events, an effective program can also save money for the hospital. Preventable adverse events are extremely costly. For example, one recent review estimated that ventilator-associated pneumonias cost approximately $23,000 per case, catheter-associated bloodstream infections cost over $18,000, and wound infections from coronary bypass surgery cost approximately $18,000 (9). Another study showed that wound infections from orthopedic infections cost approximately $18,000 per case *(10)*. Because there are large numbers of healthcare-associated infections, these costs add up rapidly. It has been estimated that more than 1.7 million healthcare-associated infections occur each year: 290,000 surgical site infections, 250,000 pneumonias, 250,000 bloodstream infections, and 561,000 urinary tract infections (11). Overall, the direct cost of healthcare-associated infections ranges from $28 billion to $45 billion each year (12). This total does not include the indirect costs of lost productivity.

Among noninfectious adverse events, medication errors and misdiagnoses are among the most common and serious events, respectively *(13)*. Medication errors include using the wrong dose, providing illegible prescription orders, using ambiguous abbreviations, giving the medication to the wrong patient, not paying attention to drug interactions or allergies, and using the wrong medication. It has been estimated that each hospital patient experiences approximately one medication error per day *(8)*. Most of these errors do not result in apparent harm, but some are serious. It is estimated that medication errors cause 1.5 million adverse outcomes and 7,000 deaths each year in the United States *(8)*.

Misdiagnoses are particularly problematic, because they necessarily involve human judgment that is necessarily fallible. Yet judgment can be augmented by systems that facilitate effective diagnoses. For example, the turnaround time on tests could be reduced so that clinicians have more data on which to base their diagnoses. Electronic medical records reduce errors by ensuring that a complete, legible record is available instantly to all members of the patient care team (14). Improved communication among physicians and between the outpatient and inpatient settings allows decisions to be based on a more complete understanding of the patient's history and condition. Much remains to be done in these areas. The prevention of wrong diagnoses and delayed diagnoses represents an important area for future study (15).

Having established that healthcare-associated adverse events are common and problematic, the question remains: What proportion is truly preventable? The efficacy of infection control has been established by several studies. A 2003 review of these studies (16) found that infection control measures reduced rates of healthcare-associated infections by 10% to 70%. This broad range reflects the varying effectiveness of the interventions that were studied, the baseline infection rates, and the settings for the studies. Overall, the authors estimated that at least 20% of healthcare-associated infections could be prevented by effective healthcare epidemiology programs. Although this represents a cost savings of $6 to $7 billion per year (12), more recent studies suggest that the 20% figure underestimates the potential to reduce rates (17,18) even for the most problematic infections.

Given the large number of medication doses that are given each day in a busy hospital, eliminating errors may seem like a daunting task. However, studies have shown that most errors are due to illegible prescriptions, ambiguous abbreviations, overlooking known drug allergies, or writing for the wrong dose of drug (19,*20*,21). A simple but expensive solution is to use computer-based prescribing instead of a handwritten record. Studies have shown that computerized physician order entry of medication orders consistently reduces errors, although the effect on adverse outcomes varies among studies (14,*22*).

Thus, although healthcare in the hospital setting has the potential to cause harm, much of the harm can be prevented by an effective healthcare epidemiology program. Hospitals should be motivated to support such programs to improve outcomes, reduce costs, and comply with regulatory requirements *(23)*, even—and some might argue especially—in an era of limited resources (24,*25*).

BASIC PRINCIPLES OF HEALTHCARE EPIDEMIOLOGY

The criteria for the optimal infrastructure and essential activities for healthcare epidemiology have been published by expert panels *(26)* and accreditation organizations such as the Joint Commission *(27–29)*. Effective healthcare epidemiology programs are data-driven, evidence-based, outcome-oriented, and fully engaged throughout the institution and community (Table 4-1). Data are derived from active surveillance systems. Passive surveillance, such as asking physicians to report patient infections, may supplement but not replace active surveillance. The goal of surveillance is to provide data on which to base interventions. Surveillance data are used to calculate endemic rates for key infections and to identify outbreaks. Active surveillance traditionally involves review of medical records by team members. Because this requires significant time and cost, such active surveillance may be concentrated in areas that are likely to have the highest yield of infections or events, such as the intensive care units.

With the rise of electronic health records, active surveillance has become easier and may eventually make hospital-wide surveillance economically feasible (30,*31*). One issue is that most electronic health record programs are not designed to produce the specific reports that are needed for surveillance. For example, computer-based surveillance may be able to provide a list of patients who

TABLE 4-1

Attributes and Functions of an Effective Healthcare Epidemiology Program

Attribute	*Function*
Data-driven	Active surveillance is performed for infections and adverse events using standardized case definitions
Evidence-based	Data analysis is based on sound statistical principles using appropriate denominators
	Data are risk-adjusted when appropriate
	Results are compared to internal and external standards
	Interventions are based on scientific evidence whenever possible
Outcome-oriented	Programs are both reactive and proactive, responding to increases in event rates and working to reduce endemic rates
	Programs are compliant with regulatory requirements
Fully engaged	Multidisciplinary committees such as the infection control committee review data, provide input, serve as conduits to disseminate information, and identify ways to leverage resources to improve patient outcomes
	All areas of the hospital, including administration, are engaged in and take responsibility for the outcomes of the program
	Strong liaisons exist with community health officials to facilitate planning and emergency preparedness

had fever after a surgical procedure, but the computer is unlikely to be able to identify a postoperative wound infection accurately. Thus, there is still a need for the epidemiology team to review the individual patient data to confirm potential cases. Surveillance data may be augmented from other computerized sources available in the hospital, such as microbiology laboratory reports. Optimally, as hospital information systems become more sophisticated, the healthcare epidemiology team will be able to focus more on control and prevention and less on data collection.

To maximize results, surveillance should be evidence-based and objective. To this end, the Centers for Disease Control and Prevention (CDC) has established standard definitions for infections (32). Surveillance data should include both a numerator (number of cases) and an appropriate denominator (hospital inpatient days or device days). Crude event rates may be calculated from the data and compared to the hospital's historical rates. Risk adjustment is used to compare rates between populations or settings (33). It is also important to compare hospital rates to an external standard or "benchmark." The National Healthcare Safety Network (NHSN) is an Internet-based surveillance system that allows member hospitals to enter their data securely and compare their rates with other participating hospitals. Administered by the CDC, the NHSN system includes both infectious and noninfectious adverse events. In return, the network provides hospitals with risk-adjusted data that can be compared with peer hospitals and is able to produce reports based on aggregate data from member hospitals *(34,35)*. Data contained in the system are confidential.

Data analysis must be based on sound biostatistical principles, as described elsewhere in the text. Within this framework, attention and resources should be focused on the most clinically relevant findings. Thus, an outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) in the newborn nursery would provide more fertile ground for intervention than an increase in contaminated urinary specimens sent to the laboratory. It is important to note that relying on statistics alone may provide a false sense of accomplishment. For example, a hospital that merely tries to keep its rates within a preestablished confidence interval compared to historical rates will miss opportunities to improve endemic problems. Many hospitals previously tried to keep ventilator-associated pneumonia rates or catheter-associated bloodstream infection rates within 95% confidence limits of national norms. Recent evidence shows, however, that many of these institutions can eliminate these infections or achieve near-zero rates (17,18).

Effective healthcare epidemiology programs are both reactive and proactive. When analysis of surveillance data indicates an outbreak has occurred, effective programs respond promptly to locate the source and eliminate the problem. The healthcare epidemiology team works proactively to prevent adverse events and infections, thus reducing endemic rates.

Interventions should be logical and evidence-based. For infectious issues, a strong understanding of microbiology is essential. For example, an outbreak of *Legionella* pneumonia should prompt an examination of the water system and a review of procedures that aerosolize water. The presence of *Aspergillus* should raise concern about dust from nearby construction. Knowledge of the literature is also essential, because there are likely to be reports of similar outbreaks. In some cases, randomized controlled trials have been done and identify an optimal intervention (18) or show that an intervention does not work (36). When randomized trials are not available, a meta-analysis or systematic review may be useful (*37–40*,41). Finally, if no clear answer is available from scientific studies, the literature often contains consensus guidelines based on expert opinion. When there is no good study or consensus guideline to address a particular topic, top-notch healthcare epidemiology programs will publish their own results or design a study to address the issue.

Because adverse events occur in every area of the hospital, effective healthcare epidemiology programs are hospital-wide efforts, involving multiple disciplines and

functions. Many programs consist of a core team including infection preventionists, quality improvement specialists, a physician healthcare epidemiologist, an infection control committee, and a quality committee. This core team is responsible for organizing an effective surveillance system, analyzing data, producing reports, receiving input, and designing interventions. However, it is critical that the entire organization take responsibility for reducing infections and adverse events. For example, a campaign to improve hand hygiene would have optimal success if the director of nursing, the chief of staff, the hospital leadership, and unit directors all took responsibility for ensuring that standards are consistently met. To engage the entire organization, it is important that multidisciplinary committees receive regular reports from the healthcare epidemiology team. An effective infection control committee provides input to the team, identifies ways to leverage resources, and helps disseminate information throughout the hospital. Members should be chosen with these abilities in mind. Committees that specialize in quality improvement or safety play a similar role in managing infectious and noninfectious adverse events. Depending on the issue at hand, subcommittees may be formed from members with special expertise. An effective committee, therefore, does not simply receive reports. Rather, it assumes a level of responsibility for the outcome of the healthcare epidemiology program.

Outreach is a critical component of healthcare epidemiology. Hospitals have an important and growing role in the health of their community, especially in emergency preparedness (42,*43*,*44*). Hospital participation is crucial in community preparedness planning and the community should be part of hospital planning. In part, this is because of the resources available within the hospital that might be required on short notice in the event of a community emergency. More broadly, a coordinated response to an emergency is more likely to be effective and to instill public confidence in the process *(44)*. The hospital also benefits from close liaisons with emergency providers, resource managers, and community leaders. Healthcare epidemiology programs also can provide expertise, assistance, and support to public health and community leaders during community outbreaks as well as during response planning.

UNIQUE ASPECTS OF THE HOSPITAL ENVIRONMENT

The hospital environment presents several unique challenges to the epidemiology team. The hospital functions as a therapeutic milieu where treatments that improve patient health may simultaneously cause increased susceptibility to adverse events. Such is the case with treatments that are known to suppress the immune system, indwelling devices that serve as conduits for microbes, sedatives that increase susceptibility to falls, and antibiotics that cause resistant pathogens to replace normal flora. Moreover, populations at risk for adverse events may also serve as vectors for the events. For example, visitors with respiratory infections may acquire secondary infections in the hospital or may spread infection to others. Healthcare providers who do not observe hand hygiene standards are at risk to acquire and spread resistant pathogens such as MRSA. The 2009 novel H1N1 influenza pandemic demonstrated this dual role of victim and vector as providers acquired the virus at home and at work, providing opportunities to spread the infection within hospitals *(45)*.

As discussed above, inpatient populations in the hospital are transient. For some adverse events, such as falls or medication errors, the event is confined to the hospital stay, and it is relatively easy to attribute the event to the hospital setting. Because bacterial infections have a 2- to 4-day incubation period, infections acquired in the hospital may not become manifest until after discharge. This complicates classification of infections as healthcare-associated or community-associated. Stochastic definitions have been developed based on whether a patient has been in a hospital within a certain time frame. Such definitions are useful for surveillance, but are not necessarily accurate on an individual basis. In the past, some highly resistant bacteria were almost exclusively acquired in the hospital setting, and their mere presence was enough to identify them as hospital-associated pathogens. More recently, however, pathogens like MRSA and *Clostridium difficile* have begun to spread within communities, further complicating classification.

Because the hospital environment is so complex and because resources are limited, healthcare epidemiology programs often focus on patients at highest risk for adverse events and on adverse events that are highly likely to cause mortality and morbidity. It is important to realize that this is the tip of the iceberg. Thus, high-quality epidemiology programs will include both initiatives focused on high-risk settings such as intensive care units and hospital-wide initiatives such as hand hygiene programs. In some cases, interventions in a focused population may have the ability to improve outcomes throughout the hospital.

Healthcare epidemiology programs are increasingly involved with mitigating environmental hazards related to buildings, including construction, renovation, maintenance, and housekeeping activities. The facility's environment serves as a reservoir for microorganisms that may be implicated in healthcare-acquired infections and a potential source of patient or worker injury *(46)*. Healthcare epidemiology has multiple approaches to reducing the risk from the environment. Isolation precautions have been developed to restrict the spread of selected pathogens from patient to patient or from patient to healthcare worker. Barrier precautions such as gowns, gloves, and masks are an integral part of these measures. In most instances, there are no rigorous scientific studies to support recommendations for isolation (36,47,*48*). Rather, guidelines are based on interrupting the known means of transmission of pathogens.

The complexity of the hospital environment requires multifaceted interventions. For example, successful programs to reduce medication errors usually involve pharmacists, nurses, physicians, and health information technology experts, each of whom have one or more roles in the intervention. At times, a series of actions are combined together to create one unified intervention "bundle." In effective bundles, each individual action is evidence-based and has proven efficacy, and each compliments the others. Highly effective bundles are an important part of the modern approach to healthcare epidemiology (18).

CONCLUSION

As the science and practice of healthcare epidemiology have advanced, healthcare-associated adverse events are no longer considered an inevitable result of hospitalization. Once an unimaginable goal, zero rates are becoming a reality for some adverse events. In concert with this new reality, third-party payers are withdrawing reimbursement for events that they consider to be wholly preventable (49). Moreover, regulatory agencies have begun to incorporate these new expectations into their accreditation standards. In this sense, regulatory agencies and third parties function as motivators for hospitals to support healthcare epidemiology programs. Optimally, this movement will lead to the discovery of additional evidence-based interventions that can be incorporated into contemporary practice standards. This new culture has increased pressure on healthcare epidemiology programs to perform at the highest possible level.

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CHAPTER 5

Data Collection in Healthcare Epidemiology

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Data for healthcare epidemiology come from three sources: direct ascertainment of information from subjects using questionnaires or direct observation; review of medical records; and electronic sources, such as billing records, laboratory records, and medication administration records. Although we provide an overview of each of these data sources, we emphasize the development of questionnaires. After data from any of these sources are collected, they are entered and organized (usually in a database) and analyzed, usually using a statistical package. We offer suggestions on the preparation and formatting of data to facilitate the transfer from data collection to data analysis.

QUESTIONNAIRES

Questionnaire Development

Questionnaires are often the most labor-intensive form of data collection but are required in situations where surveillance using electronic data sources or medical record review is inadequate.

After deciding what data need to be collected, the investigator has to decide how to collect it. This means developing the form(s) to guide data collection, identifying the data sources (e.g., individuals, proxies, medical records, direct observation), identifying data gatherers, and deciding on a mode of data collection. Decisions in each of these areas affect the others, and investigators should understand the trade-offs between them in order to make good decisions when planning an investigation.

Writing the Questions The first step in developing a data collection form is writing the questions to elicit the information required by the study. Good questions are clear and unambiguous and match the verbal skills of prospective participants. Poorly worded questions result in answers that are unreliable or uninterpretable. Although writing good questions is something of an art, there are several common problems that can result in bad questions.

Choosing Verbiage If respondents do not understand the words used in questions, they will not be able to answer them (or worse, they will answer them anyway). In general, the words used in the questions should be ones used by respondents in their usual conversation (e.g., use "help" rather than "assist" and "enough" rather than "sufficient"). Avoid medical jargon and abbreviations that may not be commonly understood. Be aware of regional or cultural differences in the meanings of words and the names of diseases (e.g., diabetes may be called "the sugar" by some respondents). Avoid using loaded words (i.e., those carrying excessively negative connotations).

Consider these questions:
Should smoking be banned in the hospital?
Should smoking be allowed in the hospital?

The word *banned* is loaded, and some answers to the question may be a reaction to the word itself rather than to the content of the question.

Ambiguous Questions One of the most difficult tasks in writing a question is asking it in such a way that the respondent has the same concept in mind when answering it as the investigator did when asking it. The investigator wanting to identify current cigarette smokers might ask: "Do you smoke?" Cigar and pipe smokers will answer this affirmatively, contrary to the investigator's intention. There may also be those who have very recently quit smoking (and may soon begin the habit again). They would answer no, but the investigator might want them classified as smokers for the purposes of the study. "Have you smoked two or more packs of cigarettes in the past 2 months?" is a better version of the question. Cigarettes are specifically named, and the amount of consumption and the period are specified. In some cases, visual aids such as pictures of products or models may be helpful in orienting the respondent.

In an outbreak investigation of central line infections, hospital personnel might be asked, "Did you see patients on [a particular ward]?" This question has two ambiguous referents. Does "see" mean "care for," or is the question intended to detect less formal contact as well? Also, does the investigator mean if the respondent has ever seen patients on a ward, or just during the epidemic period? A better phrasing might be, "Did you provide care for any patients on [the ward] since March of this year?"

Causes must precede effects in time. Therefore, when assessing the relationship between a behavior that may change over time and disease occurrence, it is important that the questions refer to the period prior to the onset of disease symptoms. Failure to make this clear can lead to

biased results if the behavior changes in the face of symptoms. Both the failure to elicit exposure information from the appropriate period and the inclusion of irrelevant exposure information can lead to bias.

Hypotheticals Avoid hypothetical questions. Consider a question that might be asked of nurses in an infection control project: "Is it important to wear gloves when placing an IV?" The question is problematic, because it may refer to either what is important in a hypothetical sense or what is personally important to the respondent. The responses will be a mixture of these two interpretations, with the investigator having no way of distinguishing the two.

Asking More than One Question Each question should try to elicit only one piece of information. Consider the question, "Have you experienced nausea, vomiting, night sweats, or loss of appetite?" This set of symptoms may be useful in arriving at a diagnosis, but in an epidemiologic investigation, it may be important to document each symptom individually for later use in applying a consistent case definition. Furthermore, respondents may focus on the last symptom named. A respondent may have had night sweats but answer, "No, my appetite's fine." A checklist is often used to systematically identify symptoms of potential interest.

Assumptions in the Questions Answers to questions that make tacit assumptions can be difficult to interpret. Consider the example from Kelsey et al. (1): "Do you bring up phlegm when you cough?" The question assumes that a cough is present. A negative response might mean that no phlegm is produced or that the respondent does not have a cough.

Vague Questions and Answers Avoid the use of words such as "regularly," "frequently," and "often," both in questions and as response options. Different responders will interpret these words differently. The potential for qualitative responses to introduce unwanted variability was vividly demonstrated by Bryant and Norman (2), who asked 16 physicians to assign a numerical probability to qualitative adjectives such as "probable," "normally," and "always." The numerical probability assigned to the word "probable" ranged from 30% to 95%. The probability assigned to "normally" ranged from 40% to 100%, and that to "always" ranged from 70% to 100%. Whenever possible, try to elicit a quantitative response.

Threatening Questions Care needs to be taken when asking questions of a somewhat embarrassing nature. Embarrassing questions concern respondent behaviors that may be illegal or socially undesirable or concern areas of life that may threaten the respondent's self-esteem. Research has indicated that the self-reported frequency of potentially embarrassing behaviors can be increased if long, open-ended questions are asked. Open-ended questions are those to which categories of set responses are not supplied by the investigator (as opposed to closed questions, in which the respondents select answers from a list of supplied alternatives). Bradburn and Sudman (3) contrasted various question styles ranging from short questions with fixed response categories to very long questions with open-ended responses. They also contrasted using the respondent's familiar term for the behavior versus a term supplied by an interviewer. Respondents were randomized in a $2 \times 2 \times 2$ factorial design into one of eight different question formats (i.e., long vs. short response format, open vs. closed response format, and familiar vs. standard wording). One short question (with standard wording and closed response format) read: "In the past year, how often did you become intoxicated while drinking any kind of beverage?" The respondents picked a response from a list of eight alternatives. The long form (with respondent's wording and open response format) read:

> *Sometimes people drink a little too much beer, wine, or whiskey so that they act different from usual. What word do you think we should use to describe people when they get that way, so that you will know what we mean and feel comfortable talking about it?*
> *Occasionally, people drink on an empty stomach or drink a little too much and become [respondent's word]. In the past year, how often have you become [respondent's word] while drinking any kind of alcoholic beverage?*

The respondents were given no response categories but asked to supply their own best estimate. The question format did not seem to affect the percentage of people reporting that they had engaged in an activity. It did, however, strongly influence the self-reported frequency of the activity. Those responding to long questions with open-ended responses using familiar terms reported significantly higher frequencies of the behavior of interest. The mean annual consumption of cans of beer calculated using responses from the long, open format with familiar wording was 320 cans; that calculated using the short, closed format with standard wording was 131 cans. Large differences in responses attributable to question format were seen for questions dealing with the frequency of sexual activity as well. Most of the difference was attributable to the use of an open-ended response format and longer questions. The effect of using familiar wording was weaker but was associated with consistently higher reported frequencies of potentially embarrassing behaviors.

Asking Questions about Events in the Past Asking individuals about the occurrence and/or frequency of specific events in the past is a special measurement challenge. An investigator whose study depends on the validity of human recall must be particularly attuned to the shortcomings of human memory. Respondents to epidemiologic questionnaires are often asked to perform one of three memory tasks: (a) recall whether a particular event occurred to the individual, (b) recall when the event occurred, or (c) recall how frequently it occurred. Research has shown that it takes some time for people to access their memory for the occurrence of events. Longer questions seem to be useful in giving respondents more time to recall events and may increase the percentage of events recalled (4). Nevertheless, people frequently forget specific events in their past. As a rule, an event is harder to remember if (a) it occurred a long time ago, (b) it is one of a series of similar events, or (c) the respondent attaches little significance to it (4).

People also frequently misplace remembered events in time. There is a tendency to judge events that are harder to recall as less recent and, conversely, there is a tendency to date events about which a lot of detail is recalled as more recent. This problem is termed "telescoping" in survey research (4). Consider the question: "Have you been to a doctor in the past 12 months?" Respondents frequently answer affirmatively if the visit was 15 months ago. People may remember the event better than its date and import the event into the time interval of interest.

Aspects of the design and administration of questionnaires can improve both remembering and dating events. Questions starting with recent events and working backward in time can improve recall. Also, providing date cues can help. One common technique is to provide the respondent with a calendar. Before asking about events of interest, the respondent identifies personally relevant dates such as birthdays and holidays. Then, the respondent is walked back through time and assigns dates to the occurrence of the events of interest with respect to the personal landmarks. As reported by Means et al. (5), a sample of George Washington University Health Plan enrollees was asked to try to recall all health plan visits in the past year. All study participants had at least four visits in the past year. Before using the landmarking technique, participants were able to recall 41% of the health plan visits recorded in the medical record. After the landmarking, 63% of health plan visits were remembered. In a separate study group using only the landmarking technique, 57% of visits were recalled. The use of landmarking also led to an improvement in dating accuracy.

The frequency of a behavior is often of epidemiologic interest insofar as it may serve to quantify the amount and/or rate of an exposure. Humans tend to rely on two strategies for recalling the frequency of events (4). The first is simply trying to remember every instance of a behavior over a period. The second is referred to as the event decomposition method. People first estimate a rate at which a behavior is performed and then apply it over the period of interest. For example, if a respondent is asked how many times she went to a restaurant in the past 2 months, she may figure that she goes to a restaurant twice a week, and therefore, she ate at a restaurant eight times in 2 months. In general, the decomposition method seems to lead to more accurate estimates than the recall of individual events. Investigators planning studies to measure the frequency of exposure may wish to structure questionnaires to explicitly elicit these frequency estimates.

PRETESTING THE DATA COLLECTION INSTRUMENT

Prior to full-scale data collection, it is useful to pretest all study procedures. This includes pretesting any data collection documents. The pretest may include a number of steps. An expert in the field should review the data collection forms. This expert should be able to identify any content omissions. The review by nonexpert colleagues can be useful to give overall impressions, to identify troublesome questions, and to determine if the skip patterns flow logically. In the next phase of pretesting, test the data collection procedures under study conditions on a number of potential study subjects (frequently 20–30). In this phase of pretesting, one can identify questions that don't work and whether the needed information is indeed available from the intended data source. If the data collection form is being used to elicit information from respondents, debrief your pretest subjects to discover what they had in mind while they were answering and how some questions might be asked better. A pretest also provides the opportunity to ascertain preferences among varying question wordings and answer formats.

Schlesselman (6) describes an example indicative of the kind of problems that a pretest can identify. In a study involving analgesic use, the following series of questions were tested:

Q. HAVE YOU EVER HAD FREQUENT HEADACHES?
Yes
No

Q. HAVE YOU EVER HAD VERY SEVERE HEADACHES?
Yes
No

Q. HAVE YOU HAD HEADACHES ONCE A WEEK OR MORE DURING THE PAST MONTH?
Yes
No

The third question was used as a filter for a series of questions relating to analgesic use for headache. The purpose of the questions was to identify individuals who were likely to be frequent analgesics users for headache relief. Schlesselman states, "The third question was included under the assumption that recall is better for the most recent period, and that a person with a history of recurrent headaches in the past would retain this pattern in the present." In pretesting, however, it was found that there were many patients who had frequent headaches but for whom the past month was atypical. Thus, contrary to the intention of the investigator, a number of study participants were skipping the series of headache-analgesic questions. In light of the pretest, the third question was modified to:

Q. HAVE YOU EVER HAD HEADACHES ONCE A WEEK OR MORE FOR AT LEAST ONE MONTH?

OPTIONS FOR ADMINISTRATION

The primary options for administering a questionnaire are respondent self-administered and interviewer-administered. Self-administered questionnaires are usually either given in a supervised setting or mailed to the respondent; however, there are an increasing number of questionnaires that are being administered using e-mail or the Internet. Interviewer-administered questionnaires can be administered either in person or over the phone. Each method has its advantages and drawbacks. Self-administered questionnaires are usually less expensive to administer but need to be simpler and shorter than interviewer-administered questionnaires. Also, when a portion of the study population is of low literacy, the use of self-administered forms results in unacceptable losses of information. Internet-based surveys can

be more complex but require that respondents have access to and are comfortable with computers and the Internet. Interviewer-administered questionnaires can be more complicated and longer, and the literacy of the respondent is not an issue. Also, the use of an interviewer permits the probing of the respondent for clarifications and elaborations. The major drawback of using an interviewer is the cost.

Differing modes of administration have their advantages and disadvantages. Mailed questionnaires are relatively inexpensive to administer, but response rates tend to be low (typically 40–60%). Response rates can be increased by a number of techniques such as hand-addressing the envelopes, using certified mail, using postage stamps instead of metered mail, and rewarding the respondent. Collecting data over the phone is more expensive than by mail, but the response rates are higher (frequently 75–85%). Completion rates for telephone interviews can be increased by sending an introductory letter to the home introducing the study. Using the phone as the sole mode of contact may introduce subtle biases into a study. The portion of the study population that does not own a phone is systematically different from the portion that does. Also, the ability to contact certain segments of a population may differ. For example, young, single, smoking males are harder to contact by phone than some other segments of the population. Internet surveys appear to be a reasonable substitute for mailed surveys given that respondents have Internet access. Initial response rates can be low but can be increased with reminder letters/e-mails (7).

Face-to-face interviews have the highest completion rates (up to 90%), and they are also the most expensive to conduct. In face-to-face situations, visual aids and more elaborate questioning techniques can be used, providing the opportunity to improve the quality of the collected data.

MEDICAL RECORDS

Collecting data from recorded information is a part of nearly all epidemiologic studies conducted in a hospital setting. Recorded data sources include diagnostic reports, physician notes, prescription records, and culture reports. In addition to routinely collected medical data, administratively collected data are also available from billing records, insurance claim files, etc. The advantages of recorded data are clear: they provide a concurrent source of information concerning the study subject's medical experience. However, the limitations of routinely recorded data should also be borne in mind. Data are put in the medical record by a number of different individuals who are not standardized in their recording habits, and they certainly do not record information with a particular epidemiologic study in mind. Two studies illustrate the problems with the medical record as a tool for epidemiologic research.

Massanari et al. (8) compared the ability of one hospital's medical records personnel to identify and code the presence of nosocomial infections to that of an epidemiologic surveillance system. They discovered that only 43% of nosocomial infections identified through epidemiologic surveillance were reported in the discharge abstract. On inspection of a sample of incongruent cases, 44% of the cases were missed by medical records, because the physician failed to document an infection. However, medical records personnel failed to note infections clearly recorded in the chart about 16% of the time. Other studies concerning the usefulness of the medical chart in infectious diseases investigations in the hospital have documented even poorer performance (9,10).

Gerbert et al. *(11)* compared four methods to determine whether specific drugs had been prescribed to chronic obstructive pulmonary disease patients. The methods were a physician interview, a chart review, a patient interview, and a review of a videotape of a physician–patient encounter. The four methods agreed only 36% of the time in determining whether the patient had been prescribed theophylline. According to the physician, 78% of patients were on theophylline, the medical chart indicated that 62% of patients were on the medication, and the videotape, 69%. Only 59% of the patients reported themselves to be on theophylline. The investigators determined that each method had good specificity (i.e., few respondents reported being on theophylline when they were not) and that the physician interview had the best sensitivity.

ELECTRONIC DATA

Electronic data come from two sources: administrative data, which are used by all hospitals primarily for billing, and clinical data, such as medication administration records, laboratory, and radiology reports. The richness of clinical data available to the investigator varies among hospitals.

Administrative data from hospitals include demographic information, admission and discharge dates, codes for principal and other diagnoses, procedure codes, disposition of the patient, and expected payment source *(12)*. Although universally available, administrative data should be used with great caution for healthcare epidemiology, primarily because of issues relating to sensitivity and specificity in diagnosis codes (13). In studies examining the reliability of discharge data forwarded to the Health Care Financing Administration, data items such as admission date, discharge date, date of birth, gender, and payment source were found to agree well with those found in the medical record (14). However, on review, the reported principal diagnosis agreed with that found in the medical record only 57% of the time. Similarly, Johnson and Appel (15) found that the diagnosis-related group reported to Medicare matched the one listed in the medical record approximately half of the time.

Even if data are reliably collected, the failure to understand how administrative databases are maintained can introduce artifactual findings. For example, Iezzoni et al. *(16)* found lower death rates among hospital inpatients with diabetes listed as a comorbidity in an administrative database. The reason was that the database accommodated only five comorbidities. Therefore, the relatively healthy patients (i.e., the ones with fewer acute problems) were the ones for whom the diagnosis of diabetes made it into the database.

Clinical data may be more useful for surveillance in healthcare epidemiology (*17*,18,*19–20*). Classen et al. *(19)*

described surveillance using the Health Evaluation through Logical Processing (HELP) system, of LDS Hospital in Salt Lake City, Utah. This system includes data from pharmacy, laboratory, surgery, radiology, admitting, microbiology, and pathology. Furthermore, clinical data (e.g., International Classification of Disease codes) and charge data are also a part of this system. Initial studies revealed that a computer algorithm identified more hospital-acquired infections than traditional surveillance methods, while requiring only 35% of the time *(20)*. Several subsequent investigations of infections (*21*,22,*23*) and adverse drug reactions (24,25) have been conducted using this system.

PREPARING DATA FOR STATISTICAL ANALYSIS

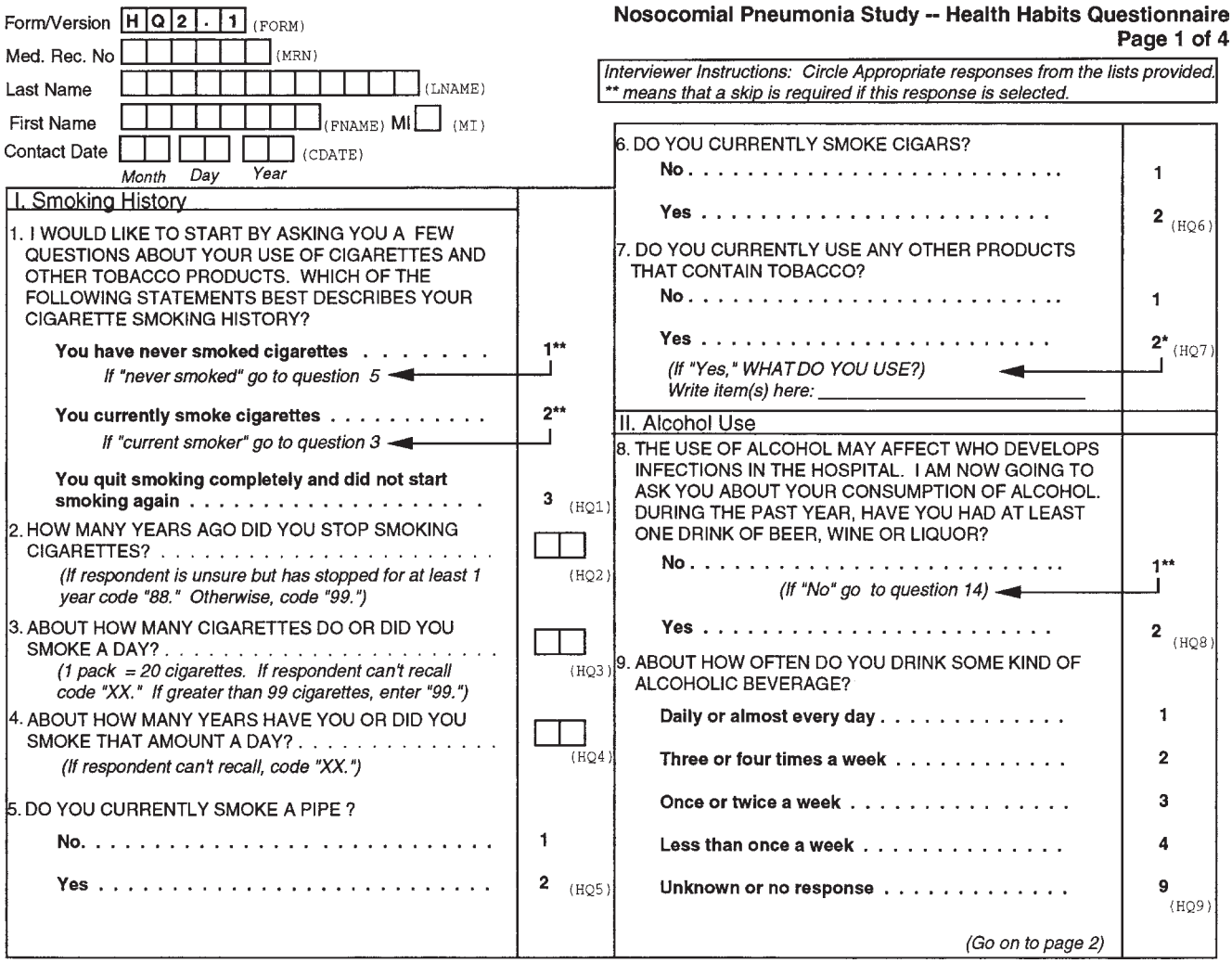
Organization of Data Collection

Attention to the format of a data collection document can speed data collection and data entry and increase data quality. The physical appearance of the data collection document is also important. A professional-looking tool can inspire the respondent's confidence in the investigator.

A data collection form has two sections: the header and the body. The header should contain a form code, a form version number, and a unique identifier corresponding to the participant about whom data are being collected. In healthcare epidemiology, it is tempting to use a patient's medical record number. However, it is necessary to assign a study identification number to place on the forms instead of a medical record number to protect patient confidentiality should the form become misplaced or lost. The identification number allows the data collected on the form to be linked with data collected from other sources. A code for the form and its version are useful in establishing the data's provenance after computer files have been generated.

The body of the basic data collection form has three elements: the questions, the responses, and the directions. In Figure 5-1, each element is typographically distinct. The questions are in all capital letters, the responses are in bold, and the directions to the interviewer are in italics.

The questions should flow in some sort of natural order. For instance, if the data collection form is being used to abstract a medical record, the questions should appear in the order that the information is found in the medical record. If the questionnaire is to be administered to an


Form/Version H Q 2 . 1 (FORM)
Med. Rec. No (MRN)
Last Name (LNAME)
First Name (FNAME) MI (MI)
Contact Date (CDATE)
Month Day Year

Nosocomial Pneumonia Study -- Health Habits Questionnaire
Page 1 of 4

Interviewer Instructions: Circle Appropriate responses from the lists provided.
*** means that a skip is required if this response is selected.*

I. Smoking History

1. I WOULD LIKE TO START BY ASKING YOU A FEW QUESTIONS ABOUT YOUR USE OF CIGARETTES AND OTHER TOBACCO PRODUCTS. WHICH OF THE FOLLOWING STATEMENTS BEST DESCRIBES YOUR CIGARETTE SMOKING HISTORY?
- **You have never smoked cigarettes** 1**
  If "never smoked" go to question 5
- **You currently smoke cigarettes** 2**
  If "current smoker" go to question 3
- **You quit smoking completely and did not start smoking again** 3 (HQ1)

2. HOW MANY YEARS AGO DID YOU STOP SMOKING CIGARETTES? . . . . . (HQ2)
(If respondent is unsure but has stopped for at least 1 year code "88." Otherwise, code "99.")

3. ABOUT HOW MANY CIGARETTES DO OR DID YOU SMOKE A DAY? . . . . . (HQ3)
(1 pack = 20 cigarettes. If respondent can't recall code "XX." If greater than 99 cigarettes, enter "99.")

4. ABOUT HOW MANY YEARS HAVE YOU OR DID YOU SMOKE THAT AMOUNT A DAY? . . . . . (HQ4)
(If respondent can't recall, code "XX.")

5. DO YOU CURRENTLY SMOKE A PIPE ?
- **No.** 1
- **Yes** 2 (HQ5)

6. DO YOU CURRENTLY SMOKE CIGARS?
- **No** 1
- **Yes** 2 (HQ6)

7. DO YOU CURRENTLY USE ANY OTHER PRODUCTS THAT CONTAIN TOBACCO?
- **No** 1
- **Yes** 2* (HQ7)
  (If "Yes," WHAT DO YOU USE?)
  Write item(s) here: _____

II. Alcohol Use

8. THE USE OF ALCOHOL MAY AFFECT WHO DEVELOPS INFECTIONS IN THE HOSPITAL. I AM NOW GOING TO ASK YOU ABOUT YOUR CONSUMPTION OF ALCOHOL. DURING THE PAST YEAR, HAVE YOU HAD AT LEAST ONE DRINK OF BEER, WINE OR LIQUOR?
- **No** 1**
  (If "No" go to question 14)
- **Yes** 2 (HQ8)

9. ABOUT HOW OFTEN DO YOU DRINK SOME KIND OF ALCOHOLIC BEVERAGE?
- **Daily or almost every day** 1
- **Three or four times a week** 2
- **Once or twice a week** 3
- **Less than once a week** 4
- **Unknown or no response** 9 (HQ9)

(Go on to page 2)

FIGURE 5-1 A page from a data collection form from a study of nosocomial pneumonia.

individual, an introduction should be included, questions on the same topic should be grouped together, and when the topic of the questions changes, a short transition statement should be included. It may be a good idea to begin questionnaires with less challenging and personal questions. This gives the respondent an opportunity to become familiar with the interview situation and to develop some rapport with the interviewer.

A different form should be developed for each data source. This allows data entry to move forward on the sections of the data collection effort that have been completed. If multiple data sources are used in a study, consider using differently colored paper for each data form. This allows quick identification of misfiled forms and incomplete sets of data forms. Do not squeeze too much type on a page. Blank space allows data collectors to make annotations as needed.

Formatting Responses to Questions

Moving a concept to a study result involves three steps: (a) design of the data collection instrument, (b) data entry from data collection instrument to an electronic database, and (c) querying the database to obtain "flat files" suitable for statistical analysis. Because collected data are ultimately transferred to statistical analysis software, selecting appropriate formatting in the data collection instrument saves time and aggravation in the long term. Thus the adage "begin with the end in mind" is particularly germane to design of the data collection instrument.

Closed- or Open-Ended Responses An important decision is whether to have open-ended or closed-ended response formats. An open-ended response format allows the respondent to provide any answer (question 1 in Table 5-1) and is more appropriate for exploratory or hypothesis-generating research. A closed-ended response format requires the respondent to select an answer from a list of possible responses supplied by the investigator (question 2 in Table 5-1). Open-ended formats allow respondents to elaborate on the answer and to provide details that may be missed by a closed-ended format. In general, however, open response formats are to be avoided. Answers can be lengthy, hard to analyze, and hard to standardize. The problem with open-ended formats can be seen in question 1 of the table. Respondents could answer "big" or "old." The responses provided in the closed-ended format cue the respondent to the frame-of-reference of the question. Because of the opportunities for misunderstandings, questionnaires using open-ended responses often need to be administered by a trained interviewer to probe incomplete answers and to lead respondents if they do not understand the intent of the question.

The answers to open-ended questions need to be assigned codes for use in data analysis. Closed-ended response formats allow data collection forms to be precoded. This means that, prior to the administration of the form, responses have already been assigned the numerical codes to be used in the data analysis. When respondents pick a response, they actually mark its code (question 3 in Table 5-1).

If there are a great number of potential responses (e.g., a respondent's occupation or place of birth), a closed-ended response may be impractical. In this case, the response is recorded for coding at a later time.

TABLE 5-1

Examples of Three Different Question Response Formats

A question with an open-ended response format:

1. How would you describe your residence, that is, the place where you usually live?

   _____(answer here)

A question with a closed-ended response format:

2. How would you describe your residence, that is, the place where you usually live? *(Circle the correct response):*

   House
   Duplex
   Condominium
   Apartment
   Hotel
   Other

A question with a precoded closed-ended response format:

3. How would you describe your residence, that is, the place where you usually live? *(Circle the number of the correct response):*

House	1
Duplex	2
Condominium	3
Apartment	4
Hotel	5
Other	6

Closed-ended response categories should be exhaustive and mutually exclusive. That is to say, every possible response should be provided, and no two responses should be logically possible at the same time. It should be recognized, however, that closed-ended responses impose the investigator's preconceptions concerning the universe of possible responses. There are certain to be unanticipated responses. A compromise between closed-ended and open-ended formats can be made.

Coding "Other" Responses One can precode the most frequently expected responses and include an "other" category along with a space for recording what is meant by "other." These "other" responses can be logged and assigned codes during the data editing process. The value of accommodating "other" responses is illustrated by the experience of Kelsey et al. (1). In a case-control study of the etiology of lumbar disc rupture, participants were asked what type of chair they sat in at work. The main difference between case patients and control subjects was the selection of the "other" category by the case patients. The excess of "other" responses was attributable to the omission of motor vehicle seats as a response option. This led to the finding that the vibration associated with frequent motor vehicle use was associated with disc disease, a finding that was subsequently corroborated by further epidemiologic and biomechanical studies.

A common error is to omit the categories "not applicable," "unknown," and "refused" from response lists. Their omission causes a problem when editing the data. If a "not applicable" code is omitted, then when an item is indeed

not applicable, the question will be left unanswered. During editing, however, it is impossible to tell whether the question was skipped inadvertently or purposefully left blank. For record abstraction forms, a "not found" category is needed.

Do not try to force actual measurements into a closed-ended format; this may result in the unintended loss of information. Take, for example, the following question:

Q8. WHITE BLOOD CELL COUNT ON ADMISSION?
(*Circle the appropriate finding*)

Less than 10,000	1
10,000–15,000	2
More than 15,000	3
Not ordered	8
Not found	9

Collecting data in this manner automatically constrains the investigator to analyze white blood cell (WBC) count as a categorical variable. Although a categorical approach may or may not be appropriate, the investigator is further constrained, because the only categories that can be used in the analysis are those specified by the form. It is usually better to collect data in as much detail as the data source will permit, as this maintains greater flexibility in the data analysis. For example:

Q8. WHITE BLOOD CELL COUNT ON ADMISSION?
Q8. (*code -88,888 if not ordered, code -99,999 if not found*)

Again, special codes for "not found" and/or "not applicable" should be included to allow the later identification of missed items on the data form.

To ease data entry, the responses should be placed along the right margin of the form and presented as vertical lists (Fig. 5-1). Including question numbers with the responses helps data entry clerks keep their place when entering the data into a computer.

Often a number of questions do not apply to every study subject. Instructions to guide respondents past nonapplicable questions need to be clearly made. In the example (Fig. 5-1), in addition to the text instructions, visual cues are provided to guide the interviewer. Failure to skip properly can be a frequent source of error in filling out data collection forms. If the data collection form is to be self-administered by a study participant, try to keep the number of skips to a minimum.

Frequent skips are demanding even on experienced study personnel and can lead to errors in filling out study forms. Often, if there is only one question to be skipped, adding an additional response category can avoid the need for a skip instruction altogether. For example, consider the two questions:

4. DO YOU NOW SMOKE CIGARETTES?

Yes	1
No	2 (*If no, go to question 6*)

5. HOW MANY CIGARETTES DO YOU USUALLY SMOKE IN A DAY?

1 to 10	1
11 to 19	2
20 or more	3

In this situation, a skip can be avoided by dropping question 4 and providing a fourth response option in question 5: "I do not currently smoke cigarettes."

Use Numeric Rather Than Text Entry If questions are to be precoded, codings should be consistent throughout the form. Pocock (26) suggests using 1 for "No" and 2 for "Yes," because "No" is the more common response. Often an 8 is used for "not applicable" and 9 for "missing." Sometimes negative integers are used if the "8" and "9" could be valid responses.

Questions That Require Calculation Avoid questions that require calculation on the part of either the data collector or the respondent. If the number of days between two events is important, collect the actual dates of the events and calculate the difference later. Asking individuals to calculate introduces an additional opportunity for error.

Multiple Observations Occurring in the Same Subject It is not uncommon that data collection requires the management of multiple observations occurring in the same subject. Examples might be recurrent laboratory values over time, or the recording of multiple medications at a single point in time. If the number of measurements per subject is large or highly variable, it may be useful to have separate data collection forms for each collection time point. Forms can get lost or damaged if they are overhandled. The critical issue is to have a unique study identifier that allows the data to be combined from multiple sources in a study database.

Users should be aware that the management of data of this sort requires thought and may benefit from assistance from persons knowledgeable in database structure and management. The following example exhibits the issue:

Assume one is studying the response of a WBC count to the administration of an antibiotic. Counts are collected multiple times per day until discharge. One might consider laying out the data as follows:

Patient ID	WBC1	Time1	WBC2	Time2	WBC3	Time3	WBC4	Time4
1	X_1	T_1 h	X_2	T_2 h	—	—		
2	Y_1	T_1 h	Y_2	T_2 h	Y_3	T_3 h	Y_4	T_4 h

While this format is not wrong, it is generally more efficient and flexible to create a second data file, which is organized listing each WBC observation with the corresponding subject ID as:

ID	WBC	Time
1	X_1	T_1 h
1	X_2	T_2 h
2	Y_1	T_1 h
2	Y_2	T_2 h
2	Y_3	T_3 h
2	Y_4	T_4 h

This type of database is called a *relational* database. The data tables are related to each other through a common variable, in this case the ID. The advantages of such a database are (a) they provide a more efficient way to handle multiple observations, especially when the number of repeated measures is large or highly variable, (b) it is easier to create subcategories or flag observations, (c) it may also be easier to collect/enter data into this type of format, and (d) some statistical packages for modeling change over time require data in this general format The disadvantages of using a relational database are (a) it may require special knowledge of database architecture and (b) additional manipulation of the data will always be required prior to merging data back into the "parent" dataset.

CONCLUSION

Hierholzer (27) has called data the epidemiologist's sand. A lens maker takes sand, refines it, melts it, and, through a long process of grinding and smoothing, fashions a lens with which to see the world more clearly. Similarly, an epidemiologist takes data, refines it, and smooths it until a clearer picture of nature is revealed. If the sand is dirty or impure, the lens will be cloudy and distorted. If data are unreliable or invalid, the epidemiologist's understanding of nature will be clouded and distorted. By paying close attention to the data collection process, from the conception of the data collection document through the editing of the data after they are collected, the epidemiologist helps keep his sand pure so that, in the end, nature may be viewed with as much clarity as possible.

This chapter provided a practical overview of data collection in hospital settings. To find more complete discussions of issues surrounding the strengths and limitations of various data sources, and the design and administration of opinion surveys, consult several useful reviews that have served as the basis of this chapter (*11*,*28*,29,*30*).

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CHAPTER 6

Practical Application of the Principles of Epidemiology to Study Design and Data Analysis

Joseph H. Abramson

Suppose that examinations of 200 workers in a hospital reveal that 24 are carriers of methicillin-resistant *Staphylococcus aureus* (MRSA). Does this mean a prevalence of 12% in the hospital's personnel?

A study of adults undergoing mandatory health examinations (1) revealed that MRSA carriage (based on nasal swabs) was about twice as high among nonsmokers (4.3%) as among smokers (2.2%); the difference was statistically significant ($p = .019$). Does this mean that smoking protects against MRSA carriage?

Suppose this study had not found a significant difference, that is, $p > .05$, would this mean that smoking has no effect on the prevalence of MRSA carriage?

Suppose that a program to encourage hand washing by personnel is followed by a reduced rate of *S. aureus* infections among patients. Does this mean that the program reduced the incidence of these infections?

Suppose we are told that a review of the literature has found 16 controlled trials that show that a certain treatment for MRSA is efficacious and 4 that do not (a highly significant difference: $p = .007$). Can we conclude that the treatment works?

The answer to all five of these questions is "No."

Why?

Read on.

MAKING SENSE OF DATA

Bias is the bugbear of epidemiologists (2). Bias does not here refer only to preconceived opinions and preference but (as defined by the *Dictionary of Epidemiology*) to any "error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results that are systematically (as opposed to randomly) different from truth" *(3)*. Its commonest forms, in any kind of study, are *information bias*, which is caused by shortcomings in the collecting, recording, coding, or processing of data, and *selection bias*, which is the distortion produced by the manner in which subjects are selected for study or by the loss of subjects who have been selected. In an analytical study, bias may also be caused by *confounding*.

This chapter deals with ways of minimizing or dealing with biases and uncertainties, both when planning and conducting a study and when handling its results, in order to make the study as valid as possible, with reference both to the study's soundness (its *internal validity*) and, when relevant, to its generalizability or applicability in other contexts (its *external validity*).

The focus is on epidemiological studies, that is, on studies of the occurrence, distribution, and determinants of health-related states or events in specified populations. This is a rubric that embraces all studies in the field of healthcare epidemiology and infection control, except maybe some laboratory studies.

Separate consideration will be given to epidemiological studies of various types, namely, descriptive studies and analytical observational studies, and (more briefly) ecological and multilevel studies, program reviews, trials, and meta-analyses. *Descriptive studies* may be cross-sectional ones that describe a situation at or around a given time ("snapshots") or longitudinal ones (such as *surveillance* procedures) that describe changes or events in an ongoing way or during a given period ("motion pictures"). Descriptive studies of disease occurrence may be termed *prevalence studies* if they are cross-sectional and *incidence studies* if they extend over a period. Changes may also be appraised by comparing the findings of repeated cross-sectional studies. *Analytical observational studies* include *analytical cross-sectional studies*, which examine the associations between variables (e.g., between suspected causal factors and their assumed effects) that exist at or about a given time; *cohort studies*, which are follow-up studies of people with various degrees of exposure to supposed causal factors; *case–control studies*, which compare the characteristics and prior experiences of people with and without a given disease or other outcome; and *ecological and multilevel studies*, which use data about groups or populations as such, unlike other studies, which are based only on data about the individuals in the groups that are studied. *Program reviews* are observational or analytical studies of the operation and outcome of healthcare procedures or programs, *clinical trials and program trials* may be seen as epidemiological experiments that test the value of healthcare procedures or programs,

and *meta-analyses* are critical reviews and syntheses of different studies of the same topic.

These types of epidemiological studies are not mutually exclusive. A study may have multiple objectives. It may, for example, be both descriptive and analytical, as in a study of colonization of group B streptococcus in pregnant women and neonates that was not confined to a description of prevalence and susceptibility to antimicrobial agents, but extended to an exploration of the effects (on the colonization rate in the newborn) of possible risk or protective factors, such as prolonged labor or the administration of antibiotics to the mother *(4)*.

For each type of study, we consider the main biases and uncertainties that may arise and briefly enumerate the steps that can be taken when planning the study and when analyzing and interpreting the findings, so as to minimize these biases and uncertainties or permit account to be taken of their effects.

Although a number of statistical procedures are mentioned and numerical examples based on them are cited, these procedures are not explained. It is assumed that readers either have statistical consultants or collaborators, or themselves have a sufficient grounding in statistical principles to be able to make intelligent use of statistical software. A number of multipurpose commercial programs (such as those listed on Chapter 15, pp. 216–217) are available, but they have to be learned and may be difficult for an unversed nonstatistician to use. The Internet offers many simple interactive programs ("Web pages that perform statistical calculations") (5), and a plethora of shareware and freeware statistical programs is available for downloading (6). The user-friendly WinPepi programs (7) for epidemiologists, for example—which can be downloaded free from www.brixton-health.com with their extensive and fully referenced manuals—can perform all the statistical procedures mentioned in this chapter (except Cox regression analysis and multilevel analyses). WinPepi was used to provide all the numerical examples cited in the text.

There are numerous sets of publication guidelines for epidemiological studies—witness the title of a recent review (8)—and these checklists can serve as reminders of what kinds of data should be collected and what kinds of analyses should be done. Particularly useful are the STROBE (*St*rengthening the *R*eporting of *Ob*servational Studies in *E*pidemiology) (9) and (for randomized trials) CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) (10) guidelines.

Before embarking on a study of any kind, ethical matters must of course be considered. Confidentiality should be taken into consideration even if the study is based only on existing medical records, and informed consent should be obtained whenever special test procedures—even questioning—or interventions are required. Approval by an appropriate ethics committee may be needed.

DESCRIPTIVE STUDIES

Information bias

Epidemiological studies do not always have clear *purposes*. It is not always clear why the study was performed; that is, what it was hoped to achieve by performing it. But every epidemiological study should have clearly defined *objectives*, that is, an answer to the question "What knowledge is the study planned to yield?" These objectives dictate the variables to be measured, and these variables must be clearly defined.

We have been told, at the outset of this chapter, that a simple descriptive study, whose objective was presumably to measure the prevalence of MRSA carriage, revealed that 24 of 200 hospital workers were carriers of MRSA (1). A number of obvious questions come to mind.

What, for example, is meant by "carriers of MRSA"? First, what is the *conceptual definition* (the "dictionary definition" of the characteristic that it is hoped to measure)? Carriers of these bacteria with no evidence of acute infection, or all carriers? Persistent carriers only, or transient carriers also? And secondly, how was this concept translated into an *operational (working) definition*, expressed in terms of the method of examination? From what sites were swabs taken? If from nostrils, one or both? Once only, or repeatedly? What type of swabs? Were the swabs stored or used immediately? Which of the available tests for MRSA was used? Precisely what results, using these methods, were taken as evidence of MRSA carriage? (And, of course, were all the workers examined in the same prescribed manner?)

Once we know the conceptual and (especially) the operational definition of the variable, we can ask how *valid* the measurement was; that is, how well did it measure what the researcher wanted to measure? The validity of a measure or a method of measurement can be appraised by comparing the findings with a criterion (a reference standard or "*gold standard*") that is known or believed to be close to the truth, if such a criterion is available. For a "yes–no" (dichotomous) variable, validity can then be calculated (see Chapter 3, pp. 54–55) and expressed as *sensitivity* and *specificity*. The sensitivity of the MRSA measure tells us what proportion of the true carriers (according to the gold standard) are detected by the examination, and its specificity tells us what proportion of noncarriers are correctly classified as noncarriers. The false-positive rate is 100% minus the specificity. It may also be enlightening to calculate the *predictive value* of the findings—when MRSA is detected by the measure, what is the probability that it is truly present (*positive predictive value*)? and when it is not detected, what is the probability that it is truly absent (*negative predictive value*)? But it must be remembered that these calculated predictive values (unlike sensitivity and specificity) are dependent on the prevalence of the condition. For example, if sensitivity and specificity are both 90%, the positive predictive value can be shown to be 79% if the true prevalence is 30 per 100, 55% if the true prevalence of MRSA is 12 per 100, and only 32% if the true prevalence is 5 per 100. If no "gold standard" is available, other methods of appraising validity can be used (11), for example, by checking the results against other (although not necessarily better) measures of the variable (*convergent* and *discriminant validity*), against related variables (*construct validity*), or against subsequent events (*predictive validity*). Often, reliance can be placed on common sense—that is, a judgment that the measure is obviously valid (*face validity*). If the validity of a measure is not known, it is sometimes decided

to appraise it in the course of the study (e.g., by using a "gold standard" measure in a subsample) or in a pretest.

It may be helpful, although it is not essential, to also know how *reliable* (i.e., repeatable) the measure is; that is, whether the same result is obtained when the examination is repeated. High reliability does not necessarily mean that the measure is valid (what is more reliable—or less useful—than a broken watch?) But low reliability will always cast doubt on validity. Many measures of reliability are available. In this instance, use would probably be made of the *kappa* coefficient (see Chapter 3, p. 72) or the apparently preferable AC1 coefficient, which express the proportion of subjects who are classified in the same way each time, after allowing for the effect of chance agreement. If we were appraising a numerical measure, other indices of reliability would be appropriate, such as St Laurent's *gold-standard correlation coefficient (12)* and the *95% limits of agreement (13)*.

The question that was asked at the start of this chapter was "Suppose that examinations of 200 workers in a hospital reveal that 24 are carriers of methicillin-resistant *Staphylococcus aureus* (MRSA). Does this mean a prevalence of 12% in the hospital's personnel?" If there is no misclassification, the prevalence is obviously 12% in these workers—that is, in the very unlikely event that the sensitivity and specificity of the measure are both 100%. But if there is misclassification—and there almost always is—the prevalence is unlikely to be 12%. Suppose, for example, that only 5 of the 200 subjects (2.5%) truly have MRSA and that the measure of MRSA has a sensitivity and specificity of 90%. Then it can be expected that 90% of the 5 will be found to have MRSA (4.5 true positives), and so will 10% of the other 195 (19.5 false positives), so that the total number who apparently have MRSA will be 24 (12% of the 200). In other words, a true prevalence of 2.5% will yield an apparent prevalence of 12%. And, conversely, an apparent prevalence of 12% points to a true prevalence of only 2.5%. Taking account of misclassification, the prevalence of MRSA in these 200 workers would thus be only 2.5%. An appropriate computer program, such as WinPepi, can easily do this reverse calculation, if fed the sensitivity, specificity, and apparent prevalence.

Descriptive epidemiological studies are usually concerned with more than one dependent variable and may involve independent variables as well, since they often aim to describe the findings in different subgroups, for example, different age groups or occupational groups, or in patients with different diagnoses. A failure to define appropriate working definitions for any of the variables, sufficiently valid for the purposes of the study, may result in a study flawed by information bias.

Any deficiencies in the collection of data may bias the results. The case-finding procedures used in an outbreak investigation, for example, may be inadequate however clearly a case is defined. Information bias may also be caused by missing data and by deficiencies in the recording or management of data, for example, by errors or omissions in the recording of findings or in the transfer of data to a computer for analysis.

In a longitudinal descriptive study, information bias may be caused by any changes that occur with time in disease definitions, case notification systems, or case-finding methods.

Data collected by observation (e.g., clinical or laboratory examinations) are generally more valid than data collected by interviewing or questioning (except of course in studies of feelings or attitudes). Numerous factors may reduce the validity of data based on questions—faulty memory (recall bias), a tendency to give socially acceptable responses, the interviewer's attitude, the wording of the question, etc. (see Chapter 5, pp. 87–90). Medical records too are often disappointing as a source of valid data unless they have been planned and maintained as a basis for research; a high proportion of the healthcare-associated infections detected by a surveillance program may not appear in the diagnostic record *(14)*. All records maintained solely for administrative purposes may be problematic with respect to their completeness or accuracy. An examination of the feasibility of appraising the immunization status of hospital workers in England, for example, revealed that only 85% of hospital trusts knew the exact number of staff employed, and only 68% had records of all immunizations *(15)*.

The above considerations apply to all epidemiological studies, not only to descriptive ones—namely, the need for defined study objectives, for clear operational definitions expressed in terms of the methods of study, and (if face validity does not suffice) for assurance of the validity of these methods. Information on the validity of methods may be available from other studies, but this should be handled circumspectly, since sensitivity and specificity may be affected by the characteristics of the sample in which validity was appraised and may by chance be different in different samples.

Selection Bias and Sampling Variation

To return to the MRSA example, we have not been told how the 200 workers were selected. Can the findings be validly applied to "the hospital's personnel," or do they apply only to a not necessarily representative group of 200 workers? Were the 200 a *random sample*, chosen from the total personnel by using random numbers or a computer program that uses an algorithm that makes an as-good-as-random selection? Or, were they an equally representative *systematic sample*, selected (for example) by taking every fifth person in a list of all personnel? Or, on the other hand, were they a haphazard and possibly unrepresentative sample; for example, were they the more easily persuaded workers encountered in a particular part of the hospital at the time of the study and possibly only junior personnel to boot (because what researcher would want to get up the noses of senior physicians or nurses, and administrators?).

In whatever way the sample was selected—even if it was selected randomly—it would be helpful to be assured that the characteristics of the workers who were studied were in fact similar to those of the total personnel if the latter information is available. Was the sample sufficiently similar in age, sex, occupation, etc. to the population from which it was drawn to allay concerns about selection bias?

To reduce sampling variation, use is often made of *stratified random sampling*. Representativeness with regard to age and sex, for example, can be enhanced if the sample is made up of separate random samples selected from each age–sex stratum.

A common source of selection bias is the *loss of subjects*, that is, the loss of members of the selected sample, as a result of refusal, failure to find subjects, mishaps in the laboratory, etc. Were the 200 workers who were studied in the MRSA study the total selected sample, or were they part of a selected sample of (say) 300? If the latter, it would be helpful to know whether and how the workers who were lost differed from those who were included. May the reasons for noninclusion be connected with the variable under study?

Even if the sample in the MRSA study was a representative randomly selected one, we cannot be sure of the 12%. There are a very large number of alternative random samples that might have been chosen, and the findings in different random samples of workers would, by chance (*random sampling variation*), obviously differ. We cannot be certain that the true prevalence in the total personnel is 12%, just because the prevalence in one representative sample is 12%. The best we can do is to use a computer program to obtain a *confidence interval*, which we can interpret, with a given level of confidence, as expressing the range within which the prevalence probably falls. In this instance, we can be 95% sure that the prevalence is between 8% and 17%. If a lesser level of confidence satisfies us, the range is narrower—the 90% confidence interval is from 9% to 16%. If we want to be more certain of the result, we can compute the 99% confidence interval, which is wider, namely, from 7% to 19%. The confidence interval depends on the size of the sample; it is wider if the sample is small, and narrower if it is large. If the sample size was only 50, uncertainty would be greater, the 95% confidence interval being from 5% to 23% instead of from 8% to 17%. If the sample size was 1000, the 95% confidence interval would be narrow—from 10% to 14%.

If the sample was randomly selected and we ignore possible misclassification, we can thus conclude with 95% confidence that the prevalence in the hospital's personnel is between 8% and 17%. But if we assume a sensitivity and specificity of 90% (in which instance the adjusted prevalence is only 2.5%), the 95% confidence interval for prevalence ranges from just above 0% to 9%.

The *sample size* required in a descriptive study depends on the desired width of the confidence interval—if a more precise result is wanted, a larger sample is required. The basic requirements for the calculation of sample size (or for the computer program that calculates it) are a guess, a wish, and a precaution. If the aim is to measure a proportion or rate, a guess must be made at its expected value; to be on the safe side, a proportion of 0.5, or 50%, can be assumed—this is a "worst-case scenario" that maximizes the required sample size. If the aim is to measure a mean value, the expected standard deviation is required. The wish is for a narrow confidence interval—that is, a specified acceptable error (i.e., half the width of the confidence interval) at a given (say 95%) level of confidence. The precaution (required by some computer programs) is allowance for the expected loss of members of the chosen sample because of refusal or for other reasons; taking this into account ensures an adequate sample size despite the losses, but of course does not remove the possibility of bias caused by selective losses. The size of the population from which the sample is drawn may also influence the required sample size, but only if the population is very small.

In a study that sets out to measure more than one dependent variable, the sample size requirement will usually differ for different variables (with different expected frequencies). It then becomes necessary to either select the largest sample size or decide on a compromise that will sacrifice precision with respect to the less important variable or variables.

Planning a Descriptive Study

When planning a descriptive study (or any epidemiological study, for that matter), thought should be given to both information bias and selection bias.

To minimize information bias, clear operational definitions are required for all variables and (if categorical scales are used) for their categories; valid methods of measurement should be used, and they should be applied in a standard way. Validity should be measured if necessary. Quality control measures (including checks on correct performance and on reliability) should be built in; and data cleaning (16), including the correction of errors where possible, should be performed both before and during or after entry of data to the computer. Data entry can be made easier and more accurate by using software, such as the freeware programs EpiData (see p. 202) and Epi Info (see pp. 201–202) that provides help in the design of a data entry form, a data entry screen, and a data set and can apply rules and calculations during data entry, for example, by restricting data to legitimate values. A record should be kept of the amount of missing data.

In a *surveillance* program (see Chapter 89), which is an ongoing descriptive study of health data (permitting, *inter alia*, the detection of outbreaks) or healthcare data, standardized working definitions and standardized methods of reporting and recording are especially important and may be particularly difficult to enforce because of the involvement of a large and constantly changing body of observers.

Especially in studies that set out to describe beliefs, perceptions, or practices regarding health or healthcare, consideration should be given to the use of *qualitative methods*, whose findings are described in words rather than numbers, as well as the usual quantitative methods. These methods, based on (for example) observations, conversations and in-depth interviews, or focus group sessions, can provide useful insights concerning beliefs and behavior (although not their numerical prevalence) and ways of exploiting or changing them. Reluctance of health workers or members of the public to be immunized (e.g., against swine flu) and unwillingness of parents to have their children immunized can best be combated if the motivations for and against immunization are understood. If done properly, qualitative research is as rigorous as quantitative research, but it needs special skills and generally requires the involvement of professionals who have had the requisite training. The designs used in "mixed-method" studies that integrate qualitative and quantitative data collection and analysis include the use of qualitative data as a basis for planning quantitative data-collection methods, the comparison and integration of qualitative and quantitative findings, and the quantitative analysis of qualitative data *(17)*.

If a sample is to be used in a descriptive study, it should be a representative one (random or systematic), possibly selected after stratification, and large enough to ensure an acceptable degree of precision. Sampling generally requires a sampling frame, for example, a list of the subjects from whom the sample is to be selected. To sample newly diagnosed cases of a disease as they crop up, use may be made of systematic sampling, for example, every fourth case, or of a sampling scheme whereby a case is randomly selected from each successive block of (say, two or four) cases.

Efforts should be made to ensure full coverage of the sample. If the study is a longitudinal one, entailing repeated examination of the same subjects, it may be necessary to plan tracking procedures, including the collection of information about addresses, places of employment, and the whereabouts of family members.

To permit the assessment of sampling bias, so that its possible effect can be taken into account when interpreting the findings, the characteristics of the sample studied should be compared with those of the total study population, using whatever demographic or other information is available; and the characteristics of subjects lost from the sample (or those of a sample of the lost subjects) should, if possible, be compared with the characteristics of the sample studied. Records should of course be kept of the reasons for noninclusion in the sample, since they may point to possible bias.

In addition to these precautions to ensure the internal validity of the study, thought should be given to the usefulness of the results in other contexts, unless there is no intention to publish the results. There will usually be other health workers or researchers who will be interested in the applicability of the findings in their own healthcare services or populations, even if the study was planned to meet a specific local need. Care should therefore be taken to collect, and provide, any information about the group or population studied, or about the context, that may help others to decide on the relevance of the study findings elsewhere.

Analysis of a Descriptive Study

The analysis of a descriptive study is usually simple. The frequency distribution of each variable in the total study sample or its subgroups is tabulated; rates or proportions, preferably with their confidence intervals, are computed for "yes–no" or other categorical variables; and measures of central tendency and dispersion (see Chapter 3, pp. 50–51) are computed for metric (noncategorical) variables. One-sample significance tests (see Chapter 3, pp. 57–58 and pp. 61–62) can be used to see whether the rate or proportion, or the mean or median, conforms with some standard value or with an expected or other hypothetical value. And two-sample significance tests (see Chapter 3, pp. 58–64) can be used to make comparisons with findings elsewhere.

The possible effect of misclassification can be appraised, as in the above MRSA example. Occasionally, the effect of information bias can be controlled in other ways. If, for example, there is a constant bias in laboratory results, due to a mistake in the preparation of a standard solution, it may be rectified by applying a correction factor.

The possible effect of selection bias should be taken into account when interpreting the findings, particularly if there was poor coverage of the sample. Sometimes it is possible to control selection bias by statistical manipulations during the analysis. If there was a low response rate in one sex, for example, the findings can be weighted in accordance with the sex composition of the total study population to obtain an estimate that compensates for this selectivity. A disadvantage is that this is based on the assumption that, in each sex, the subjects included and excluded are similar, which is not necessarily true.

In a longitudinal study, such as a surveillance program, the analysis is complicated by the need to describe changes with time. Numerous statistical procedures are available for the appraisal of trends (18), with or without controlling for seasonal variation and with or without controlling for deviations that may be caused by extraneous factors, such as fluctuations in diagnostic criteria. Outbreaks may be detected by changes from the "endemic" baseline values. But algorithms for the early detection of outbreaks usually use surveillance data from multiple sites.

A need sometimes arises to combine the results of two or more case-finding methods that yield different and incomplete, but overlapping, lists of cases. An estimate of overall prevalence can then be obtained by feeding the numbers, including the numbers of overlaps, into a computer program that can use the *capture–recapture* (or a similar) technique (19). This procedure, which is based on assumptions that are not always met *(20)*, takes its name from its original use in estimating animal populations by capturing, marking, and releasing a batch of animals and then seeing how many of them are recaptured in the next batch of animals caught. Its earliest use in healthcare epidemiology was to estimate the number of hospital patients using methicillin *(21)*, followed by its use in the surveillance of healthcare-associated infections *(22)*, and it has since been used in many other studies of incidence or prevalence and of the effectiveness of ascertainment systems *(23)*. In a capture–recapture study based on notifications of invasive neonatal group B streptococcus infections, made separately by pediatric wards and by microbiological laboratories, for example, the analysis led to the conclusion that the total number of cases was about double the total notified number *(24)*. The capture–recapture technique may yield an overestimate if all cases have in fact been found or an underestimate if some types of case are "uncatchable" by any procedure.

ANALYTICAL OBSERVATIONAL STUDIES

The key feature of an analytical study is the examination and interpretation of *associations between variables*. This brings new possible biases and uncertainties in its train in addition to those besetting descriptive studies.

Associations between variables are usually detected by observing that the value of the dependent variable (e.g., the mean value, proportion, or rate) is different when the value of the independent variable (e.g., a suspected causal factor) is different. The difference in the values of the dependent variable may lie in the same direction as the difference in the values of the independent variable (a positive association) or in the opposite direction (a negative or inverse association). The *strength* of the association is measured by the extent of the discrepancy between the two values of the dependent

variable (say, the two rates), as measured by the ratio of the two values or by the difference between the two values. The further the ratio is from 1, the stronger the association. The discrepancy can be in either direction, depending on whether the association is positive or negative; ratios of 8 and 0.125 (i.e., one-eighth) point to associations of the same strength but different in direction. If the difference between means, rates, or proportions is used, the further it is from zero (in either direction), the stronger the association.

These two methods of measurement (using a ratio or a difference) do not necessarily lead to similar conclusions about the strength of the association or the factors affecting it. Etiological studies generally use ratios and assume that exposure to a risk or protective factor has a multiplicative effect; that is, exposure multiplies the risk of the condition under study by a given amount. The effects of different exposures can then be combined by multiplying them by each other. A multiplicative model is used in logistic regression analysis (see Chapter 2, p. 44) and Cox regression analysis (see Chapter 2, pp. 44–45). On the other hand, if a study is concerned with the absolute magnitude of a problem or with the resources needed to deal with it, it is more appropriate to use the absolute difference between risks or mean values and assume that an exposure has an additive effect; that is, exposure increases (or decreases) the risk or mean value by a given absolute amount. The effects of different risk factors can then be combined by adding them. This is the model used in linear regression analysis.

The ratios commonly used as measures of the strength of an association are rate ratios, risk ratios, odds ratios, and hazard ratios.

A *rate ratio* is the ratio of two rates that have person-time denominators (e.g., rates per 1,000 patient-days or per 1,000 person-years). A subject who was observed for 10 days would contribute 10 patient-days to the total denominator, as would 2 subjects who were each observed for 5 days or 10 subjects who were each observed for 1 day. Incidence and mortality rates (sometimes referred to as *incidence density* or *mortality density*) are of this type.

A *risk ratio* (confusingly, often also called a rate ratio) is the ratio of risks, which are measures that use count denominators, that is, the size of the population at risk (e.g., 10 cases per 1,000 subjects), and not person-time denominators. Prevalence (the number of cases at a given time) and cumulative incidence (the number of new cases during a given period) are measures of this type, as are simple proportions and percentages (which express the number of cases or episodes per 1 subject or per 100 subjects, respectively).

An *odds ratio* (see Chapter 2, pp. 23–24) is the ratio of two odds. An odds is the probability that something is present or will occur, divided by the probability that it is not present or will not occur. If the proportion of people exposed to a risk factor who develop a disease is 0.8, the odds in favor of the disease in this group is 0.8 divided by 0.2, or 4 (4 to 1). If the proportion of people not exposed to the risk factor who develop the disease is 0.2, the odds in favor of the disease in this group are 0.2 divided by 0.8, or 0.25. The odds ratio expressing the strength of the association is the ratio of these two odds, that is, 4 divided by 0.25, or 16.

Odds ratios have useful statistical properties, but may be hard to understand and are easily misunderstood. In the above example, use of the odds ratio, which is 16, gives an impression of a much stronger association than would be indicated by the risk ratio of 4 (0.8 in the exposed group divided by 0.2 in the nonexposed group).

Case–control studies yield odds ratios only (unless ancillary information is available), and not rate ratios or risk ratios. But if the condition under study is rare, there is little difference between the odds ratio and the risk ratio, and the odds ratio can be used as a substitute for the risk ratio. Under certain conditions, depending on the manner of selection of controls, the odds ratio observed in a case–control study can also be used as a proxy for the rate ratio (25).

Odds ratios are the ratios that are generally used in studies that employ logistic regression analysis, since the logistic coefficients provided by the analysis are the logarithms of odds ratios and can be converted to odds ratios by taking their antilogarithms. Some computer programs (like WinPepi) can use the logistic regression results to estimate risk ratios, risk differences, and other measures of effect that are less misleading than odds ratios sometimes are.

Hazard ratios are used in studies based on person-time denominators, particularly those using Cox regression analysis, where the hazard ratios are the antilogarithms of the computed coefficients.

Information Bias

As in a descriptive study, *information bias* may result from inadequate operational definitions of variables, inadequately standardized methods, errors in the recording or management of data, and (in a longitudinal study) from changes in disease definitions, case notification systems, or case-finding methods.

An especially insidious type of information bias, with effects that are not always easy to predict or control, may occur in an analytical study if the validity of a measure differs in different groups. For a "yes–no" variable, this effect is referred to as *differential misclassification*, as opposed to the *nondifferential misclassification* that occurs if validity, although not perfect, does not differ.

As an illustration, suppose that 20 of 100 men and 5 of 100 women report that they have had sexually transmitted diseases (STD). The observed risk ratio expressing the association between sex and a history of STD is then 4. If the sensitivity of the STD information is 80% in both sexes (with a faultless specificity of 100%)—that is, if most cases are reported and there are no false positives, and misclassification is the same in both sexes—our trusty software tells us that a true risk ratio of 5 would produce the observed risk ratio of 4. If there is nondifferential misclassification, the observed association is generally weaker than the true association. But now suppose that sensitivity is 80% in men and 40% in women. The true risk ratio that would give rise to an observed risk ratio of 4 would then be computed as 2. But if, on the other hand, sensitivity is 40% in men and 80% in women, the true risk ratio would be computed as 8. Differential misclassification can bias the result in either direction, and (without the aid of a computer) its effect is difficult to predict and difficult to compensate for.

In studies of the effect of a supposed risk factor on a disease, differential validity can express itself as diagnostic or exposure suspicion bias. *Diagnostic suspicion bias* can occur if the information about the disease comes from a subject, interviewer, or examiner whose report about the presence of the disease is colored by knowledge that there has been exposure to the risk factor and who is more likely to report the disease if there has been exposure. This is possible in a cohort study or a cross-sectional analytical study. *Exposure suspicion bias* can occur if the information about exposure comes from a subject, interviewer, or examiner whose report about the presence of the exposure is colored by knowledge of the presence of the disease. This is possible in a case–control study or a cross-sectional analytical study. Both forms of bias are less likely if there is effective blinding and if subjects, interviewers, or examiners are not aware of the study hypothesis.

Clearly, information on validity in different subgroups of the study population would be helpful when interpreting the findings.

In cohort studies, where information about exposure to risk factors is obtained at the outset of a follow-up period, this information may be biased if there are changes of exposure status during the follow-up period. Smokers may not remain smokers. This bias can be reduced by seeking and using information about these changes.

Selection Bias and Sampling Variation

The strength of associations observed in analytical studies is subject to sampling variation, and confidence intervals must be computed for the rate ratios, differences, or other measures used. The sample size required in order to obtain acceptably precise results can be calculated manually or by a computer program. If strength is measured by the ratio of two rates or proportions or odds, the calculation is based on the known or assumed value of one of the rates or proportions, the value of the ratio that it is wished to detect (at a given confidence level), and either the desired width of its confidence interval or the required power of a test to determine statistical significance. If strength is measured by a difference between two values, the calculation is based on the known or assumed standard deviations of the two values, the difference that it is wished to detect (at a given confidence level), and either the desired width of its confidence interval or the required power of a test to determine statistical significance. The expected loss of members of the chosen sample can also be taken into account. In a case–control study, the number of controls per case influences the required number of cases. Calculation of the required sample size is less simple if there are a number of independent variables.

The same possibilities of selection bias resulting from inappropriate sampling or incomplete coverage of the sample exist in analytical studies as in descriptive studies.

In addition, there are special issues to be considered in case–control studies and in cohort studies.

Case–Control Studies The study of associations in case–control studies is based on a comparison of cases (generally of a disease) with controls (who are free of the disease), with respect to their prior exposure to suspected risk or protective factors. To avoid bias, the controls should be drawn from the same population as the cases. They should represent the people who, if they had the disease in question, could have become cases in the study.

But many case–control studies are vitiated by the inappropriate selection of controls.

If the study includes all the cases occurring in a defined population, or a representative sample of them, suitable controls can be found by taking a representative sample of the individuals without the disease in the same population. This is relatively easy to do in a primary healthcare service that caters for a defined population, but it is not easy in a hospital-based study. Hospital cases with a given disease, for example, are usually drawn from an ill-defined catchment population. Even if the study is restricted to hospital cases living in a defined neighborhood, and it is practicable to select "community controls" drawn from the same neighborhood, it cannot be certain that the controls would have been treated in the same hospital if they had the disease. Population controls who are selected because of their relationship with the cases, for example, friends, neighbors, spouses, siblings, fellow workers, or classmates, may tend to resemble the cases in their circumstances, lifestyles, or (for blood relatives) genetic characteristics. In other words, there may be similarities between the cases and controls that have nothing to do with the disease and can lead to false conclusions about associations with the disease. Controls drawn from other patients in the same hospital also present problems. They do not have the disease in question, but they have other diseases, which may have their own associations with the risk or protective factors under consideration. Moreover, bias may be caused by differences between the hospital admission rates for different diseases (*Berkson's bias*, *admission rate bias*). To minimize these problems, controls with similar diseases or clinical pictures may be selected (e.g., cancer controls for cancer cases, or women referred for breast biopsies of suspicious nodules, but not found to have breast cancer, as controls for cases found to have cancer or precancerous conditions). Patients admitted after traffic accidents or for elective surgery, blood donors, or hospital visitors are sometimes used as controls, in the hope that they represent the population base. It is usually found that the use of community controls overestimates the association between the disease and the risk factor, and the use of hospital controls underestimates it *(26)*.

It is seldom easy to find a source of controls that is both convenient and free of possible bias. Each instance must be considered on its merits, and a careful choice made of the least of the alternative evils. It is sometimes decided to use two or more control groups (of different kinds) and to see whether different comparisons yield the same conclusion; discrepancies may throw light on the study's biases.

Cohort Studies A cohort study examines the associations between selected risk or protective factors and diseases (or other selected outcomes) by following up a sample (cohort) of subjects whose exposure is known and determining whether the outcomes occur. In a prospective cohort study, information about the status at the outset is obtained by examinations or interviews; and in a historical ("retrospective") cohort study, information about the initial status of the cohort is obtained from records of past exami-

nations or interviews. In both instances, loss of members of the cohort to follow-up can cause serious selection bias (*follow-up bias*). Bias is particularly likely if the reasons for loss to follow-up are illnesses, deaths, or other events or circumstances that may be connected with the outcomes under study.

Unless loss to follow-up is negligible, the lost subjects should be compared with the subjects remaining in the study to see whether they differ with respect to whatever demographic or other information is available, as well as their initial exposure status.

Confounding Effects

Confounding, or *confounding bias*, can be defined as the distortion of an association between variables by the influence of another variable. As a simple example, all studies show that children with larger feet tend to know more words. This is of course explained by the influence of an extraneous variable, namely, age, which is associated both with foot size and with vocabulary size. Older children have larger feet, and because they are older, they also know more words. If we studied children of the same age, we would probably find no association between foot size and vocabulary size.

An extraneous variable can have a confounding effect on the association between an independent variable **A** (e.g., hypertension) and a dependent variable **B** (e.g., a healthcare-associated infection)—that is, it is a *potential confounder*—if two conditions are met: (a) it must influence **B** (or be a stand-in for something that influences **B**); and (b) it must be associated with **A** in the population, but not because it is affected or caused by **A**; if it is caused by **A**, it is an intermediate cause in the causal chain connecting **A** and **B**, rather than a potential confounder. Diagrammatically, **A – C** $\rightarrow$ **B**, where **C** (the confounder) is linked with **A** and influences **B**, but not **A** $\rightarrow$ **C** $\rightarrow$ **B**.

Only if the associations of **C** with **A** and **B** are strong can there be a confounding effect of any importance.

If potential confounders are identified and measured in the study, a number of ways may be used to determine whether they actually have appreciable confounding effects or to control these effects in the analysis.

Methods used to control for confounding in observational studies include the following (see the illustrative studies described in Chapter 88, pp. 1322–1324):

1. *Restriction* of the study to a homogeneous group, with no variation in the potential confounder, for example, restriction of the study to a specific narrow age group.
2. *Matching*, for example, by selecting controls of the same age and sex as the cases in a case–control study. Matching alone does not prevent confounding, but may introduce bias by making the cases and controls unduly similar in their exposure to possible causal factors; but if matching is followed by stratification or a neutralization procedure, the bias is removed and the results are more precise than without matching. Matching on a variable that is affected by the exposure or by the disease may also introduce bias (25).
3. *Stratification*, that is, division of the study sample into strata in accordance with the categories of the suspected confounder (e.g., age–sex strata), followed by separate analysis of the association in each stratum.
4. *Neutralization* of the confounder by a statistical technique that holds the suspected confounder constant and thus nullifies its effect and computes an adjusted measure of the strength of the association. The adjusted measure is a fictional value, a "counterfactual" estimate of how strong the association would be if the suspected confounder were neutralized. The difference between the adjusted measure and the corresponding crude measure (i.e., without controlling for confounding) is an indication of the degree of confounding; small differences (say, of <10%) are often ignored. Methods of neutralization include standardization (see Chapter 2, pp. 32–33), the Mantel–Haenszel (see Chapter 2, p. 31) and similar stratification-based procedures, and linear, logistic, Poisson, and Cox regression analysis.
5. Use of a rather elaborate *propensity score* that expresses the effect of a set of possible confounders on the probability of inclusion in the treatment group (in a nonrandomized trial) or the group exposed to the suspected causal factor (in an observational study) and that can be held constant in the analysis (27).
6. Use of an *instrumental variable*, which, in an appraisal of an **A** $\rightarrow$ **B** relationship, is a variable **Z** that does not share a common cause with **B** and can affect **B** because of, and only because of, its effect on **A**; that is, **Z** $\rightarrow$ **A** $\rightarrow$ **B**. If the study shows an effect of **Z** on **B**, this can be taken as evidence for an effect of **A** on **B**, whatever confounders may be affecting the observed **A–B** relationship (25,28). An instrumental variable has been likened to a coin flipped to decide whether a subject in a trial will be put in a treatment or control group—it determines the treatment, but has no independent effect on the outcome *(29)*. To be useful, the instrumental variable must be strongly associated with the causal factor under consideration. As an example, if the day of symptom onset can influence a health outcome because of, and only because of, its effect on the quality of hospital care, an association between day of onset and the health outcome can be taken as unconfounded evidence for the effect of the quality of care on the health outcome. Similarly, meteorological data on sunlight exposure during pregnancy and the health of the neonate may provide unconfounded evidence for the effect of maternal vitamin D status *(30)*; and distance from a hospital has been used as an instrumental variable in appraising the effect of intensive treatment for myocardial infarction on the (possibly unfounded) assumption that geographical location is not in itself associated with severity of illness *(31)*. In one study setting, the doctor's prescribing preference (inferred from prior prescriptions) was found to be a useful instrumental variable in examining the effect of various drugs on mortality *(32)*.

It is also possible to explore the possible effect of unmeasured confounders by "*external adjustment*," that is, by using a set of assumptions that are not based on the study data (28,33). A sensitivity analysis (i.e., a comparison of the results when different assumptions are made) can show the strength of the association in scenarios that differ with respect to the assumed strength of the unmeasured confounder's association with the dependent variable and its prevalence in the two groups (cases and controls, or exposed and unexposed) that are compared. If the adjustment renders the association negligible or

nonsignificant, or reverses its direction, and the scenario is a plausible one, this points to a need to be circumspect when drawing conclusions or to measure and take account of extra variables. For example, if the observed odds ratio is 2 (with a 95% confidence interval of 1.2 to 2.9) and an odds ratio of 3 is assumed for the effect of the confounder, an appropriate computer program would indicate that the adjusted odds ratio becomes nonsignificant if the unmeasured confounder's prevalence is greater by 20% or more in one group than in the other (or by 30% or more if the prevalence in both groups is above 50%). If either of these scenarios is plausible, it can be concluded that confounding by an unmeasured confounder or confounders may explain the association's statistical significance.

Modifying Effects and Intermediate Causes

An analytical study is usually concerned not only with the existence and strength of associations but also with the factors that influence the associations. If the association between some factor and healthcare-associated infections is stronger in men than in women, sex is an *effect modifier*; or in statistical terms, there is *interaction* between the factor and the sex in their effect on healthcare-associated infections.

Effect modifiers are of obvious interest in studies concerned with causes and effects, since they are among the factors that influence (or "cause") the outcome that is under study, and their detection may point to new avenues of investigation. Information about effect modifiers may also have practical implications, for example, by identifying high-risk groups or pointing to possible practical healthcare procedures. Unlike confounding, which is an unwanted effect that we try to prevent or remove, effect modification is an effect that it is useful to find and report and investigate.

Effect modification may be detected and measured by stratification, that is, by comparing the strength of the association in different strata of the suspected modifier (e.g., in the two sexes) or by including interaction terms in linear, logistic, or Cox regression models. If there is interaction between factors **X** and **Y** in their effect on **B**, this means that **X** modifies the association between **Y** and **B** and **Y** modifies the association between **X** and **B**.

There may also be interest in studying *intermediate causes*. In a study concerned with the effect of **A** on **B**, for example, **C** might be an intermediate cause that is influenced by **A** and, in turn, influences **B**. Diagrammatically, $\mathbf{A} \rightarrow \mathbf{C} \rightarrow \mathbf{B}$. Information about intermediate causes too may have practical implications, since a healthcare procedure might target **C** rather than **A**.

Planning an Analytical Observational Study

Every study design has its advantages and disadvantages. Case–control studies are generally easier, faster, and less costly than cohort studies and require much smaller samples if the outcome is uncommon. However, they deal with only a single outcome, provide no direct measures of risk, and are particularly subject to recall bias and exposure suspicion bias and, if unsuitable controls are used, to selection bias. Cohort studies, on the other hand, are prone to diagnostic suspicion bias and follow-up bias.

In any analytical study, the list of variables to be studied should extend beyond the dependent and independent variables whose associations are the focus of the study. It should also include possible confounders and maybe possible effect modifiers and intermediate causes. These variables can be selected from a list of all the factors that are known or suspected to be appreciably associated with the dependent variables and that it is practicable to measure. Consideration should always be given to the possible inclusion of the "universal variables" that are so often of relevance in epidemiological studies, namely, sex, age, parity, ethnic group, religion, social class and related variables, and place.

The same precautions to minimize information bias should be taken as in descriptive studies: clear operational definitions for all variables and their categories; valid methods of measurement, applied in a standard way; quality control measures; data cleaning; computerized data entry; and a record of missing data. Blinding of anyone who may influence the findings may be advisable to minimize exposure suspicion bias and diagnostic suspicion bias.

If samples are to be used in an analytical study, they should be representative ones, large enough to ensure an acceptable degree of precision. In a case–control study, incident (i.e., new) cases are generally preferred to prevalent (i.e., existing) cases, both because they are closer in time to their causal factors and because this prevents bias caused by the absence of deceased or recovered cases (*Neyman's bias*, *incidence–prevalence bias*). To sample newly diagnosed cases of a disease as they crop up, use may be made of systematic sampling, for example, every fourth case, or of a sampling scheme whereby a case is randomly selected from each successive block of (say, two or four) cases.

In a case–control study where duration of exposure is taken into account by the use of person-time denominators, controls should be selected at the same time as the cases, rather than at a single point in time.

Efforts should be made to ensure full coverage, especially in studies entailing repeated examination of the same subjects, where it may be necessary to plan tracking procedures.

As in descriptive studies, the characteristics of the samples studied should be compared with those of the populations from which they are drawn and the characteristics of lost subjects (or of a sample of the lost subjects) should, if possible, be compared with those of the sample studied. Records should be kept of the reasons for noninclusion in the sample.

Thought should be given to the external validity of the study and its applicability in other contexts. Care should be taken to collect, and provide, any information about the group or population studied, and about the context, that may help others to decide whether the findings can be applied elsewhere.

To facilitate decisions on the practical usefulness of the findings, ways should be found of expressing them in terms—when it is appropriate and practicable to do so—of costs and of estimates of potential impact. Easily calculated estimates of the impact of exposure to a given factor on the incidence or prevalence of a given disease, for example, include the *population attributable fraction* (the proportion of cases attributable to the factor; see Chapter 88, pp. 1320–1321) and (if the factor can be eliminated) the *preventable fraction*.

Analysis of an Analytical Observational Study

The exploration of associations between variables provides the knowledge that an analytical study sets out to gain. But simple descriptive results are usually sought first. Examination of the frequency distributions of all relevant variables (in the total study sample or its subgroups) enables the investigator to find gaps, patterns, and inconsistencies, and "get to know" the data. As in a descriptive study, rates or proportions, preferably with their confidence intervals, may be computed for "yes–no" or other categorical variables and measures of central tendency and dispersion for metric (noncategorical) variables.

The next step is usually bivariate analyses, that is, the examination of relevant associations between pairs of variables—particularly relationships with the dependent variable or variables. In some studies, this may yield all the information that is required. In others, this process of "screening for associations" may facilitate decisions about the variables that should be included in subsequent analyses. (Bivariate analyses are sometimes called univariate analyses because a single independent variable is considered each time.)

Statistical significance and estimates of confidence intervals for measures of association should (at this and subsequent stages of the analysis) be computed by appropriate statistical procedures whose selection is determined by (for example) the variables' scales of measurement (dichotomous, nominal, ordinal, or metric), whether observations are paired or independent, whether count denominators or person-time denominators are used, and whether a normal distribution can be assumed.

The selection of variables that may act as confounders, and that should therefore be incorporated in subsequent analyses, may be based on the strength of their associations with the dependent variable or variables as demonstrated in the bivariate analyses. The selection may also be based on significance tests, eliminating the variable as a possible confounder only if p exceeds, say, .2 (25).

Multivariate Analyses The bivariate analyses are usually followed by multivariate analyses that involve more than two variables. There may be a temptation to jump in at the deep end and start with a multivariate analysis (e.g., multiple logistic regression), knowing that this will provide the main results required to meet the study's objectives, but most experts would consider it unwise to skip the prior examination of the data and their bivariate associations.

The simplest multivariate method of analysis is *stratification*. The sample is divided into strata, in accordance with the categories of a suspected confounding or modifying variable, so that the relationship between an independent variable and the dependent variable can be examined separately in each stratum, and the comparison of the results in the strata can be based on, say, risk ratios or odds ratios. Each analysis may have a single stratifying variable (e.g., sex), or there may be more than one stratifying variable (e.g., by stratifying by both sex and age).

The analysis of the stratified data generally uses the *Mantel–Haenszel procedure* (see Chapter 3, pp. 75–76) or a similar procedure. Different formulations are used for dichotomous, nominal, ordinal, and numerical dependent variables, for measures based on count denominators and person-time denominators, and for matched and independent observations. The Mantel–Haenszel analysis does two things. First, it provides a heterogeneity test that compares the associations observed in the different strata and may hence point to effect modification by the stratifying variable or variables. And secondly, it brings together the findings in the different strata by computing an adjusted odds ratio ("summary odds ratio," "underlying odds ratio") or an adjusted rate ratio or other measure that controls for the effect of the stratifying variable or variables. The adjusted measure can then be compared with the crude measure (based on unstratified data, and thus not controlling for the effect of the stratifying variable or variables). A discrepancy will suggest confounding by the stratifying variable or variables.

Here is a fictional example to make this clear. Imagine a cross-sectional epidemiological study that finds that MRSA carriage is associated with infrequent hand washing (<7 times a day), with an odds ratio of 2.8, and also with overweight (body mass index above 25), with an odds ratio of 3 (a crude association between MRSA infection and overweight has in fact been reported in a study of prison inmates) *(34)*. Suppose that we wish to see whether overweight has a confounding or modifying effect on the hand washing–MRSA association, using stratification and the Mantel–Haenszel method. To this end, we would stratify the sample by overweight, using two strata (overweight absent or present) or more than two strata (with different degrees of overweight). First, we would compare the odds ratios (expressing the association between infrequent hand washing and MRSA carriage) in the various strata. If these are all 2.8 or close to 2.8, overweight is not a modifying factor. But if they differ and the heterogeneity test gives a significant result, we would regard overweight as an effect modifier. But a word of caution: these heterogeneity tests have a low power to detect significant differences, and it is usually recommended that a p level of .1 or higher should be used as a cut-point for significance. Because of the low power of the tests, use may instead be made of indices of heterogeneity, namely, Higgins and Thompson's H (a value of 1.5 or more suggesting notable heterogeneity) and *I-squared* (the proportion of variation attributable to heterogeneity) (35). In this instance, let us imagine that the odds ratio for the hand washing–MRSA association is 1.5 in the "not overweight" stratum and 12 in the "overweight" stratum. This would clearly show that overweight has a modifying effect. (Remember that these findings are imaginary.)

Now let us look at the adjusted odds ratio computed by the Mantel–Haenszel procedure. This odds ratio should be compared with the unadjusted ratio (2.8). If there is an appreciable difference, this is evidence that overweight has a confounding effect on the hand washing–MRSA association. The adjusted measure then provides a better measure of the direction and strength of the association than the unadjusted measure, which is confounded by the effect of overweight. It should be noted however that if overweight is also a strong effect modifier, the adjusted measure may not be a very helpful basis for practical healthcare procedures. It is a kind of average and would obscure the information that the association between infrequent hand

washing and MRSA is very strong only in the overweight subjects, who might be selected as a high-risk group requiring special attention. The Mantel–Haenszel odds ratio in our fictional study is 2.9, very close to the unadjusted value of 2.8; in other words, in this case overweight is a modifier but not a confounder.

Stratification is unwieldy if there are more than one or two stratifying variables. Stratifying by age (say five age categories) and sex would mean 10 strata, and the addition of two more stratifying variables would boost the number of strata to 40 or more. Except in very simple studies, the multivariate method of choice is generally the use of a mathematical model that permits the simultaneous examination of relationships involving a number of independent variables, permitting estimation of the strength and statistical significance of their associations with the dependent variable, the identification of confounding and modifying effects, and the control of confounding effects. The available procedures, which use different models, include multiple linear regression, which assumes that effects are additive, and multiple logistic regression, which assumes that effects are multiplicative, as do multiple Poisson regression and Cox proportional hazards regression (which are appropriate for person-time data).

A decision must be made about the variables to be included in the regression analysis. Variables that are of interest as possible effect modifiers should obviously be included, and all potential confounders should be considered for inclusion. The selection of potential confounders may be based on the strength of the associations demonstrated in bivariate analyses and by comparisons of the findings in different strata. Sometimes it is decided to base the selection on a series of stepwise multivariate analyses in which a single variable is eliminated or added at each step. In stepwise "backward deletion" *all* the potential confounders are initially included; the variable with the smallest effect is then deleted, and this process is repeated until the removal of a further variable produces an appreciable difference (say of 20%) in the total effect. In stepwise "forward selection," one or two variables, e.g., age and sex, are included in the first analysis, and the potential confounder with the strongest effect is then added; this process is repeated until the addition of extra variables makes no important impact on the effect.

In some circumstances, the inclusion and neutralization of a variable that is *not* a confounder may introduce rather than remove bias (25). "Overadjustment" should be avoided.

The regression methods usually used are logistic regression analysis or (if duration of exposure to the suspected risk or preventive factor has to be taken into account) Cox proportional hazards regression analysis. If we apply logistic regression analysis in our fictional study of hand washing and MRSA carriage, using a model that includes infrequent hand washing, overweight, and the interaction between infrequent hand washing and overweight, the computer program will provide coefficients that can be transformed into odds ratios that are identical or very similar to those provided by the Mantel–Haenszel procedure, together with confidence intervals and significance tests.

Three precautions (often ignored) are worth noting with respect to logistic and Cox regression analysis. First, the analysis is invalid if the model is inappropriate in that it does not conform with reality—that is, if the effects of the various variables are not in fact multiplicative. For logistic regression analysis there is a simple goodness-of-fit test, comparing the observed findings with those predicted by the mathematical model, which should always be performed. Secondly, unless there is no interest in effect modification, interactions between variables should always be specified in the model; if the interactions turn out to be insignificant they can then be removed. And thirdly, a choice must be made between alternative analysis procedures—for example, conditional logistic regression should be used for matched data, and unconditional logistic regression in other instances.

Interpretation: Making Sense of Associations

Most analytical studies in the health field aim either to throw light on causal processes or to provide the means for predicting outcomes. They examine associations between variables and seek evidence that variables that are associated with the disease or other condition under study are risk factors (or preventive factors) that influence the development or severity of the condition, or, if they do not play an etiological role, that they can be used as predictors of the outcome (risk markers). Healthcare procedures directed at risk and preventive factors may, if these are modifiable, modify the outcome; and risk markers may identify individuals or groups at whom these procedures should be directed.

The first questions to be asked about an observed association concern the possible effects of bias. Is the association a true one, or may it be an artifact—a bogus association—attributable to information bias, selection bias, or confounding bias? May these biases have influenced the strength and direction of the association? And, on the other hand, if no association is observed, may biases account for its absence? If marked bias is strongly suspected and there is no way of correcting or controlling its effects, further examination of the observed association is usually pointless. Confounding should, if possible, be controlled by one of the methods mentioned above.

An association may be misleading for other reasons also. For example, in a follow-up study of persons selected because of their extreme values, they will tend, by chance, to have less extreme values the second time *(regression toward the mean*) if there is any degree of random variation. Hypertensives will tend to have lower pressures the second time they are measured. In an uncontrolled study this reduction might be spuriously attributed to treatment. An appropriate computer program can assess this effect or neutralize it in the analysis.

The strength of an association may be a measure of its importance—the stronger it is, the more likely that it is important. Attention should of course be paid to the confidence interval. Appraisals of strength are best delayed until possible confounders and modifiers have been incorporated into the analysis. Multivariate analysis can reveal that an association is stronger than it initially seems.

If effect modification is detected, its possible reasons should be considered.

Statistical Significance Anything may happen by chance. However strong the association that is observed between two variables, it may be fortuitous, unlikely though this may be. The absence of an association may also be a fortuitous occurrence. The question is not whether an observed association may have occurred by chance—the answer to which is almost always "Yes"—but whether we are prepared to regard it as nonfortuitous.

Significance tests (see Chapter 2, pp. 26–27) generally appraise the probability that there is no association (i.e., no difference in either direction); this is the *null hypothesis*. And the study hypothesis (the *alternative to the null hypothesis*) is that there is an association (a difference in either direction). A two-sided test should then be used. But if the study hypothesis is that there is difference in a particular direction, a one-sided significance test can be used. A one-sided test is more likely to give a significant result than a two-sided test, but it should be used only if it is warranted by a one-sided null hypothesis, stated before the test is performed.

If the probability that there is no association (p) is low, we can be reasonably sure that the association is not fortuitous. If the p value is under .05, for example, we can be 95% sure. But we can never be *quite* sure that the finding is not due to chance. And, on the other hand, if the test result is "not statistically significant," this does not necessarily mean that the association is fortuitous (any more than a negative sputum test for the tubercle bacillus necessarily means that a patient does not have tuberculosis). The verdict is "not proven." If samples are large, however, a "not significant" result may be taken to mean that there is unlikely to be a nonfortuitous association of any great strength.

We should mention that for some significance tests, the null hypothesis is that the means, proportions, or rates that are compared are different, not that they are the same, and its alternative (the study hypothesis) is that they are the same. These are *equivalence tests* and *noninferiority tests* that are conducted in order to decide, for example, whether a new treatment is as good as, or at least not worse than, an established treatment. In these tests, a low p value points to similarity and not (as in most significance tests) to a difference.

One of the questions asked at the start of this chapter was if a study of MRSA carriage showed no significant association with smoking ($p > .05$), this would mean that smoking has no effect on the prevalence of MRSA carriage. The answer is obviously "No," since even if there are no biases (and we do not know this), the negative significance test tells us only that there is no convincing evidence that there is no relationship, not that there is no relationship. "Absence of evidence is not evidence of absence" *(36)*. Even a strong association may be statistically nonsignificant if the sample is small, and we do not know the size of the sample in this study. Only if the study was based on a very large sample might we be reasonably safe in concluding that smoking has no effect.

Significance tests have "built-in errors." Using a significance level of 5%, purely random processes will produce a verdict of "statistically significant" in about 5 of every 100 significance tests performed, even if no real associations exist. This may be an important consideration if many tests are performed on the same body of data, and statistical procedures that take account of multiple testing are available.

Confidence intervals can be used to provide an indication of statistical significance. If, for example, the 95% confidence interval for a difference between two rates or means does not include 0, or if the 95% confidence interval for a rate ratio or odds ratio does not straddle 1, this usually means a significant difference (by most two-sided tests) at the 5% level.

Useful though it may be to know whether an association is significant, it must be remembered that it tells us nothing about the strength or importance of the association. A very weak association can be significant if the sample is large, and a strong association can be nonsignificant if the sample is small.

Significance tests should not be done when they are not needed. In some studies, especially in simple descriptive studies not based on random or systematic samples, the issue of fortuitousness may have little importance. For practical purposes it may be enough to know that patients with MRSA infections are concentrated in certain hospital wards or that these infections are much more prevalent in patients with certain disorders, without worrying about deciding whether these associations might have occurred by chance. In Bradford Hill's words, "there are innumerable situations in which (tests of significance) are totally unnecessary because the difference is grotesquely obvious, because it is negligible, or because, whether it be formally significant or not, it is too small to be of any practical importance" (37). There is little point in doing a significance test on an association that is likely to be an artifact or on one that is so weak that it would be of no consequence even if it were regarded as nonfortuitous.

Causal Inferences The question of causality is a knotty one. Using the findings of an observational study, how can we infer that the association between **A** and **B** is a cause–effect one? How can we infer that **A** (or a factor for which **A** is a proxy measure) produces or influences **B**—or, of course, that **B** (or a factor of which **B** is a proxy measure) produces or influences **A**? How can we infer that exposure to the one variable, or a change in its amount or quality, results in an alteration in the amount or probability or quality of the other variable?

There are two obvious prerequisites, without which an observed association cannot be regarded as definitely causal. First, the assumed cause must precede the assumed outcome. Time relationships are, of course, always known in trials. In an interesting impeccably performed randomized controlled trial of the effect of intercessory prayer on hospitalized patients with bloodstream infections, in which there was perfect blinding of patients and staff not only to the allocation of patients but even to the existence of the trial, it was found that patients who were prayed for had a significantly shorter duration of fever, a significantly shorter hospital stay, and a (nonsignificantly) lower mortality *(38)*. But the inference that this was a cause–effect relationship was somewhat vitiated by the fact that the praying took place 4 to 10 years after the patients' hospitalization. Time relationships may also be known in longitudinal observational studies and some case–control studies.

They may be uncertain in cross-sectional and in other case–control studies. However, it is essential that there should be at least a possibility that the assumed cause preceded the assumed outcome.

Secondly, the observed association must not be wholly attributable to selection bias, sampling bias, or confounding bias. The effects of bias are usually uncertain, and even in the best-planned and best-performed study there may be doubts about possible unknown or unmeasured confounders. Hence there is usually a degree of uncertainty about the validity of causal inferences.

All we can hope for is reasonable evidence for a causal relationship, strong enough to be used as a basis for decision and action. Basically, what we can do is see how well the facts fit in with what we might expect to find if the association was causal. This is not quite the same thing as "proving" a causal association, but it is the best we can do. The following additional criteria, taken together, may strengthen or weaken the case for causality, although none of them is essential or conclusive:

1. *Statistical significance* does not necessarily support the case for a causal association, but its absence weakens the case if the test is sufficiently powerful (which usually means "if the sample is large enough").
2. *Strength* of the association—the stronger it is, the more likely that it is causal, and not produced by bias or confounding. But a weak association may also be (weakly) causal.
3. *Dose–response relationship*—the case for causality is supported if there is a correlation between the amount, intensity, or duration of exposure to the "cause" and the amount or severity of the "effect." But a dose–response relationship does not "prove" causality, and nor does its absence disprove it; there may, for example, be an "all-or-none" response that appears only when a causative factor reaches a threshold level, or a relationship between cause and effect that is U- or J-shaped (or inverted U- or J-shaped) rather than linear.
4. *Time–response relationship*—if the incidence of the "effect" (e.g., the rate of new cases of a disease) peaks some time after a brief exposure to the "cause" and then decreases, this supports the case.
5. *Predictive performance*—if the study results provide new knowledge supporting an *a priori* hypothesis concerning a predicted effect, this supports the case; a failed prediction weakens the case.
6. *Specificity*—the finding that the "effect" is related to only one "cause," or that the "cause" is related to only one "effect," may be regarded as supporting the case. But a lack of specificity in no way negates a causal relationship.
7. *Consistency*—if the same association is found repeatedly, in different subgroups of the study population and in other populations or circumstances and in studies by other investigators or methods, this strongly supports the case. If results are inconsistent and the variation cannot be explained, this weakens the case.
8. *Coherence* with current theory and knowledge—in particular, the availability of a satisfactory explanation of the mechanism by which **A** may affect **B**—supports the case. But investigators can usually think up a plausible causal explanation for any association. If no plausible explanation can be suggested, a cause–effect relationship may be difficult to accept, but should probably not be ruled out. Incompatibility with known facts weakens the case.

These are not clear-cut hard-and-fast "rules of evidence." In the words of Bradford Hill's seminal paper on "association or causation": "None … bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question, is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" (37). The appraisal of causality is thus a matter of judgment, which means that experts may differ in their conclusions. But there is no substitute for considered judgments based on the available evidence, as the basis for decisions about healthcare in situations where (as almost always) there is no completely valid answer.

At this point, let us return to one of the questions asked at the start of this chapter: "A study of adults undergoing mandatory health examinations revealed that MRSA carriage was about twice as high among nonsmokers (4.3%) as among smokers (2.2%); the difference was statistically significant (p = .019). Does this mean that smoking protects against MRSA carriage?" The answer must of course be "No" if only because the association may be attributable to confounding. We might think of age as a possible confounder, since (in many countries) the proportion of smokers is higher among younger than among older adults, and both healthcare-associated and community-associated MRSA infections have been found to be much less prevalent in younger than in older adults *(39)*. Actually, confounding by age could not have caused this association since although age was not controlled in the study that found the association, age was not associated with MRSA carriage in that study, which was conducted in Taiwan. The authors of the study suggested that "it might be that smoking creates a microenvironment in the nose that protects against the growth of *S. aureus*." But it might also be that the association was a chance occurrence, a fluke—significance tests may be misleading if many tests are done on the same body of data, and the test for the association with smoking in this study was 1 of 21 tests for associations. We should agree with the authors that this "requires further study," and wait and see whether the association is replicated in other studies.

ECOLOGICAL AND MULTILEVEL STUDIES

Ecological studies are studies in which the units of analysis are populations or groups of people, rather than individuals *(3)*. In other words, the variables whose associations are examined are the characteristics of the groups that are studied, and not the characteristics or experiences of the individual members of the groups. Analytical ecological studies may be cross-sectional or longitudinal.

Ecological studies permit the examination of factors that affect a whole group. These factors include *aggregate measures* (or *derived measures*) that summarize the attributes of individuals, such as the level of herd immunity or the prevalence of carriage of a microorganism, or *global*

measures that do not, for example, the accessibility of health services, or cultural norms affecting interpersonal contacts. In the context of healthcare-associated infections, ecological studies may aim to determine the effects of characteristics of the unit or ward in which the patient is treated, including the use of infection-control measures, personnel size, and personnel functioning, or characteristics of the hospital.

Examples of ecological studies are a 2-year study of two neonatal intensive care units in New York, where a multivariate analysis revealed an inverse relationship (in one of the units) between the number of hours of nursing care per day in the unit and the risk of bloodstream infections *(40)*; a Spanish study that found that the rising prevalence of *Clostridium difficile* infection in a large number of hospitals between 1999 and 2007 was strongly correlated with the rising prevalence of use of antimicrobials in the hospital *(41)*; and a study of a Danish hospital, where the incidence of healthcare-associated bloodstream infection remained stable during a 4-year period despite a significant increase in the amount of alcohol-based hand rub used *(42)*.

If operational definitions and methods of a study are in the investigators' control, ecological studies require the same precautions to prevent information bias as do individual-based studies. Unfortunately, it is often necessary to use information of questionable accuracy or appropriateness, collected for administrative or fiscal purposes by hospital administrations or obtained from statistical offices or other official sources. In such instances, circumspection in its use is essential.

The analysis should follow the same lines as in other analytical studies. Use is frequently made of the correlations between variables, so that ecological studies are sometimes called *correlation studies*. Possible confounding by other group-based variables should be, if possible, appraised and controlled.

Multilevel studies use both group-based and individual-based variables. They examine the effects of both sets of variables and can explore the relationships between their effects. Group-level factors may not only change the risk of an infection but also modify the association between individual-level risk factors and risk of an infection. Examples cited in a review of the potential value of multilevel studies *(43)*, with respect to the association between number of sex partners and the risk of an STD, are the effects of the prevalence of STD in the population, the degree of assortative (within-group) mating, and the availability of STD clinics. The effects of group-level factors can be estimated after adjustment for individual-level variables, and vice versa. Multilevel studies can thus pinpoint the possible value of interventions directed both at groups and at individuals.

An example in the field of hospital-associated infections is a Finnish study performed in 60 wards in 6 hospitals, which collected individual-level data concerning a number of risk factors, together with hospital-level data (a university hospital or not?), and ward-level data that emphasized work hours and measures of work stress and collaboration between personnel. Multilevel logistic regression analyses, controlling for hospital factors and patient-level risk factors, showed that the risk of infections was raised if the staff had long work hours or a high level of work stress, as expressed in a low trust of other unit members, a perceived imbalance between efforts and rewards, a poor collaboration between ward supervisors, and other indicators *(44)*.

PROGRAM REVIEWS

Evaluative studies of healthcare programs can be usefully categorized as program reviews or program trials (11).

Program reviews are studies that evaluate specific healthcare programs and are motivated by concern with the welfare of the patients, community, or population to whom care is given, with the intention of helping whoever runs and makes decisions about the program. They do not question or test the assumptions on which the program is based, for example, the assumption that certain procedures will have beneficial effects. They examine the operation and outcomes of the program, but are not concerned with cause–effect hypotheses or inferences.

Program reviews are basically descriptive epidemiological studies, and in principle they require the same precautions to avoid information bias and selection bias as do other descriptive epidemiological studies. However, there are two constraints: to be useful, a review must usually be rapid and (if possible) ongoing, that is, performed in real time; and the review is usually conducted in a service-oriented setting, where evaluation is not seen as a major priority, and little time and resources may be available for special information-collecting procedures. Very rigorous definitions, elaborate methods, and extensive lists of variables may therefore not be practicable.

Some associations between variables may be relevant and therefore examined in a program review. But, since no hypotheses are tested, attention need not be paid to confounding or to causal inferences. If there *are* hypotheses to be tested, the more rigorous methods appropriate in program trials (see below) should be used.

Like other evaluative studies, program reviews aim to collect objective facts that provide a basis for subjective decisions on the value of the program. The topics to be considered when defining the study objectives include the following (11):

1. The *requisiteness* of the program—to what extent is it needed? What is the extent and severity of the problems that the program aims to solve?
2. The *outcomes* of the program—the occurrence of desirable effects (*effectiveness*) and undesirable effects (*harmlessness*).
3. The *process*—the performance of planned activities by the program's personnel, and compliance and the utilization of services by the recipients of care.
4. The *structure*—the availability of personnel and facilities, and geographic and economic accessibility.
5. *Efficiency*—the cost incurred in achieving results: in monetary terms (the study of which requires special expertise) or in nonmonetary terms, for example, the number of nurses, hours of work, hospital days, hospital beds, waiting time, or screening tests required for a particular purpose.

6. *Differential value*—differences in the above features in different categories or groups or in different circumstances.

One of the questions asked at the start of this chapter was: "Suppose that a program to encourage hand washing by personnel is followed by a reduced rate of *S. aureus* infections among patients. Does this mean that the program reduced the incidence of these infections?" The answer is "No," since the reduction in the rate might well have other causes. A "Yes" answer would require a controlled study, using the stringent methods of a program trial. However, in a review of a program that does not question the assumption that hand washing by personnel can reduce the probability of *S. aureus* infections among patients, this would be regarded as a satisfactory outcome, indicative of the program's effectiveness.

Unless there is no intention to publish the results, there will always be other health workers or researchers who will be interested in the applicability of the findings in their own healthcare services or populations, even if the study was planned to meet a specific local need. Care should therefore be taken to collect, and provide, any information about the group or population studied, or about the context, that may help others to decide on the relevance of its findings elsewhere.

TRIALS

Clinical trials and program trials may be seen as epidemiological experiments designed to evaluate healthcare procedures or programs. *Clinical trials* evaluate therapeutic, preventive, rehabilitative, or educational procedures applied to individuals, and *program trials* evaluate intervention programs applied at a group level (i.e., in a total hospital or other care unit), possibly including, but not limited to, procedures applied to individuals.

Unlike program reviews, both clinical and program trials generally aim to produce generalizable results, applicable in settings other than that in which the trial was conducted. In addition to the precautions required to ensure the internal validity of the study, thought should be given to its usefulness in other contexts, and full information should be collected and provided about the characteristics of the samples, and the context in which the trial is performed.

To facilitate decisions on the usefulness of the findings, ways should be found of expressing them, when it is appropriate to do so, in terms of impact (such as attributable or preventable fractions) or the number needed to treat in order to cure or prevent one case, or cost.

Clinical Trials

Clinical trials are generally *parallel studies*, which compare outcomes (both desired and undesired), in independent groups of individuals who have been exposed and not exposed to the procedure being tested or exposed to different procedures. They may also be *externally controlled studies*, in which the exposed group is compared with data obtained from other sources, or "*self-controlled*" *studies*, in which the subjects are their own controls (before–after studies and crossover studies).

Uncontrolled trials are obviously of limited usefulness.

Externally controlled studies have obvious limitations because of possible differences between the experimental and control subjects with respect to their characteristics or management or manner of appraisal or the time at which they were treated. Even patients treated in the same way, but at different times, may have very different outcomes; variations of up to 46% have been reported in the death rates of control groups (who had the same treatment) used by the same investigators in different cancer chemotherapy trials *(45)*. This is an important consideration in studies using historical controls (patients treated in the past).

"Self-controlled" before–after studies avoid many possible confounding effects but are subject to biases connected with extraneous events, time-related changes, and other factors. "Self-controlled" crossover studies are practicable only for interventions that do not have protracted "carryover" effects, and their analysis requires special statistical procedures.

The following remarks apply to parallel studies.

Selection Bias and Confounding Bias A key feature of well-designed clinical trials is their avoidance of selection bias and confounding bias in order to ensure internal validity. This is accomplished by comparing groups that are initially similar, or have only chance differences, with regard to prognostic factors (factors that may affect the outcome), and it is generally achieved by *randomization*, that is, by a random allocation of individuals who are eligible and have given their informed consent. To make the groups even more similar, randomization may be performed after stratifying the subjects by chosen prognostic factors; or use may be made of *minimization (46,47)*, a technique that permits the control of more variables. The same eligibility and exclusion criteria are applied in each group.

If randomization or minimization is not used, the trial will have the same selection biases as an analytical observational study.

But even in the best run of clinical trials, the subjects may not all remain in their assigned groups throughout the study. Nor only may losses occur due to death or other reasons, but subjects may switch from one group to another, for example, because of noncompliance or a decision that, in the interests of their health, treatment should be stopped, changed, or started. These changes should be documented, and the resultant possible bias should be taken into account when the findings are analyzed and interpreted.

Whatever the internal validity of the trial, the generalizability of its results depends on who is studied and the circumstances of the study. External validity may be compromised by the study's eligibility and exclusion criteria or by selection bias, for example, the unreadiness of eligible subjects to participate. Internal and external validity may be inversely related—the more stringent the eligibility and exclusion criteria, the less generalizable the results may be. The trial's results may be applicable only to persons similar to the study's subjects, and then only if the setting is similar *(48)*. The results of a trial of selective decontamination of the digestive tract in critically ill patents, for example, might be generalizable only to intensive care units with a low prevalence of antibiotic-resistant bacteria *(49)*. An

assessment of the applicability of the results requires information not only about eligibility and exclusion criteria but about ethnic, socioeconomic, and other characteristics that may influence the outcomes, the proportion of eligible subjects who were included in the trial, treatment facilities and settings, etc. *(48)*.

Information Bias As in observational studies, precautions should be taken to avoid information bias. Standardized operational definitions and methods of measurement and ongoing monitoring of the performance of the study are particularly important in multicenter trials. If there is reason to believe that there may be bias if the subject or observer knows to which group a subject has been assigned, blinding (e.g., of subjects, clinicians, technicians, or other observers) is advisable; this may entail the use of placebo treatments and concealment of the allocation scheme.

Analysis The analysis should commence with a comparison of the groups (usually treatment and control groups) with respect to characteristics that may affect the outcome, in order to provide assurance that the groups are indeed similar, and that confounding by these characteristics need not be considered.

The main thrust of the analysis is a comparison of the outcome and (if known) the intermediate effects in the treatment and control groups. The effects of modifiers can be appraised by the same methods as those used in analytical observational studies.

If there were subjects who switched groups during the study, that is, by moving from a treatment to a no-treatment group, or vice versa, two sets of analyses are advisable. First, *intention-to-treat analysis*, that is, a comparison of the outcomes in the subjects originally allocated to each group. This minimizes confounding but may underestimate the efficacy of the procedure that was tested. And secondly, *per-protocol* (or *on-randomized treatment*) analysis, which compares the experience of subjects while they were still in their allotted groups. This generally overestimates the efficacy of the procedure and has the disadvantage that it is not based on randomized groups, so that possible confounding must be considered.

The easily calculated *NNT* or *number needed to treat* (to produce, avoid, or cure one case) may he a helpful yardstick for the value of the intervention, although it expresses only the results of a particular trial conducted on selected subjects over a particular time period and is easily misinterpreted as a measure of the probability that an individual person will benefit from the intervention *(50,51)*. Different NNT measures are appropriate for different purposes *(52,53)*—expressing, for example, the effect in the total population of a treatment or exposure to some factor, the hypothetical benefit in subjects who are exposed to the treatment or factor (*EIN*, or *exposure impact number*, expressing the effect of removing the exposure), or the hypothetical benefit in subjects who are not exposed (*NNE*, or *number needed to be exposed*).

Program Trials

Trials of healthcare programs are important and may have far-reaching implications. They are unfortunately beset with difficulties. The distinctive feature of an experiment designed to study the effects of an intervention is that it is the researcher who decides to whom the intervention will or will not be applied. Many trials of healthcare programs are not true experiments, but *quasi-experiments*, where the decision to run a program was not made by the researcher. The outcomes in a unit where the program is applied may be compared with those in a control unit, but the units cannot necessarily be regarded as similar, and such trials must be analyzed as if they were analytical observational studies. Before–after comparisons may be used, but it may be difficult to know to what extent the outcome is attributable to the program rather then to other causes.

Randomization would seem to be the answer, but even if a random allocation of two units is feasible, randomization is here irrelevant—the same differences will exist, and there will be the same possibility of confounding, whichever of the two units is exposed to the program. Again, the trial would have to be analyzed as if it was an analytical observational study.

For randomization to be effective, a reasonably large number of entities must be available for allocation. In a study of the use of disposable thermometers instead of electronic thermometers to prevent *C. difficile* infections, for example, 20 nursing units were randomly divided into two groups, one of which used single-use disposable thermometers exclusively and the other electronic thermometers, with a switchover after 6 months *(54)*. A number of program trials have been done by running a program in randomly chosen healthcare units, and not in others. For example, randomized controlled trials of the effects (on patients) of programs to encourage the immunization of personnel against influenza have been conducted in samples of long-term hospitals *(55)* and primary-care community clinics *(56)*. Villages, or groups of adjacent villages, can also be randomized, as in African studies that tested the value of community programs for the control of an STD as a means of preventing AIDS *(57,58)*. The validity of trials based on randomly allocated clusters of subjects can be enhanced if the clusters are stratified before randomization and the same inclusion and exclusion criteria and methods of study are used in each cluster *(59)*, and if the analysis uses special statistical procedures that take account of the tendency of members of a cluster to be similar to one another.

Randomization of individuals is sometimes practicable if the individuals cared for can be randomly allocated to an intervention program or to a control group or other program. The trial is then essentially a clinical trial, performed in order to evaluate a program. As an example, in three hospitals in Denmark a smoking intervention program, applied 6 to 8 weeks before elective hip or knee replacement, was tested by randomly allocating patients to this program or to a control group *(60)*. The rates of wound infection (with a positive culture) were 4% in the program group and 23% in the control group ($p = .002$).

If the evaluation of a program is based on a before–after comparison (a "*self-controlled*" study), attribution of the outcome to the program rather than to other causes can be reinforced by information about intermediate outcomes. The evaluation of an educational program for intensive care unit nurses concerning venous catheter insertion and care, aimed at decreasing the rate of blood stream infections, for example, would be strengthened by

information on changes in actual behavior, such as the frequency of inspections of the catheter site for tenderness, and prior hand washing *(61)*. With some programs, it would also be helpful to know what happens if the program is withdrawn.

Externally controlled program trials, which compare the outcome of a program with national or other data obtained from other sources, may have questionable validity, since definitions and study methods may be different, the populations may have different characteristics or circumstances, and the data may refer to different time periods.

Case–control studies can sometimes be used to evaluate programs, by comparing people who have experienced an undesirable outcome (cases) with controls, to see whether they differ in their prior exposure to the program. In the Netherlands, for example, the value of a cancer screening program was confirmed by a study of women who died of breast cancer and matched survivors, comparing their history of participation in the screening program *(62)*.

Meta-analyses

A meta-analysis (see Chapter 7) is a critical review and integration of the results of separate studies of the same topic (63). To avoid bias, it requires an exhaustive search for studies, clear criteria for their inclusion, and possibly (when appraising the quality of studies and extracting their findings) blinding to authors, institutions, and journals.

Google and Google Scholar, although handy and extraordinarily useful tools for most searches, are not sufficiently accurate, thorough, or up-to-date for this purpose *(64)*, and the searches are usually conducted in PubMed, which currently provides access to almost 20 million citations, and other special databases. The possible effect of unfound studies should be assessed, since *publication bias* is an established fact in the health field—negative or inconclusive studies are often "tucked away in desk drawers" or rejected by editors. A *fail-safe N* is therefore computed by WinPepi and other computer programs that perform meta-analyses; this is the number of unfound negative studies that would suffice to render the overall finding of the meta-analysis nonsignificant or trivial; if it is small, the results may be questioned.

When the studies have been found, the first step is to appraise their quality, using clear and objective criteria (this is a *qualitative meta-analysis*). This may lead to a decision to exclude some studies from the statistical analysis of results, to perform separate analyses of studies of higher and lower quality, to incorporate a measure of each study's quality in the analysis, or even to a decision to abandon the meta-analysis as fruitless and issue a call for better-designed studies.

The next step is comparison of the study results. This may be based on a significance test for heterogeneity or (since such tests have a low power) on indices of heterogeneity (Higgins and Thompson's H or I-squared) (35). Heterogeneity may be caused by (for example) differences in study design and performance (including differences in working definitions), differences between the characteristics of the subjects, and differences in the circumstances of the studies. The reasons for differences should be explored. This may yield information on modifying effects, which may be the most important benefit of the meta-analysis.

The optional next step is integration of the results, to produce an overall measure of the association. This may be done for all the studies together (an analysis that may be deemed unnecessary and not very meaningful if they are very heterogeneous), or, if they are not all regarded as "combinable," for subgroups of the studies. Analyses that exclude specific studies, one by one (*sensitivity analyses*), may help to pinpoint those that have an especial influence on the overall measure. The results of individual studies are usually measures of association—rate ratios, risk ratios, odds ratios, hazard ratios, differences, or standardized differences ("effect sizes"). These individual results can be combined by statistical procedures (offered by WinPepi and other software) that take account of sample sizes and avoid confounding caused by imbalances in sample sizes. Use is generally made of the Mantel–Haenszel method or other procedures that assume that the various individual results are estimates of the same fixed effect, or the DerSimonian–Laird random effects procedure, which assumes that the effects in the various studies differ and are randomly positioned about some central value. These procedures compute summary measures of association and estimate their confidence intervals. The results of studies of different types can be brought together in this process, provided that they used the same measures of association.

Interpretation of the findings and their practical implications must take account of the quality of the studies, possible biases, and generalizability.

The following final comments center on the last question asked at the start of this chapter, namely, "Suppose we are told that a review of the literature has found 16 controlled trials that show that a certain treatment for MRSA is efficacious and 4 that do not (a highly significant difference: $p = .007$). Can we conclude that the treatment works?"

Why is the answer "No"?

First, we are told that 20 trials were found. But trials are not easy to find. Were there in fact only 20? How were these 20 found? We do not know. Was the search systematic, and if so, what database or databases and what search terms were used? According to the *Cochrane Handbook* (65), an exhaustive hunt for randomized controlled trials in PubMed's computerized database requires 26 search terms over and above those specifying the topic of the trials.

Publication bias—that is, a tendency for negative or inconclusive trials to be "tucked away in file drawers"—is a bugbear of meta-analysis. Were any registers of controlled trials searched? Were unpublished studies sought in conference proceedings? Was a statistical test done for asymmetry of the funnel plot (a test indicative of a paucity of small negative studies)?

What is the *fail-safe N*?—That is, how many unpublished negative findings would suffice to make the difference nonsignificant or negligible?—Would a mere handful of studies do this if they were found?

Secondly, the statistical test comparing the figures 16 and 4, and yielding a p value of .007, gives the same weight to each study. But maybe the 16 positive studies were very small ones, whereas the 4 negative studies may have been large ones, whose results should carry more weight. Also,

no attention was paid to the strength of the associations. "Vote counting" (how many for? how many against?) is not an appropriate method. A Mantel–Haenszel analysis, based on the strength of the effect and sample sizes in each study, and yielding an overall measure of strength, with its confidence intervals, would be more convincing.

Thirdly, we know nothing about the quality of the positive and negative studies. What, for example, does "controlled" mean? How were the controls selected? Was randomization used?

Without extra information, we certainly cannot conclude that the treatment works.

Further investigation is needed (a recommendation by no means unfamiliar in epidemiological research).

PRACTICAL IMPLICATIONS

The findings of all epidemiological studies—descriptive or analytical, but especially those of analytical observational studies and trials—may point to a need for action as well as a need for further research. But whether it is the epidemiologist's job to make practical recommendations is a matter of opinion. Probably most epidemiologists would consider it a dereliction of duty if they did not do so and if they abstained from calling for the specific interventions whose potential value is indicated by their findings. They usually undertake their studies with the stated or unstated purpose of improving health or healthcare, and they wish to see their findings translated into action. If **A** was found to be a risk marker, then screening for **A** is advocated. If **B** is a risk factor, this calls for appropriate action to deal with it. If **C** is a preventive factor, then an appropriate educational or other prophylactic program is needed. If **D** is an effective and safe treatment, it should be used. If program **E** is effective, it should be introduced as a routine. And so on. These recommendations may extend beyond the healthcare facilities in which the studies were conducted. Many hospital studies of the burden of gastroenteritis, for example, have led to calls for the routine vaccination of children against rotavirus *(66)*.

But there is an opposite view. Not all epidemiological researchers really understand the process of policymaking. The respected epidemiological journal *Epidemiology* discourages policy recommendations in research reports, saying "it is simply too facile to toss off a policy recommendation in the closing paragraph of a scientific paper without giving the implicit decision analysis the due consideration it deserves. Making good health policy is complicated.… Our editorial policy is intended to avoid trivializing a complex process and to increase the likelihood that policy discussions are treated with the seriousness and depth of understanding that they deserve" *(67)*. An invited commentator on this decision said that he himself would make a policy recommendation only in the unlikely instance that he had information on all its potentially important consequences, including economic benefits and costs, and could conduct a formal decision analysis *(68)*. But another commentator dissented and cited examples in which he believed the inclusion of policy comments in scientific reports had had a material influence *(69)*.

For investigators who are not skilled in policy making and decision analysis, a prudent compromise is probably best: Sufficient details should be provided to facilitate decisions on feasibility and applicability—the characteristics of the subjects who were studied, the circumstances in which the study was performed, and the efforts required to achieve effects. Appropriate lines of action may then be suggested, but in a cautious and "iffy" manner, that is, with such provisos as "if this is feasible" or "if resources are available." Take care to translate the study findings, if possible, into quantitative indicators of cost and benefit that will be meaningful to decision makers (e.g., the number of screening tests required to detect one case, the number needed to treat in order to prevent or cure one case, or the attributable or preventable fraction of the disease or mortality load that can be attributed to a given factor or prevented by a given action) and do not hesitate to estimate and mention possible savings on hospitalizations or other costly procedures. Point to the lines of action suggested by the evidence and provide evidence-based motivation. But do not pontificate—leave the decision making to the decision makers. Softly, softly, catchee monkey.

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CHAPTER 7

Meta-analysis and Systematic Reviews of the Literature in Healthcare Epidemiology and Infection Control

Nasia Safdar, Sanjay Saint, and Mary A.M. Rogers

With the growing use of evidence-based medicine and the increase in medical information available in both print and online sources, it has become increasingly difficult to keep up-to-date on medical advances. Systematic reviews and meta-analyses are important tools for summarizing the literature and critical appraisal, providing a valuable framework for medical decision making. Beyond their role in clinical medicine, systematic reviews and meta-analyses also may be used by researchers to synthesize evidence for specific hypotheses and by policymakers to examine benefits and harms of healthcare-related interventions. Recent data suggest that at least 2,500 new systematic reviews reported in English are indexed in MEDLINE annually (*1*). This chapter summarizes the key features of systematic reviews and meta-analyses, including general steps on how to undertake these methods, interpret the results, and critically appraise a published systematic review. In general, examples used will be relevant to healthcare epidemiologists, infection preventionists, and others with an interest in healthcare epidemiology and infection control.

DEFINITIONS

A *systematic review* is a synthesis of all evidence that addresses a specific research question. By using systematic, transparent methods to identify the relevant literature, with a view to minimizing bias, this method provides reliable findings from which conclusions can be drawn and decisions made (*2*,*3*).

The key characteristics of a systematic review are outlined in the *Cochrane Handbook for Systematic Reviews* (4). They are:

- A clearly framed research question with explicitly stated predefined eligibility criteria for studies
- A detailed description of methodology
- A comprehensive systematic literature search to identify all studies meeting the eligibility criteria
- An assessment of the quality and internal validity of the included studies
- A systematic analysis, presentation, and interpretation of the characteristics and findings of the included studies

A *meta-analysis* is a type of systematic review in which statistical methods are employed to summarize the results of independent studies (*5*). By combining information from all relevant studies, meta-analyses can often produce more precise estimates of the effects of healthcare than those derived from individual studies. Meta-analyses may also provide an assessment of the consistency of the evidence and an exploration of reasons behind the variation in effects across studies.

STEPS FOR UNDERTAKING A SYSTEMATIC REVIEW OR META-ANALYSIS

The general steps for conducting a systematic review or meta-analysis are:

1. Defining an appropriate healthcare question
2. Searching the literature
3. Assessing the studies
4. Synthesizing (or combining) the results
5. Placing the findings in proper context

FORMULATING THE RESEARCH QUESTION

Formulating a specific, answerable question is a critical first step when initiating a systematic review. Importance of the topic is consequential. If a research question is not worth answering, it is not worth answering *well*. One recommended approach is using the acronym "PICOS" to help formulate the research question (Table 7-1): the patient *p*opulation, the *i*ntervention of interest, the *c*omparator group, the *o*utcome of interest, and the *s*tudy design chosen. The more precise the definition of these five components, the easier it is to apply the systematic review framework (6).

The patient population of interest should be clearly defined in terms of age, characteristics of interest (disease or condition, such as mechanically ventilated

TABLE 7-1

Formulating a Research Question for a Systematic Review

	Patient or Problem	*Intervention*	*Comparison Intervention*	*Outcomes*	*Study Design*
Tips for building	Starting with your patient, ask "How would I describe a group of patients similar to mine?"	Ask "Which main intervention am I considering?"	Ask "What is the main alternative to compare with the intervention?"	Ask "What can I hope to accomplish?"	Ask "What are methodologically rigorous study designs?"
Example	In mechanically ventilated patients in the ICU	Does oral care with topical chlorhexidine	Compared with placebo	Reduce the incidence of ventilator-associated pneumonia	Randomized controlled trial

(Adapted from http://www.cebm.net/index.aspx?o = 1036. Accessed December 15, 2009. Asking Focused Questions.)

patients), and the setting, such as an intensive care unit (ICU). The interventions must be clearly and transparently reported. For example, for a question regarding the association between topical oral chlorhexidine and ventilator-associated pneumonia, it is important to detail the dose, frequency, method, and site of application. It is equally important to present details of the comparator under consideration, such as placebo or standard care. Definitions of standard care may differ among the primary studies in the systematic review. The outcomes of interest should also be clearly specified. For example, if ventilator-associated pneumonia is an outcome, a validated standardized definition should be used. Finally, study design considerations should be explicitly addressed. Many systematic reviews include only randomized trials, while others may choose to include both experimental and observational studies. The study question to be answered may drive the decision regarding what types of studies are to be included. Whatever the rationale may be, decisions regarding the population, intervention, comparison group, outcome, and study design should be clearly stated in the systematic review or meta-analysis.

DEVELOPING CRITERIA FOR INCLUDING STUDIES

A key component of a systematic review is the prespecification of criteria—the eligibility criteria—for including and excluding studies in the review (4). The patient population, interventions, comparisons, and outcomes laid out in the research question are used to derive the eligibility criteria. For the patient population, the definition should be sufficiently broad to avoid unnecessary exclusion of studies but should be narrow enough that a meaningful result is expected when they are considered in aggregate. Depending upon the condition of interest, the study population may be defined in the context of other characteristics such as sex, race, age, educational status, or venue of care (e.g., ICU, nursing home). Any restrictions with regard to population characteristics should be explicitly defined and the rationale provided. Table 7-2 provides a list of relevant questions to be addressed when evaluating the study subjects.

The intervention should also be described in detail. For those reviews in which there are slight variations in the intervention across studies, a table describing the elements of each intervention is helpful. Important considerations include decisions regarding trials with multiple interventions. The arms of the trial should be clearly stated and the comparison groups specified. This is of particular importance when the results will be pooled for meta-analysis. For example, the pooling of relative risks for septicemia that compare an intervention with usual care should be separate from the pooling of such relative risks when comparing an intervention with a placebo. Relevant questions regarding the intervention are listed in Table 7-3.

TABLE 7-2

Factors to Consider When Developing Criteria for "Types of Participants"

How is the disease/condition defined?
What are the most important characteristics that describe the participants?
Are there any relevant demographic factors (e.g., age, sex)?
What is the setting?
Should the participants be defined by a specific diagnosis?
Are there types of people who should be excluded?
How will studies involving only a subset of relevant participants be addressed (e.g., studies containing both pediatric and adult populations for age-specific systematic reviews)?

TABLE 7-3

Factors to Consider When Developing Criteria for "Types of Interventions"

What are the experimental and control interventions of interest?
Does the intervention have variations (e.g., dosage/intensity, mode of delivery)?
Are all variations to be included?
How will trials including only part of the intervention be handled?
How will trials containing the intervention of interest combined with other therapies be handled?

TABLE 7-4

Factors to Consider When Developing Criteria for "Types of Outcomes"

What are the main outcomes—those that are essential for decision making and clinically relevant?
What is the primary outcome that the review could address if sufficient studies were identified in order to reach a meaningful conclusion?
What are the secondary outcomes of interest that could provide clinical insight?
Is it important to collect information regarding side effects or other adverse effects?
Are there outcomes relevant to potential decision makers, including economic data?
Should data be collected regarding the type and timing of outcome measurements?

A clinically useful review will address clinically relevant outcomes. The outcomes for each study should be examined to determine the extent to which they are common across all studies. A decision is often necessary regarding handling of studies that have composite outcomes. For example, if the desired outcome is catheter-related bloodstream infection, should a study that fails to distinguish between catheter colonization and catheter-related bloodstream infection be included? Measurement of the outcome is also an important consideration, both in terms of the scale and timing. For example, if ventilator-associated pneumonia is an outcome, it would be important to take into account the variability in definitions used by investigators. Some studies may use a combination of clinical, radiographic, and lower respiratory tract sampling, while others may choose to use clinical and radiographic data alone or in combination with a sputum or tracheal aspirate specimen. In general, surrogate outcomes should be included with caution, because they may not always predict clinical outcomes accurately. Table 7-4 lists several outcome-related questions to be evaluated when conducting a systematic review.

The types of studies to be included in the review should be specified *a priori*. Most systematic reviews address evidence produced from randomized controlled trials. Randomized controlled trials are less likely to have selection bias, because proper randomization should prevent systematic differences between baseline characteristics of participants. Randomization of large groups of patients tends to equalize the distributions of subjects for both known and unknown potential confounders; such trials provide the best evidence of an unbiased treatment effect. Therefore, a systematic review of randomized trials has a distinct advantage. Even within randomized trials, however, there may be considerations related to study design such as whether cluster-randomized trials or crossover trials should be included (4). Importantly, there are some research questions in which a trial is not ethical or feasible. In these instances, a review of observational studies may be appropriate. Although estimates of treatment effectiveness obtained from observational studies—rather than randomized trials—are more likely to suffer from internal bias, the results may be more generalizable to broad patient populations due to the restrictive eligibility criteria usually inherent within randomized controlled trials.

The scope of the research question—either broad or narrow—is important at the outset. For example, a meta-analysis that targets whether topical oral chlorhexidine can prevent ventilator-associated pneumonia is narrower in scope than a meta-analysis that seeks to answer if oral decontamination (antibiotics and antiseptics) can reduce the risk of ventilator-associated pneumonia. Factors that should be considered when defining the scope of a review originate with underpinnings of the problem at hand, whether purely clinical, biological, and/or epidemiological. Extremely broad questions—for example, what is the epidemiology, clinical manifestations, diagnostic approach, treatment, and preventive options for ventilator-associated pneumonia—are often best addressed through a traditional narrative review.

Finally, a research question may need to be revisited over time. As evidence accumulates regarding a particular clinically relevant topic, it is important to update systematic reviews and meta-analyses with the results from the newly published studies. Therefore, systematic reviews are always time dependent and are most useful in clinical medicine when they contain all the most relevant literature available.

LITERATURE SEARCH

Systematic reviews require a comprehensive, objective, and reproducible search of multiple sources to ensure that all relevant studies are included. Healthcare bibliographic databases such as MEDLINE are a good place to start, although MEDLINE alone is not considered sufficient and should be supplemented with additional data sources. Currently, 5,200 journals in 37 languages are indexed in MEDLINE, and fortunately, PubMed provides free online access to MEDLINE. EMBASE is another electronically searchable database that is available only by subscription and has over 12 million records since 1974. While there is some overlap between EMBASE and MEDLINE, of the 4800 journals indexed in EMBASE, 1,800 are not indexed in MEDLINE, and of the 5,200 indexed in MEDLINE, 1,800 are

not indexed in EMBASE. Access to MEDLINE via PubMed is located at www.pubmed.gov and for EMBASE at www.info.embase.com.

The Cochrane Central Register of Controlled Trials (CENTRAL) is an excellent source of reports of controlled clinical trials. CENTRAL, published as part of the Cochrane Library, is updated quarterly. Although many of the records in CENTRAL overlap with MEDLINE or EMBASE, CENTRAL includes reports of clinical trials that are not part of MEDLINE or EMBASE, which may have been published only in specialized registers and other resources. If other reviews are of interest, Centre for Reviews and Dissemination is an excellent resource (http://www.york.ac.uk/inst/crd/).

Besides these key international databases, there are several national and regional databases that are useful to examine for additional studies. Many are available free of charge on the Internet. Table 7-5 lists examples of regional electronic databases (4).

When designing the search strategy, important considerations include whether the review is limited to randomized trials, whether the language of the publications will be inclusive or restrictive, the time period of the literature search, and whether data from unpublished studies are to be included. Assistance from an experienced healthcare librarian is highly recommended.

A balance between sensitivity and precision may need to be struck when undertaking searches to identify potentially relevant articles. Sensitivity is defined as the number of relevant reports identified divided by the total number of relevant reports in existence. Precision is defined as the number of relevant reports identified divided by the total number of reports identified. Article abstracts identified through a literature search can be quickly scanned for relevance to the research question; sensitivity is usually preferred over precision to ensure that the systematic review includes all potentially relevant articles.

In general, electronic databases can be searched using standardized subject terms assigned by indexers (MeSH for MEDLINE). The goal of the standardized subject terms is to ensure that articles using different words to describe the same concept are easy to retrieve. However, often the subject terms may not retrieve articles corresponding to the terms of interest. An additional challenge is that standardized subject terms may differ from one electronic database to the other; thus, a search must be customized to each database being searched.

The *Cochrane Handbook for Systematic Reviews* recommends that one way to identify controlled vocabulary terms for a database is to retrieve articles that meet the inclusion criteria and to note which subject terms have been applied to them. Those subject terms can then be put into the search to identify additional relevant articles. The "Explode" feature in MEDLINE searches narrower terms that are "under" the searched term in the MeSH hierarchy. The "Explode" feature in MeSH does not search related terms. For instance, using Explode with the MeSH term "Hepatitis" will find all articles indexed with more specific terms beneath it as well as general articles that are indexed simply, "Hepatitis." In MEDLINE, it is important to note that a report of a randomized controlled trial would be indexed as "Randomized controlled trial" while an article about randomized controlled trials would be indexed with the term "RANDOMIZED CONTROLLED TRIALS AS TOPIC." A comprehensive search strategy often includes, in addition to subject terms, a wide range of free-text terms such as pressure sore OR decubitus ulcer. Boolean operator terms such as "AND," "OR," and "NOT" are applied in searches to refine the search strategy by joining each search concept to the next. Figure 7-1 provides an example of combining search concepts to identify relevant records (4).

As most systematic reviews focus on randomized controlled trials, it is instructive to become familiar with a highly sensitive search strategy for identifying randomized trials in MEDLINE. There are two versions: a sensitivity-maximizing version and a sensitivity- and precision-maximizing

TABLE 7-5

Examples of Regional Electronic Bibliographic Databases

Country	*Web site*
Africa: African Index Medicus	www.indexmedicus.afro.who.int/
Australia: Australasian Medical Index	www.nla.gov.au/ami/
China: Chinese Biomedical Literature Database	www.imicams.ac.cn/cbm/index.asp
Eastern Mediterranean: Index Medicus for the eastern Mediterranean region	www.emro.who.int/his/vhsl/
Europe: PASCAL	International.inist.fr/article21/html
India: IndMED	Indmed.nic.in/
Korea: KoreaMed	www.koreamed.or/searchbasic.php
Latin America and the Caribbean: LILACS	Bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript = iah/iah.xis&base = LILACS&lang = i&form = F
South-east Asia: Index Medicus for the South East Asia Region (IMSEAR)	Library.searo.who.int/modules.php?op = modload&name = webis&files = imsear
Ukraine and the Russian Federation: Panteleimon	www.panteleimon.org/maine.php3
Western Pacific: Western Pacific Region Index Medicus (WPRIM)	Wprim.wpro.who.int/searchbasic.php

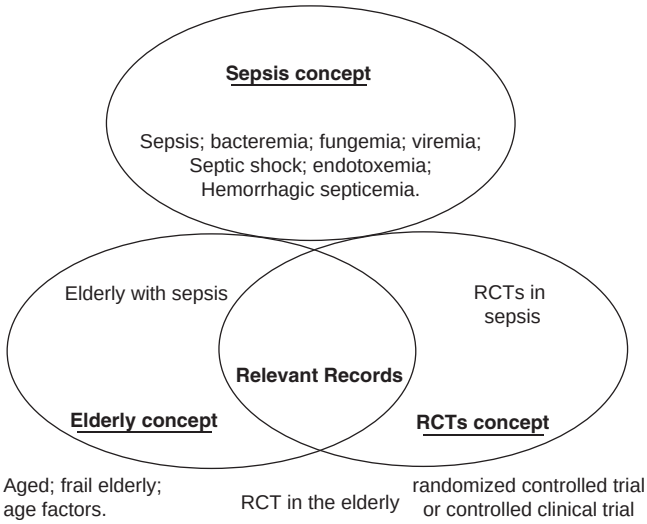

FIGURE 7-1 Combining concepts as search sets. RCT, randomized clinical trial.

version. These were developed by the Cochrane Collaboration and are shown in Tables 7-6 and 7-7.

Bibliographic software such as EndNote is useful to keep track of references. It is important to ensure that any fields that relate to subsequently published comments, retractions, updates, or errata be included in the download of references from electronic databases to EndNote or another reference manager program.

Detailed documentation of the search process is essential so that it can be reproduced. For purposes of publication, the detailed search strategy may best be reported in an online appendix to save space. The steps for reporting the search strategy in the systematic review include listing all databases searched, with dates of the last search and the period searched. Language restrictions, if any, should be noted. If additional information has been requested from authorities in the field or the authors of the included studies, the names of people contacted and what information was obtained from them should be provided. Any conference proceedings should be listed as well as additional sources found through Internet search engine queries. The number of studies identified by each of the above approaches should be reported.

TABLE 7-6

Cochrane Highly Sensitive Search Strategy for Identifying Randomized Trials in MEDLINE: Sensitivity-Maximizing Version: PubMed Format

#1	Randomized controlled trial [pt]
#2	Controlled clinical trial [pt]
#3	Randomized [tiab]
#4	Placebo [tiab]
#5	Drug therapy [sh]
#6	Randomly [tiab]
#7	Trial [tiab]
#8	Groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	Animals [mh] NOT humans [mh]
#11	#9 NOT #10

Note: PubMed Search syntax: [pt] denotes a publication-type term; [tiab] denotes a word in the title or abstract; [sh] denotes a subheading; [mh] denotes a medical subject heading; [mesh: noexp] denotes a medical subject heading (MeSH) term (not exploded); [ti] denotes a word in the title.

TABLE 7-7

Cochrane Highly Sensitive Search Strategy for Identifying Randomized Trials in MEDLINE: Sensitivity- and Precision-Maximizing Version: PubMed Format

#1	Randomized controlled trial [pt]
#2	Controlled clinical trial [pt]
#3	Randomized [tiab]
#4	Placebo [tiab]
#5	Clinical trials as topic [mesh: noexp]
#6	Randomly [tiab]
#7	Trial [ti]
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	Animals [mh] NOT humans [mh]
#10	#8 NOT #9

STUDY SELECTION

The study selection process requires an accounting of the articles that will be included, as well as a record of the number and reasons for exclusion of studies that do not meet the eligibility criteria. Depending upon the specificity of the search criteria, it is possible that a large number of records will be retrieved. Final selection should maintain the eligibility criteria as originally specified when the systematic review was initiated. It is possible that several reports detailing different aspects of the same study may be found, in which case, one should carefully assess the interventions and outcomes reported in each publication and the degree to which the eligibility criteria are satisfied. Duplicate publications may exist and often correspondence with the authors is required to clarify any uncertainties regarding the data presented. Reference management software also may assist in the identification of duplicate records.

Decisions regarding study inclusion should not rest on the opinion of a single reviewer. Rather, it is advantageous to include an expert in the area of clinical content as well as an authority in a related field or methodologist to avoid subconscious introduction of bias in study selection. Moreover, initial review should be blinded across the two reviewers. Disagreement between reviewers may require arbitration by a third independent expert, especially if the disagreement involves interpretation of study results. Agreement between authors can be measured using the kappa statistic; values of kappa between .40 and .59 reflect fair agreement, between .60 and .74 reflect good agreement, and between .75 and 1.00 reflect excellent agreement (*7*,*8*). The calculations necessary for determining kappa are given

TABLE 7-8

Data for Calculation of a Simple Kappa Statistic[a]

	Review Author 2			
Review Author 1	***Include***	***Exclude***	***Unsure***	***Total***
Include	*A*	*B*	*C*	I_1
Exclude	*D*	*E*	*F*	E_1
Unsure	*G*	*H*	*I*	U_1
Total	I_2	E_2	U_2	*K*

[a]Kappa = (PO–PE)/(1–PE), where PO (the proportion of studies for which there is agreement) = $(a + e + i)/K$ and PE (the proportion of studies for which one would expect there to be agreement based on chance alone = $[(I_1 \times I_2) + (E_1 \times E_2) + (U_1 \times U_2)]/K^2$.

in Table 7-8. Authors of systematic reviews should prepare a list of studies that, on first inspection, were thought to be eligible but later were excluded after careful review.

DATA EXTRACTION

Developing a data collection form is essential prior to data extraction. The form serves multiple functions; it provides a record of study eligibility and chronicles the steps in decision making—including agreements and disagreements regarding data collection. For those reviews in which a meta-analysis will be performed, it is the extraction tool for tabulating the estimates of effect, measures of variation, number of subjects, and other numerical data necessary for statistical pooling. Therefore, considerable thought and effort should be put into developing this collection form, also referred to as an "abstract" form. While details of the form may slightly vary, the basic template often stays the same and can be easily modified as necessary. Either electronic or paper forms may be used; the decision often rests on the preference of the author, accessibility to preprogrammed forms, and the number of studies to be included in the review. Regardless of which type is chosen, the data collection form should be piloted to identify areas of uncertainty and inconsistency.

When considering the data elements that need to be collected, authors should make an effort to eliminate unnecessary data and to focus on the key elements needed for the analysis. These key elements include author(s); date of publication; date(s) when data were collected on study participants; study design; particular features of certain designs such as single blinding, double blinding, and concealment of the randomization procedure; a description of the treatment/exposure in each of the study groups including whether a placebo or usual care was used as a comparator; and variables that describe the study population such as mean age, percentage of men/women, and other pertinent factors.

Numerical data should be recorded exactly as published in the original article; if additional calculations are warranted, these should be performed later. For studies in which both treatment and outcomes are binary, the numbers of subjects in each cell of a 2×2 table can be recorded. For studies that report odds ratios, relative risks, or mean differences, it is necessary to record measures of variability for these effects such as 95% confidence intervals or standard errors. For reviewers of randomized controlled trials, it is important to include the number of subjects randomized to each group, the number lost to follow-up, as well as whether the results reflect an intent-to-treat or compliance analysis. It is recommended that the guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) serve as a guide regarding the types of information necessary for collection (6).

Similar to the process used for decisions regarding study inclusion, more than one author should extract data and disagreement should be resolved by discussion. The kappa statistic may also be applied to key elements of data extraction to determine the extent of agreement.

ASSESSMENT OF BIAS

Just as in primary research, the validity of the studies within a systematic review should be assessed. Two general categories of validity are internal and external validity. Internal validity refers to whether a study has answered its research question in a manner that is free from both systematic error (i.e., bias) and nonsystematic error (i.e., random error or chance). External validity refers to the generalizability and applicability of a study's findings to a larger group of subjects. For purposes of systematic reviews and meta-analysis, an evaluation should be conducted of internal validity and the extent to which bias may affect each study's results.

Bias is the presence of systematic error. While some bias may be trivial, systematic error can also be of such magnitude as to invalidate study findings. A treatment effect may be either underestimated or overestimated if bias exists. Examining each study for methodologic flaws is a reasonable way to ascertain whether or not bias may be present. The risk of bias differs among study designs and is generally greater for studies without randomization. Important categories of bias are listed below.

Selection Bias

This bias occurs when there are systematic differences among the characteristics of the subjects in each group (or arm) at the beginning of the study. When randomization is correctly conducted on large numbers of people, selection bias should be avoided. However, when randomized trials are small or nonrandomized designs are utilized, this type of bias is a possibility. For evaluation of randomized designs, the reviewer should check the methods used for sequence generation during randomization and whether the allocation to study groups was concealed. Examples of studies at a higher risk of selection bias include those in which sequences were generated by odd or even date of birth or allocation was by the preference of physician or participant. A lower risk of selection bias would be likely if a computer random number generator or a random number table were used. Similarly, studies with higher risks of selection bias include those that incorporate alternating assignment or unsealed nonopaque envelopes. Allocation concealment yielding a lower risk of bias includes those instances whereby central telephone, Web-based, or

pharmacy-controlled randomization was utilized. Often it is preferable to employ a statistician who is not directly involved with the treatment or assessment of the outcome within the study, to design and conduct the randomization procedure. For evaluation of nonrandomized designs, the reviewer should check whether the patient characteristics were balanced across study groups or if such differences were accounted for during the analyses.

Performance Bias

This type of bias may occur when there are systematic differences in how the treatment or exposure is applied among the study groups. If one group is inadvertently given additional medications or procedures compared to another group, such differences may exacerbate the study's findings. Randomized controlled trials may utilize a placebo arm in which both the patient and the physician/investigator do not know the specific treatment; this element of study design is known as double blinding and it may suppress performance bias. If the study does not incorporate blinding or if blinding of the treatment is not feasible, the reviewer should evaluate whether the authors gathered additional information regarding possible differences among study groups and the degree to which these differences were addressed in the analyses.

Attrition Bias

When a study is conducted prospectively, it is possible that there may be withdrawals of patients over time. Systematic error due to differences in withdrawals among the study groups is known as attrition bias. The reviewer should carefully review the numbers of subjects initially randomized to each group as well as the numbers in each group at the end of the trial. How did the authors deal with the individuals who were lost to follow-up? Occasionally, authors will attempt to contact those persons who withdrew in order to assess the reasons for such withdrawal. When the study focuses on evaluating a pharmaceutical agent, sometimes this additional contact may give clues regarding the side effects of medications, which are often reasons for withdrawal. If enough information is available, the authors may compare the characteristics of the subjects for the initial group to the subset of patients who followed through to the end of the study. This may provide information regarding possible differences in treatment effects.

Detection Bias

This type of systematic error may occur when the outcome is assessed differently in the study groups. The definition of the outcome and how it was measured should be the same in all study groups, regardless of the type of treatment the subjects received. In some studies, it is possible to "blind" the persons who measure the outcome of the treatment status of the participants. For example, if the outcome is a positive blood culture for *Staphylococcus aureus*, the laboratory personnel are often blinded to what treatments the patients may have received.

There are other biases as well, including selective reporting of only certain outcomes. This type of bias is difficult to assess when only the published article is available for review, without additional information from the authors. It is also problematic to evaluate, because it is customary to publish multiple papers on different outcomes in various journals for a particular study. If the systematic review includes clinical trials, details regarding the entire study may be available on publicly available registration sites.

While widely used, it is not uniformly accepted that scales be used for assessing quality. Often such scales were developed for use in areas other than to which they are applied (e.g., Jadad score, developed to assess quality of trials in pain research), and moreover, they have been found to yield unreliable results (*9*,*10*). Because of these limitations, it is preferable to evaluate the extent to which bias was averted within each study. When incorporating bias assessments into analyses, the results may be graphed according to the risk of bias; pooled measures may be presented with subgroup analyses to examine the effect of the treatment at various levels of probable bias. Alternatively, studies at high risk of bias may be excluded from the meta-analysis.

STATISTICAL PROCEDURES IN A META-ANALYSIS

Initial Considerations

The mechanics of meta-analysis begins with the assessment of whether pooling, or summarizing a measure across different studies, is possible. Calculation of a pooled measure is contingent upon the availability of similar estimates of effect in each of the studies. It also requires that some measure of variability for these estimates are known, such as standard error, variance, or confidence intervals. For example, if there were 14 clinical trials testing the same hypothesis in which relative risks with their corresponding 95% confidence intervals were reported, then pooling may be attempted.

The most common types of measures to be pooled are comparisons between two groups that are expressed by a ratio—relative risk or an odds ratio. That is, within each study, the risk of the outcome (e.g., infection) in the exposed (e.g., immunosuppressed) would be divided by the risk of the outcome in the unexposed. For an odds ratio, the odds of the outcome in the exposed would be divided by the odds of the outcome in the unexposed. Hazard ratios may also be pooled, when available.

For meta-analyses of infectious diseases, considerations often involve recognition of the common methods by which infectious disease rates are expressed. Sometimes these are reported as the number of infectious disease episodes per 1,000 patient-days in the hospital or the number of infections per 1,000 device-days of observation. In other instances, the outcome may be expressed by cumulative risk such as the percentage of patients who experienced infection during their hospital stay. Since risk is time dependent and the length of hospital stay varies, it is preferable to use similar time periods for evaluating the risk of infection. For example, the risk of hospital readmission due to pneumonia in the 30 days postdischarge could be pooled if there were multiple studies with this outcome. The use of common measures such as episodes per 1,000 patient-days or infections per 1,000 catheter-days incorporates time in the denominator and, therefore, could be

pooled across studies. It is important to pool measures that express similar underlying quantities.

General Theoretical Considerations

In general terms, a pooled measure is a weighted sum. The estimates of effect from each study are arithmetically summed using weights:

$$\frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i},$$

where W indicates the weights and Y indicates the estimates of effect across all i through k studies. The weights often incorporate some derivative of the variation of the effect such as standard error or variance. Although the weights can incorporate the variation of the effect inherent within each individual study, these weights can also incorporate the variation of the effect across the various studies. This first approach, incorporation of within-studies variation (only), is known as a fixed effects model. The second approach, incorporation of both within- and between-studies variation, is known as a random effects model. The fixed effects approach makes the assumption that there is one true underlying effect in the reference population. The random effects approach assumes that there is a known underlying distribution of effects in the reference population.

Fixed Effects Models

The Mantel–Haenszel method of weighting may be used for summing a risk ratio, an odds ratio, or a risk difference (*11*,*12*). The calculations depend upon the study design and the characteristics of the variables, which determine the exposure and the outcome. In infectious diseases epidemiology, it is not uncommon to measure the incidence or risk of infection in one group of patients and compare this with the risk of infection in another group. As such, a 2×2 table may be constructed, where a indicates the number of patients exposed who developed an infection, b indicates the number of unexposed who developed an infection, c indicates the number of exposed who did not develop an infection, and d indicates the number of unexposed who did not develop an infection. In this situation, the Mantel–Haenszel method for pooling relative risks across studies is defined as such:

$$\hat{\mathrm{RR}}_{\mathrm{MH}} = \frac{\sum_{i=1}^{k} \left(\frac{b_i + d_i}{n_i}\right) a_i}{\sum_{i=1}^{k} \left(\frac{a_i + c_i}{n_i}\right) b_i},$$

where n indicates the total number of subjects in each i through k study.

Another fixed effects pooling method was developed by Peto and coworkers (*13*). Known as the Peto method, it is appropriate for odds ratios only and utilizes the expected versus observed number of events for calculation. Both the Peto and the Mantel–Haenszel methods perform well when outcome rates are rare, although unbalanced numbers of subjects in each arm (or in the exposed versus unexposed groups) are better assessed with the Mantel–Haenszel method. A more traditional method for pooling effects across studies is the inverse variance method, in which the inverse of the variance is incorporated as the weight. Since variance is calculable for many different types of statistics, this method has been utilized widely. In particular, mean differences may be summarized by incorporating the inverse of within-study variance as weights.

Random Effects Models

The random effects model assumes that, in addition to variability within studies, there are also real differences between studies. The weighting factor is more complex to include both these sources of variation. A common method utilized for pooling was described by DerSimonian and Laird and can be used to pool risk ratios, odds ratios, or risk differences (14). The inverse variance method may also be used in a random effects model to include both within- and between-studies variance. For example, mean differences in injury severity scores may be pooled using weights that incorporate within- and between-study variance. Since a random effects model considers both sources of variation, the results from a random effects model will, in general, yield more conservative results, and therefore wider confidence intervals, than a fixed effects model. When there is minimal variation between studies, the results from fixed effects and random effects models will be similar.

The Choice Between Fixed Effects and Random Effects Models

The choice of method initially involves a consideration of the underlying assumptions of fixed versus random effects models. A fixed effects model assumes that there is a single true underlying effect. For example, when repeated samples are taken from the same population, the pooled measure can be calculated using a fixed effects model. A random effects model assumes that the underlying effect follows a distribution of values and is often considered when the studies are conducted in populations with different characteristics.

It is not uncommon to calculate summary measures using both fixed and random effects models. If the results lead to similar conclusions, this can be directly stated. The Peto method (fixed effect) performs quite well when the outcome is rare, the numbers of patients in the treatment arms are balanced, and odds ratios are calculated as the estimates of effect. The Mantel–Haenszel method (fixed effect) is preferred when there are few studies with limited numbers of subjects within each study and when there is an imbalance in the numbers of subjects in treatment arms. For studies in which the outcome is continuous, the traditional weighting method of inverse variance is often used. If the purpose of the investigation is to explore the differences among studies, then a random effects model is appropriate. The reasons behind the variability across studies should be explored with consideration of the differences in the types of patients, design, and analyses of the individual studies. Often subgroup or stratified analyses may serve as a first step for this investigation, with more advanced statistics used secondarily.

Forest Plots

A useful technique for displaying the results of meta-analysis is the forest plot. A forest plot is a graphic depiction

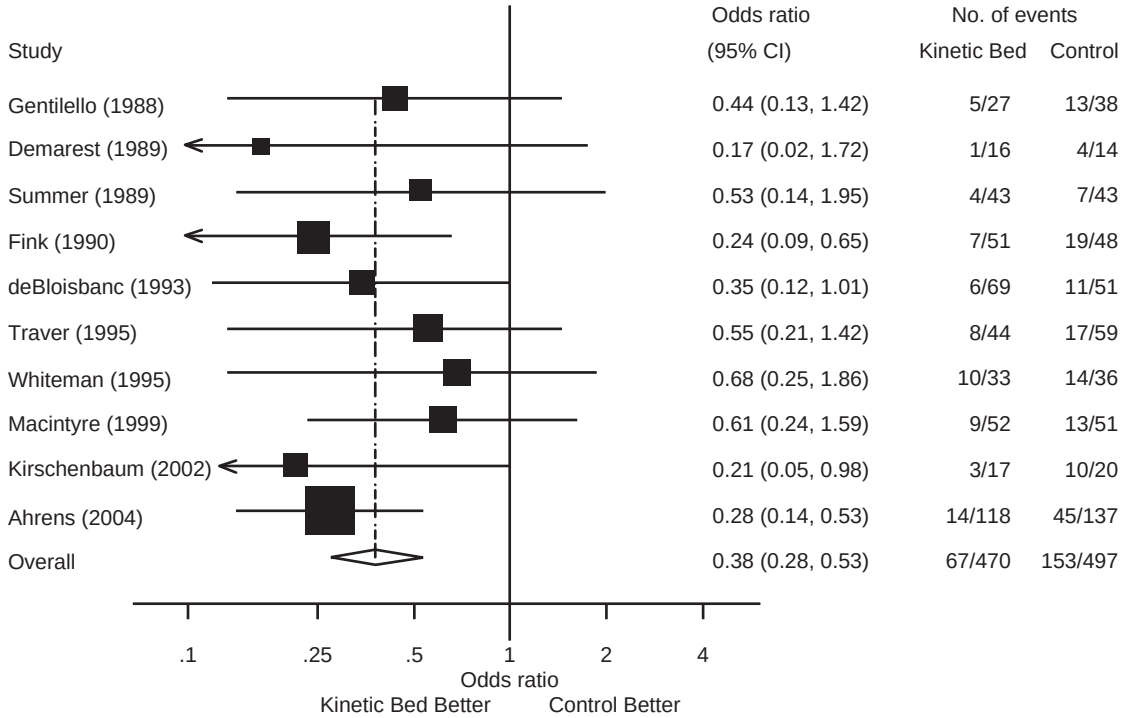

FIGURE 7-2 Forest plot showing the effect of kinetic bed therapy on the incidence of healthcare-associated pneumonia. (From Delaney A, Gray H, Laupland KB, et al. Kinetic bed therapy to prevent healthcare-associated pneumonia in mechanically ventilated patients: a systematic review and meta-analysis. *Crit Care* 2006;10(3):R70.)

of the estimates of effects and their variation within each study, as well as the summary measure. Figure 7-2 shows a typical forest plot. The results from each of the studies are displayed with the estimate of effect (in this instance, odds ratio) shown as a box, with its size proportional to the weights. The horizontal line indicates the 95% confidence interval. The null value (i.e., 1 for the odds ratio) is depicted with a solid vertical line and the pooled estimate of effect is shown with a dashed vertical line. Usually, the 95% confidence interval for the pooled summary measure is placed at the bottom of the plot in the shape of a diamond. There are variations to the appearance of the forest plot, depending upon the statistical programs chosen for generation.

Cumulative Meta-Analysis

Cumulative meta-analysis is a variation of traditional meta-analysis in which the individual studies are first sorted, usually by date (*2*). Each study-specific estimate of effect is included in the calculations one at a time so that the ensuing measure includes all studies before that date. This technique is often displayed via a forest plot and can signify trends over time. The final pooled measure using cumulative meta-analysis is the same as the pooled measure when using the traditional approach, but the forest plot will yield a different appearance. Since smaller trials for a given hypothesis tend to be published first and more definitive larger trials tend to be published at later dates, cumulative meta-analysis can visualize these effects over time. An example of such trends is shown in Figure 7-3 in a study which compared methods of rehydration in children with gastroenteritis.

HETEROGENEITY

In meta-analysis, heterogeneity refers to the variation in the estimate of effect across the studies. There are instances whereby the heterogeneity is so great that pooling the study-specific measures would not be appropriate. When this occurs, an investigation of the sources of heterogeneity is often conducted. Therefore, when study-specific estimates of effect are pooled in meta-analysis, this should be accompanied by an assessment of heterogeneity. Various quantitative measures and graphical techniques have been used to evaluate heterogeneity.

Quantifying Heterogeneity

Heterogeneity is commonly quantified by using Cochran's Q, I^2, or τ^2 (between studies variance). Cochran's Q is a statistical test in which weighted differences between study-specific measures and the pooled measure are summed (*15*). The test statistic follows a chi-square distribution and is calculated as follows:

$$Q = \sum w_i \left(\hat{\theta}_i - \hat{\theta}\right)^2,$$

where θ_i is the estimate of effect for each i study, θ is the pooled estimate of effect, degrees of freedom = k–1, and k is the number of studies. Because the number of studies tends to be limited in many meta-analyses, the power to detect differences among studies is often poor when using the Cochran's Q test. Therefore, the alpha level may be set at .10 instead of the traditional .05. If the resultant p value is <0.10, one would conclude that there is heterogeneity in the estimate of effect across the various studies.

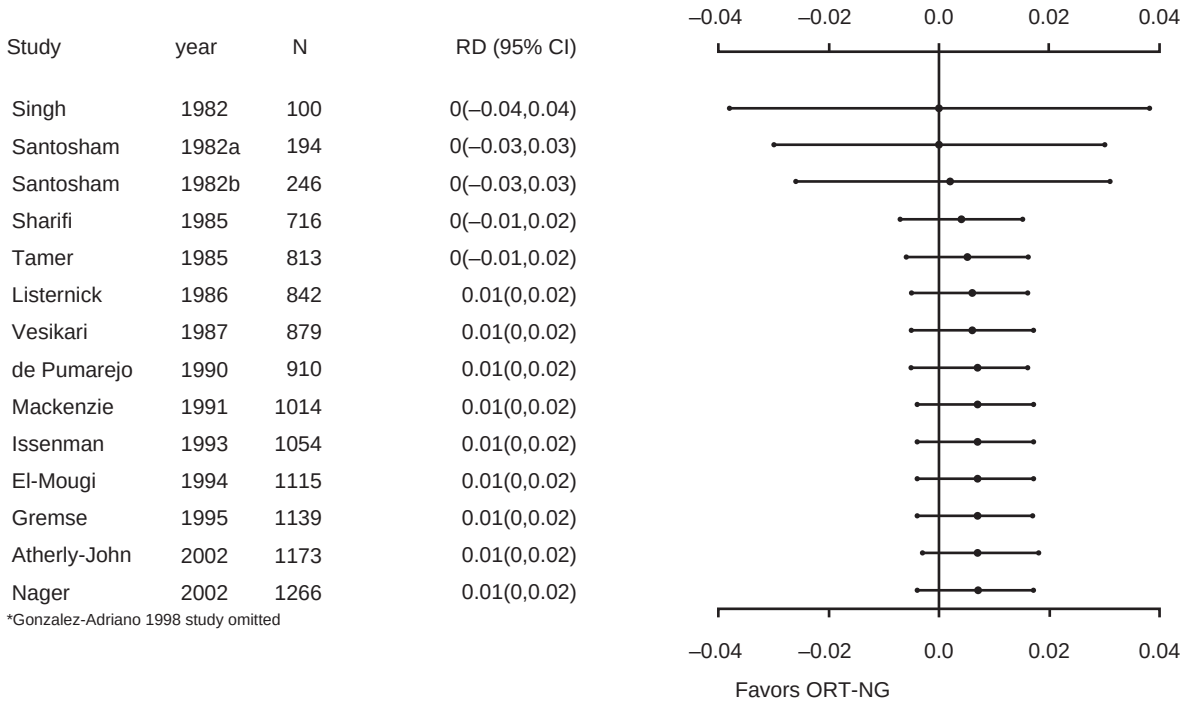

FIGURE 7-3 Example of a forest plot using cumulative meta-analysis that compares oral rehydration therapy-nasogastric with intravenous therapy in children with gastroenteritis. (From Bellemare S, Hartling L, Wiebe N, et al. Oral rehydration versus intravenous therapy for treating dehydration due to gastroenteritis in children: a meta-analysis of randomized controlled trials. *BMC Med* 2004;2:11.)

Another measure of heterogeneity is I^2, which indicates the percentage of total variability in effect size that is due to between-studies variation (16,17). I^2 is expressed as a percentage, with a minimum of 0% and a maximum of 100%; negative values are set at 0%. An advantage of I^2 is that it can be assessed across meta-analyses, so that the degree of variation found in one meta-analysis may be compared with that for a different meta-analysis. I^2 may be calculated as follows:

$$I^2 = \frac{Q - \mathrm{df}}{Q},$$

where Q indicates Cochran's Q test statistic, df = k–1, and k is the number of studies.

Between-studies variance is denoted by τ^2 and can be directly calculated and reported as well. Cochran's Q, τ^2, and/or I^2 may be presented on the forest plot as shown in Figure 7-4, which describes the effect of prophylactic fluconazole on patients with fungal infections. In a review of various graphical approaches, the forest plot was found to be more reliable than other types of graphs and a reasonably valid technique for the evaluation of heterogeneity (18).

EVALUATING PUBLICATION BIAS

While the initial steps of a meta-analysis involve a compilation of all studies that were conducted to evaluate a given hypothesis, it is possible that some studies may not be published. Such studies are more likely to be smaller with differences that are not statistically significant. With the establishment of registries of clinical trials and the requirement that trials be registered as a prior condition to publication, some of the earlier concerns regarding publication bias in meta-analyses of trials have been somewhat attenuated (*19*,*20*). Nevertheless, the possibility of publication bias should be addressed. There are several ways of evaluating publication bias, by either statistical testing or graphical techniques.

Funnel plots are the most common graphs used for evaluating publication bias. These entail plotting the study-specific estimates of effect against some measure of variability for each effect. Although there are variations to this approach, often the estimates of effect are plotted horizontally on the x axis and the measure of variation plotted vertically on the y axis. The plot gives an appearance of a funnel when the measure of variation is plotted inversely, so that the smaller studies will splay on the lower portion of the plot. Without publication bias, the funnel plot should appear symmetrical as shown in Figure 7-5. Contour-enhanced funnel plots include areas that denote contours or areas showing statistical significance and help the reader to assess whether small, nonsignificant studies may be systematically excluded (*21*). Asymmetry may indicate publication bias, although it does not provide definitive proof. Note that the location of the studies on the plot should splay from the true underlying estimate of effect, not necessarily the null.

Several statistical tests are available for assessing publication bias since visual inspection of funnel plots is subjective. If the estimate of effect is the odds ratio, Peters' test or Harbord's modification of Egger's test is appropriate for use (*22*,*23*). For meta-analyses in which the outcome is measured as a mean difference, Egger's test may be

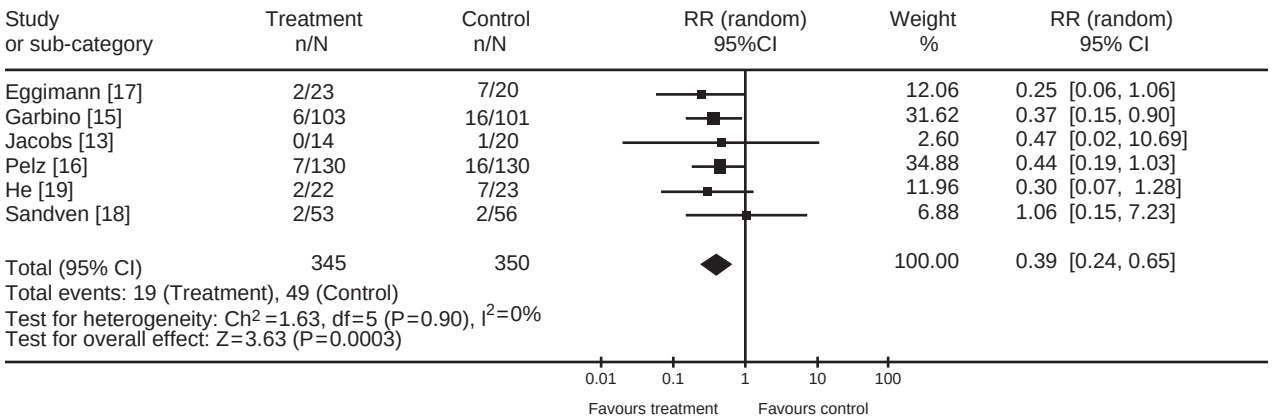

FIGURE 7-4 Forest plot showing the effect of prophylactic fluconazole on the proportion of patients with fungal infections. RR, relative risk; CI, confidence interval. (From Ho KM, Lipman J, Dobb GJ, et al. The use of prophylactic fluconazole in immunocompetent high-risk surgical patients: a meta-analysis. *Crit Care* 2005;9(6):R710–R717.)

used (*24*). Such tests may be conducted when there are at least 10 studies within the meta-analysis, but should not be considered conclusive evidence of the absence of publication bias. In this regard, a thorough initial search of the literature is superior to any posterior testing in a subset of studies.

PLACING THE FINDINGS IN CONTEXT

The results of the review should be interpreted in the context of the quality of evidence that was available for developing the systematic review. The GRADE (Grades of Recommendations, Assessment, Development and Evaluation) Working Group has developed a system for grading the overall quality of evidence (25). Factors that, if noted in a systematic review, would be considered to decrease the quality of the evidence are shown in Table 7-9. Common errors that are made in reaching conclusion include confusing "no evidence of effect" with "evidence of no effect." A true "no effect" is best observed by a fairly narrow confidence interval for the pooled measure that is centered around the null. When the data are inconclusive, it is recommended that it be stated as such. Conclusions should not extend beyond the results driven by the data and caution should be exercised when making recommendations for clinical practice.

Factors that are important for decision making beyond the results of the systematic review should be considered when making recommendations for clinical practice. These include patient values and preferences, and economic considerations. The external validity of the systematic review

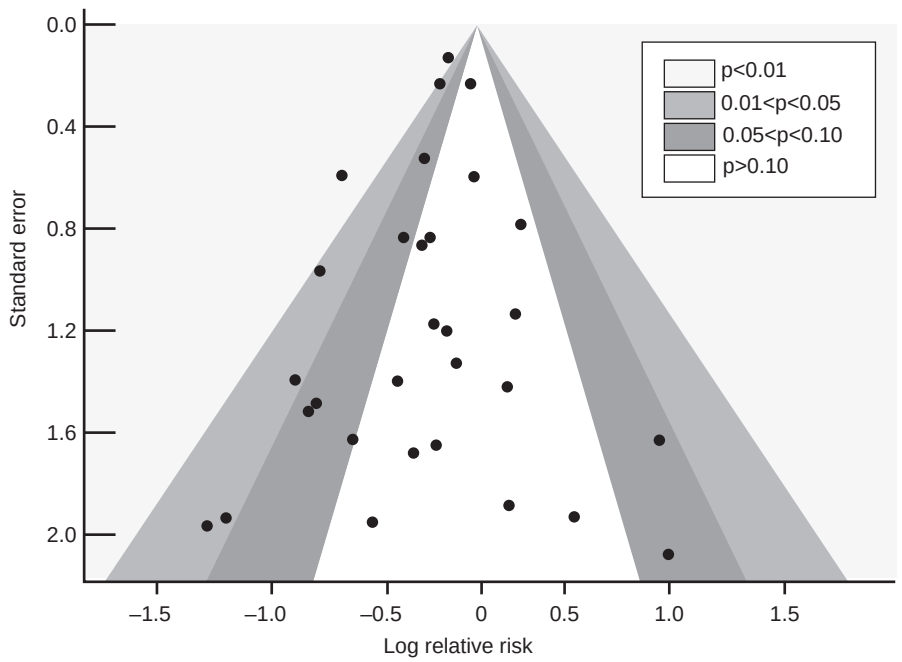

FIGURE 7-5 Contour-enhanced funnel plot.

TABLE 7-9

Factors that may Decrease the Quality Level of a Body of Evidence

Limitations in the design and implementation of available studies suggesting high likelihood of bias
Indirectness of evidence (indirect population, intervention, control, outcomes)
Unexplained heterogeneity or inconsistency of results (including problems with subgroup analysis)
Imprecision of results (wide confidence intervals)
High probability of publication bias

should also be taken into account when extrapolating the conclusions to populations not included in the systematic review.

A review should point out directions for future research. The acronym EPICOT has been proposed for reporting research recommendations (26):

E (Evidence): What is the current evidence
P (Population): (Such as) diagnosis, disease stage, risk factor
I (Intervention): Type, frequency, dose, duration
C (Comparison): Placebo, routine care
O (Outcome): Which clinical or patient-related outcomes will the researcher need to measure
T (Time stamp): Date of literature search or recommendation

For example, a review of chlorhexidine for preventing ventilator-associated pneumonia might conclude with "Current evidence suggests that topical chlorhexidine may be useful for preventing ventilator-associated pneumonia. However, variation in studies regarding the duration, dose and frequency of application creates heterogeneity making it difficult to draw robust conclusions. Future studies should examine, using a randomized controlled study design, the optimum dose and frequency of chlorhexidine oral care compared with oral care without chlorhexidine in all mechanically-ventilated patients, using invasive lower respiratory tract sampling for diagnosing ventilator-associated pneumonia."

PREPARING THE MANUSCRIPT

The PRISMA checklist can be useful when preparing the manuscript describing the systematic review (6). The following general principles serve as guidelines. The title should contain the words *systematic review* or *meta-analysis*, if possible, since this will distinguish the work from a traditional narrative review and will make it easier to retrieve in an electronic search. The abstract should be crafted with a great deal of thought since this may be the only part that many readers will peruse. The introduction section of the manuscript should describe the importance of the research question, existing gaps in the literature, and the rationale for undertaking the study. In the Methods section, in general, the following headings may be useful (unless the target journal has specific headings that are traditionally used for these types of manuscripts): data sources, data selection, data abstraction, assessment of study quality, data synthesis/statistical analyses, and proposed subgroup analyses. The Results section should describe the outcome of the literature search in a flow sheet and have a table describing the characteristics of the included studies. The main summary of results is usually represented as a forest plot. If a meta-analysis is not done, the summary estimate (usually shown as a diamond on the forest plot) may be omitted. The result of subgroup analyses may be placed in a table or figure. In the Discussion section, the authors should place their findings in the context of other studies that have been undertaken, explain how their results add to the current body of knowledge, and assess the implications for policy and future research. It is important to describe the limitations and how they were addressed within the review. The conclusions should be driven by the results and should take into account the limitations of the studies included in the systematic review. Finally, sources of funding and conflict of interest for all authors should be clearly described somewhere in the manuscript.

USEFUL READING AND RESOURCES

The *Cochrane Handbook for Systematic Reviews of Interventions* is an excellent resource for researchers undertaking a systematic review or meta-analysis. The handbook is available free online at http://www.cochrane-handbook.org/. For updates, see the following URL: http://www.cochrane.org/resources/handbook/.

ACKNOWLEDGMENT

We thank Ann Combs, MS, for her thoughtful comments on searching the literature.

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CHAPTER 8

Investigation of Outbreaks

William R. Jarvis

Although the majority of healthcare-associated infections (HAIs) in a given healthcare facility are endemic (*1*), outbreaks of HAIs may occur, usually in a specific group of patients or location. In addition, healthcare workers (HCWs) are exposed to numerous infectious agents and may be at risk of spreading pathogens to patients and other HCWs (*2–4*).

An outbreak is an increase in occurrence of an event (infectious or noninfectious) above the background rate. This assumes that surveillance for such complications exists, so that a background rate is known or can be calculated from existing data. If such data do not exist, then a retrospective review must be performed to obtain these data to calculate the rate of these adverse events to compare to the "outbreak" rate. An outbreak may be one episode of a rare occurrence (e.g., group A streptococcal surgical site infection [SSI], anthrax, and vancomycin-resistant *Staphylococcus aureus*) or many episodes of a common occurrence (e.g., methicillin-resistant *S. aureus* [MRSA] infection). Outbreaks in healthcare facilities, although infrequent, can cause great concern, require extensive personnel and financial resources to investigate and control, generate adverse publicity, negatively impact on patient safety, and can be very time-consuming.

This chapter helps healthcare epidemiologists, infection preventionists, and others to determine when a cluster of infections or other adverse events among patients or HCWs merits an epidemiologic investigation and how to conduct such an investigation. Although the methods described can be applied to infectious diseases, chronic diseases, community outbreaks, occupational diseases or injuries, or any complication of healthcare delivery, this chapter focuses on outbreak investigations of HAIs.

IDENTIFICATION OF A POTENTIAL OUTBREAK

Routine surveillance for HAIs provide the data to enable infection control personnel to calculate infection or other adverse event rates, determine secular trends, and identify unusual pathogens or events, or increased infection or adverse event rates in patients or HCWs (see Chapter 88). The key to effective surveillance is to use common, accepted definitions and to calculate rates that permit valid interfacility or intrafacility comparisons (*5–9*) (http://www.cdc.gov/nhsn/PDFs/pscManual/17pscNosInfDef_current.pdf). Rate calculations using an inappropriate denominator may be misleading and suggest an outbreak is occurring when only a change in the population at risk has occurred. Similarly, the use of variably defined numerator events may lead to an apparent increase in the rate secondary to surveillance artifact. Outbreaks of infectious diseases that are not included in routine surveillance or that occur among patients in areas where routine surveillance may not be conducted may be identified in a variety of ways. Clinical nursing or medical staff may recognize that a number of patients have the same type of infection or regular examination of microbiology or other records may reveal an increase in the isolation of a particular microorganism, thus leading to the identification of a potential outbreak.

REASONS TO INVESTIGATE A POTENTIAL OUTBREAK

Objectives

Although any cluster of patients with HAIs can be investigated, the constraints of time and resources require that each investigation has specific objectives. The most important of these is the control of further transmission (*10*). Other important objectives may be to advance the field of healthcare epidemiology and infection control by describing etiologic agents, host, risk factors, virulence, or environmental factors; to assess prevention interventions; or to determine the quality of epidemiologic surveillance at the healthcare facility (11).

Evidence of HAI Transmission of Infectious Diseases

HAI transmission should be considered when (a) a cluster of similar infections occurs on one hospital unit or among similar patients, (b) a cluster of infections associated with invasive devices occurs, (c) HCWs and patients develop the same type of infection, or (d) a cluster of infections with microorganisms typically associated with HAIs (e.g., multidrug-resistant or opportunistic microorganisms)

occurs. These clusters merit investigation to determine if HAI transmission really is occurring and to institute appropriate control measures to terminate pathogen transmission. Selection bias frequently occurs in identifying outbreaks because unusual pathogens, or common microorganisms with unusual antimicrobial susceptibility patterns, are more easily recognized. For example, although *Escherichia coli* urinary tract infection outbreaks probably occur, they are either not recognized or not investigated, because the microorganism is the most common cause of urinary tract infection and typing of the genotying of strains—to document clonal transmission—usually is not performed. In contrast, a small cluster of unusual pathogens or common pathogens with unusual antimicrobial susceptibility patterns are easily and frequently recognized.

Determination of Risk Factors for Disease

Known host risk factors for HAI include the presence of invasive devices, severity of illness, or underlying diseases (*12–14*). In addition, environmental sources of pathogens can play a role, especially among immunocompromised patients (*15–19*). Investigation of outbreaks can further define both host and environmental risk factors for HAI. Infection control personnel should be constantly vigilant for complications associated with new technologies or changes in previously safe technologies (20,*21–23*).

Institution of Appropriate Control Measures

In outbreak situations, one often must introduce preventive interventions to control pathogen transmission and adverse outcomes before an investigation is initiated or completed. Control measures that have proven effective in similar HAI outbreaks in the past can be implemented immediately. This could include measures ranging from the simple (e.g., enhancing hand hygiene through in-service education sessions for personnel) to the complex (e.g., closing a unit to new admissions or removing a product or device). The potential benefit of more drastic measures should be carefully weighed against the potential harm to patients currently residing in the facility. Subsequently, the formal epidemiologic investigation of the outbreak may help focus control measures on specific infection control or procedural techniques (*10*).

FIRST STEPS

Once an outbreak is suspected and an investigation is contemplated, all levels of the healthcare facility's personnel (e.g., the chief of the affected service, head nurse for the unit, director of microbiology, and hospital administration) should be informed and must be committed to the investigation. The cooperation of a variety of healthcare professionals is essential to efficiently conduct an investigation and to implement control measures.

A second consideration during the early stages of an outbreak investigation is the availability of microbiologic isolates for antimicrobial susceptibility testing or molecular or nonmolecular typing. Unlike community outbreaks, typing of microorganisms in HAI outbreaks may be essential to proving chains of transmission because of the ubiquitous nature of microorganisms in the hospital environment (*18*,*24*). For this reason, microbiology laboratory personnel should be informed early in the investigation so that they can save requested specimens or isolates and be alert for additional isolates that may be part of the outbreak. Laboratory personnel also may suggest other specimens that should be collected from current or future patients who develop the adverse event being studied.

Finally, before beginning an investigation, available resources (e.g., personnel, supplies, and laboratory), the lead investigator, and the person to be responsible for statistical analysis of the data should be identified. Taking these steps before initiating an investigation will allow it to proceed smoothly later.

THE INVESTIGATION

A complete investigation involves many steps; the order of steps may vary and multiple steps may be performed simultaneously. These steps, although not specific to the healthcare setting, are a useful guide in conducting an outbreak investigation (Table 8-1).

Case Definition

One of the first tasks of the investigative team is to develop a working case definition based on the known facts of the outbreak. The case definition should include, at a minimum, the time, place, and person. In addition, other important factors, such as clinical and laboratory parameters (e.g., date of onset of illness, symptoms, signs, and

TABLE 8-1

Guidelines for Epidemiologic Field Investigations

1. Prepare for field work (e.g., administration, clearance, travel, contacts, and designation of lead investigator)
2. Confirm the existence of an epidemic
3. Verify the diagnosis
4. Identify and count cases or exposures
   - Create a case definition
   - Develop a line listing
5. Tabulate and orient the data in terms of time, place, and person
6. Take immediate control measures (if indicated)
7. Formulate hypotheses
8. Test hypotheses through epidemiologic studies
9. Plan an additional systematic study (or studies)
10. Culture environment and personnel based on epidemiologic data
11. Implement and evaluate control and preventive measures
12. Initiate surveillance
13. Communicate findings
    - Summarize investigation for requesting authority
    - Prepare written report(s)

(Modified from Goodman RA, Buehler JW, Koplan JP. The epidemiologic field investigation: science and judgement in public health practice. *Am J Epidemiol* 1990;132:9–16.)

TABLE 8-2

Examples of Case Definitions from Hospital Outbreaks Investigated by the CDC's Hospital Infections Program/Division of Healthcare Quality Promotion

1. "A case of multidrug-resistant tuberculosis was defined as any patient diagnosed with active tuberculosis from January 1989 through March 1991 whose *M. tuberculosis* isolate was resistant to at least isoniazid and rifampin" (*35*).
2. "An [anaphylactic reaction] was defined as hypotension (≥30 mm Hg fall in systolic blood pressure from the preinduction blood pressure) and at least one of the following during a general anesthesia procedure at hospital A from January 1989 through January 1991: rash, angioedema, stridor, wheezing, or bronchospasm" (*21*).

CDC, Centers for Disease Control and Prevention.

specific laboratory or diagnostic findings), epidemiologic parameters (e.g., a patient's presence on a specific ward or service during a specified time) may be included. In certain instances, one may include confirmed, possible, or probable cases of disease. The process of developing case definitions is an iterative one and should be based on balancing the need for an all-inclusive (sensitive) case definition at the beginning of the investigation and more specific case definition as the investigation proceeds and more data are acquired. Case definitions may vary from the relatively simple to very complex (*21*,*25*) (Table 8-2). Occasionally, the case definition may need to be refined as the investigation proceeds and more data are acquired.

Case Finding

Once an initial case definition has been developed, additional case finding can be conducted. The case definition should be applied to the source population without bias as to known or potential underlying host or environmental risk factors. Sources most commonly used for finding cases are discharge diagnosis or International Classification of Disease codes; microbiology, infection control, or transfusion records; emergency room, outpatient clinic, or dialysis clinic logs; or patient medical records in a cohort study—if the cases are limited to a single ward/unit or if the healthcare facility is very small (i.e., where charts can be reviewed in a short period).

Confirming an Outbreak

Confirming an outbreak begins with calculating the background rate of infection or adverse event and then comparing the outbreak period rate with the background rate. The outbreak period should include the time period from the possible incubation period for the first case of adverse event until the last case or time of the investigation. The background rate of the adverse event should be based on existing data, which can be collected from a variety of resources, including microbiology, infection control, or patient records. Data may have to be collected for a period of many months to years preceding the outbreak to determine an accurate background rate, particularly if the adverse event has a seasonal periodicity. Comparison of the outbreak period attack rate to the background rate can be performed using the rate ratio:

$$\text{Rate ratio} = \frac{\text{Attack rate during epidemic period}}{\text{Attack rate during background period}}$$

Pseudo-outbreaks are increases in the incidence of infections or adverse events that are not real. This can be due to false clusters of real infections/adverse events or real clusters of false infections/adverse events. Possible causes can be (a) clusters of positive cultures in patients without evidence of infection/disease (e.g., positive cultures for *Mycobacterium tuberculosis* in a patient with no clinical evidence of tuberculosis) or (b) a perceived increase in infections/adverse events because either the specific laboratory test had not been used (e.g., introduction of polymerase chain reaction testing for MRSA or *Clostridium difficile*) or surveillance was not previously being conducted for that particular problem or surveillance definitions, intensity, or methods have changed. Pseudo-outbreaks usually are due to either increased surveillance of an area or type of infection or laboratory errors (i.e., extrinsic or cross-contamination) (*26*–*29*). Hypotheses developed during the investigation of a presumed outbreak should include the possibility of a pseudo-outbreak, particularly if laboratory clustering of the positive cultures occurs (see Chapter 9).

Chart Review

Before beginning the lengthy process of reviewing medical records, one should determine which data are important to collect for each case-patient or case-HCW and design a questionnaire for ease of data collection (see Chapter 5 for details on questionnaire design). Some important categories of information to consider in most investigations are demographic variables (e.g., age gender, race, or ethnicity), underlying illnesses, severity of illness indicators (e.g., Acute Physiology and Chronic Health Evaluation or Pediatric Risk of Mortality scores) (*30*,*31*), ward/unit, duration of hospitalization; exposures to invasive devices or procedures, personnel or other patients, or medications; and clinical aspects of the disease/adverse event being studied (e.g., date of onset of illness, symptoms, and signs). For SSI outbreaks, surgical risk factors (e.g., procedure, operating room, surgeon, or surgical team members) or surgical risk index (*7*,*32*) must also be determined in addition to the other categories.

Descriptive Epidemiology

A line listing of the case-patients and pertinent demographic and clinical information serves as a useful tool to begin the process of describing the outbreak in terms of time, place, and person. Describing an outbreak in this way helps determine who is at particular risk for the adverse event that is being studied. In turn, knowing which

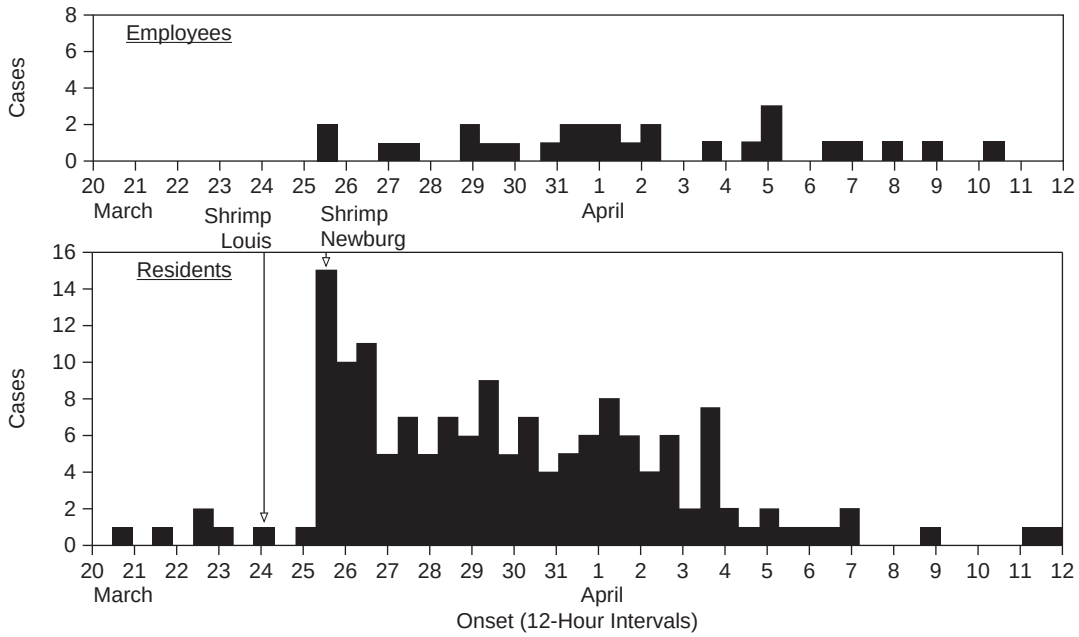

FIGURE 8-1 Epidemic curve from a common source outbreak with subsequent person-to-person transmission. (From Gordon SM, Oshiro LS, Jarvis WR, et al. Foodborne Snow Mountain agent gastroenteritis with secondary person-to-person spread in a retirement community. *Am J Epidemiol* 1990;131:702–710.)

population of patients or HCWs is at risk determines who should be included in further analytic studies.

Describing the outbreak over time is most easily done by graphing the case-patients or case-HCWs by onset of disease; the cases can be graphed by time (e.g., hours, days, months, or quarters), as appropriate. These graphs, often called epidemic or epi curves, can provide a great deal of information about possible sources and modes of transmission. For example, a common-source outbreak with subsequent person-to-person transmission is well illustrated by a foodborne outbreak in a retirement community (*33*) (Fig. 8-1). A high initial peak of onset of illness, indicating a point source of infection, followed by continued cases of illness is typical of an outbreak of gastrointestinal illness caused by a viral agent. Person-to-person transmission, on the other hand, usually is illustrated by an epidemic curve of longer duration with few, if any, peaks. A typical epidemic curve illustrating person-to-person transmission would be an outbreak of *M. tuberculosis* HAIs (*34*) (Fig. 8-2).

The epidemic curve of an outbreak caused by poor adherence to recommended infection control practices (e.g., poor hand hygiene compliance) or contaminated patient-care equipment also usually are spread over a long period. For example, an *Acinetobacter baumannii* outbreak related to reusable intravascular transducers that were not adequately sterilized between uses on different patients continued for over a year until the problem was recognized and the decontamination and disinfection technique was corrected (*18*) (Fig. 8-3). If HCWs and patients are both

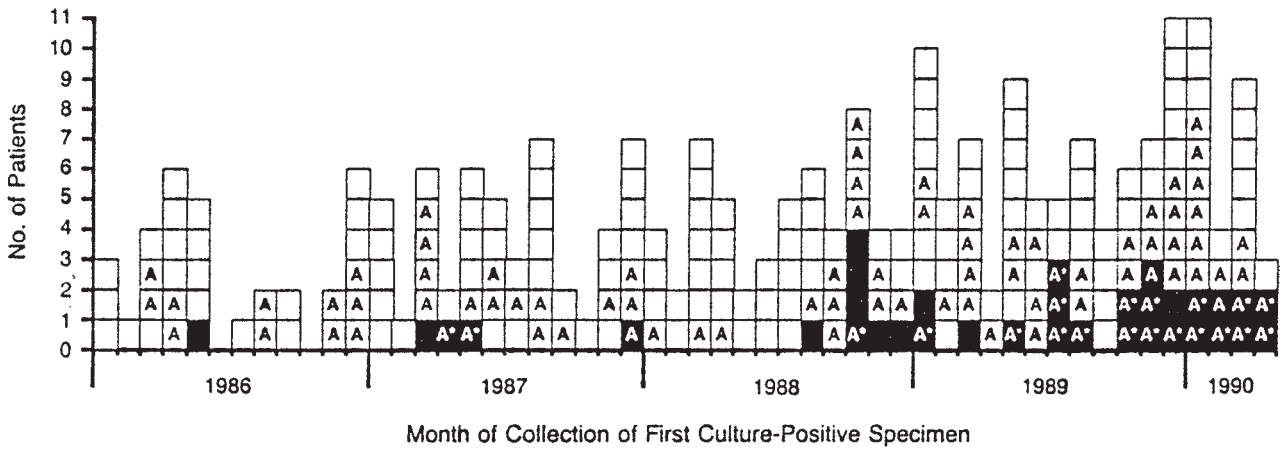

FIGURE 8-2 Epidemic curve illustrating person-to-person transmission. (From Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1992;326:1514–1521.)

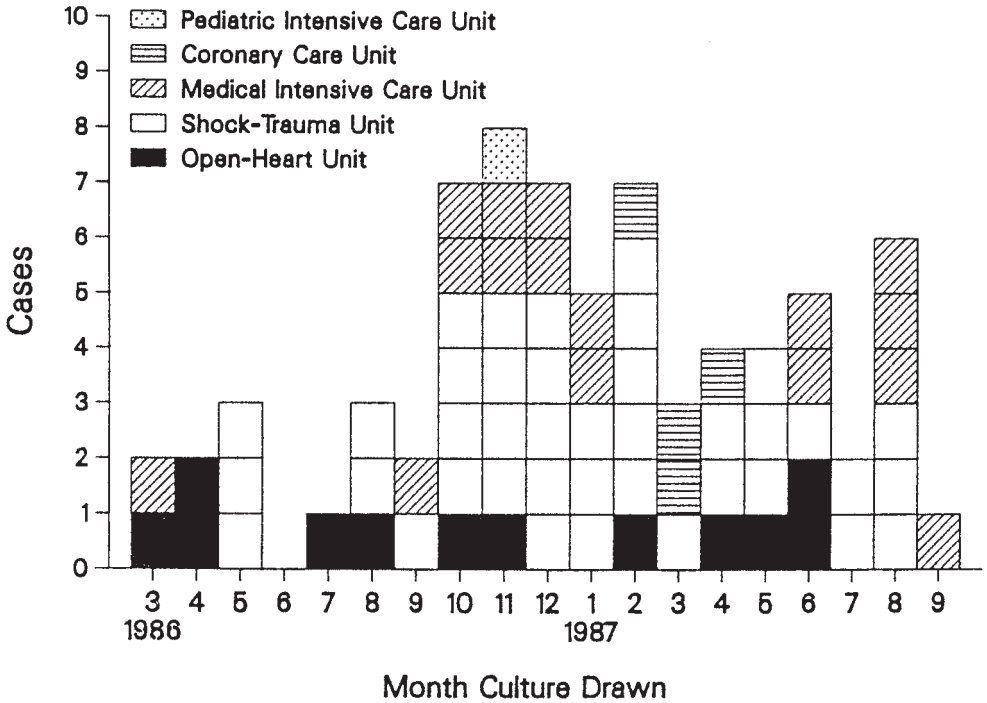

FIGURE 8-3 Epidemic curve of an outbreak caused by contaminated patient-care equipment. (From Beck-Sague CM, Jarvis WR, Brook JH, et al. Epidemic bacteremia due to *Acinetobacter baumannii* in five intensive care units. *Am J Epidemiol* 1990;132:723–733.)

affected by the outbreak, the dates of onset of disease/adverse event for patients and HCWs should be plotted both together and separately to determine if transmission occurred from patient to patient, patient to HCW, HCW to patient, or HCW to HCW.

At times, the location of the outbreak is limited to a certain ward, unit, or operating room and at other times to a certain type of ward (e.g., general surgical units). The location of the outbreak may provide a clue to the mode of transmission or to certain risk factors or exposures of particular patients.

For example, an investigation in a hospital with high tuberculin skin test (TST) conversion rates among patients and HCWs revealed that many of the TST converters were patients of or workers in the outpatient human immunodeficiency virus (HIV) clinic (*35*). The clinic had a large room with reclining chairs for patients with acquired immunodeficiency syndrome (AIDS) to receive intravenous medications on an outpatient basis. This room was immediately adjacent to two rooms with floor-to-ceiling sliding glass doors, in which aerosolized pentamidine was administered to patients with *Pneumocystis carinii* pneumonia; some of these patients had active tuberculosis. Because these treatment rooms were under positive pressure relative to the intravenous medication room, patients receiving intravenous medications, and HCWs administering the medications, were exposed to patients with *M. tuberculosis* infection when HIV-infected patients with active tuberculosis received aerosolized pentamidine. This occurred even if the isolation room doors were closed. In addition, air in the isolation rooms and waiting area was recirculated, causing a mixture of clean and potentially *M. tuberculosis* contaminated air to be circulated through the room. Thus, the location of a number of the cases led to identification of risk factors for acquisition of the disease (i.e., new onset of tuberculosis or TST conversion among AIDS clinic patients or HCWs exposed to patients with active tuberculosis) and to mode of transmission (airborne spread caused by poor isolation practices and inadequate ventilation systems).

By describing the case-patients in terms of demographics and underlying disease, one can define the at-risk population and determine possible exposures. Certain patient populations may be at risk because of either age or underlying disease-specific exposures. The entire population that meets these identified criteria is the group of patients that would have been identified as case-patients had they developed disease (*36*). This is the population from which controls or the cohort to be studied should be chosen for epidemiologic studies. The comparison population (controls or noncases) should have the same opportunity for infection/disease or adverse event as the case-patients.

Developing Hypotheses

Once cases are identified, and pertinent information from the medical records is abstracted, hypotheses about the cause of the outbreak can be generated. These hypotheses should be based on the available information, previously published literature, and expert opinion. Then, epidemiologic studies can be conducted to test the hypotheses.

In many situations, the number of cases in the cluster is very small (less than five cases) or personnel or financial resources are not sufficient to conduct epidemiologic hypothesis testing studies. Thus, a different approach, sometimes called "quick and dirty," is followed. In this situation, the line listing of the case-patients, which flowed from the case definition and case finding, is examined,

commonalities identified, and hypothesis generated about the most probable sources and mode of transmission. Then, a variety of control measures are implemented aimed at the most probable source and mode of transmission. After implementing these control measures, one continues to conduct surveillance for additional case-patients and one hopes that the outbreak is terminated. If the outbreak continues, either additional control measures may be implemented or it may be necessary to conduct the hypothesis testing epidemiologic studies.

Testing Hypotheses

Investigation of outbreaks is by nature retrospective to the development of the adverse event. Two types of retrospective analytic studies can be performed to test hypotheses formed in an outbreak investigation: case–control or cohort studies. Recently, such studies have been called "quasi-experimental" studies, as they are not prospective, randomized, placebo-controlled studies. The majority of recommendations for prevention of HAIs are based on such quasi-experimental studies. Each type of study (e.g., case–control or cohort) has inherent advantages and disadvantages, which should be taken into account before embarking on the study. A major consideration is whether the number of case-patients is sufficient to statistically identify or confirm the source and risk factors for infection/disease or adverse event (i.e., the statistical power of the study). If the number of cases is small, an epidemiologic study may be fruitless, as one may not identify a source or risk factor that is responsible (type II or beta error) or erroneously identify a source or risk factor that is not responsible (type I or alpha error).

Case–Control Studies The case-patients for a case–control study have already been selected by the occurrence of the outbreak. Choosing the appropriate controls is the next step. Case–control studies require the selection of study participants on the basis of disease/infection/adverse event status. For example, if 25 affected patients or HCWs (case-patients) are enrolled, a proportional number (25, 50, 75, etc.) of unaffected members of the at-risk population should be enrolled as controls. Specific risk factors for disease/adverse event then can be compared between case- and control-patients. Care should be taken to ensure that case-patients and control subjects have equal likelihood of the exposure (e.g., presence on the unit/ward for minimum lengths of time during which the potential source may have been present).

The main advantage of case–control studies is that they require a small number of subjects (cases [n] and controls [$1n$, $2n$, or $3n$]) and can, therefore, be conducted relatively quickly. In addition, because subjects are chosen on the basis of their disease/adverse event status (i.e., cases being ill and controls being well), case–control studies are well suited for infrequent or rare diseases/adverse events or diseases/adverse events with long latency periods. In addition, multiple exposures can be examined in the course of one study. This same feature, however, means that the design is backward (i.e., one selects subjects on the basis of disease/adverse event status and then looks backward in time to look at potential exposures). This may lead to uncertainty that the exposure actually preceded the onset of disease/adverse event. In addition, this backwardness may subject the study to both selection and recall bias. Another disadvantage of case–control studies is that they are unsuitable for rare exposures (disease/adverse event incidence rates cannot be measured because the population at risk has not been proportionately sampled) (see also Chapter 2). Most outbreak investigations use the case–control study design because of its efficiency (smaller number of case- and control-patients medical records to review) while still being able to assess multiple exposures/potential risk factors in one study. One disadvantage of the case–control study is that one cannot determine the relative risk (RR) of the identified exposures, but rather estimates this risk by calculating the odds ratio (OR) (see also Chapter 2).

Cohort Studies In contrast to case–control studies, cohort studies require the selection of study participants on the basis of exposure status. Such status can be determined on the basis of known facts about the case-patients or case-HCWs. Exposures that often are used to determine the cohort to be studied are underlying disease, being hospitalized on a particular ward, having a particular physician, or having undergone a particular surgical or invasive procedure. Once the cohort of diseased (cases) and nondiseased (noncases) patients is selected, specific risk factors for development of disease can be evaluated among the cases and noncases.

Because cohort study subjects are selected on the basis of an exposure and followed forward through time (albeit historical time) for the occurrence of disease, cohort studies have the advantage of a logical temporal sequence. The selection of subjects on the basis of exposure also facilitates studying rare exposures or the many effects of one exposure. Another major advantage of the cohort study design is the ability to calculate disease incidence rates for the affected population and the RR associated with the identified risk factors (see also Chapter 2).

Study Design The type of study that should be done and the population from which study subjects should be chosen depend on the particular hypotheses to be tested, the frequency of the adverse event, the duration of the outbreak, the number of case-patients identified, and so forth. Often, it is necessary to conduct several studies, each testing hypotheses from the different levels of the outbreak. Most of the data for the case-patients or case-HCWs for either type of study have already been collected in the initial data collection and chart review procedure. The same data should be collected for the control subjects (case–control study) or non-case-patients (cohort study), so that particular risk factors can be evaluated. Data should be collected similarly for cases and for controls or noncases.

Data Analysis

Descriptive Statistics Initial data analysis should consist of descriptive statistics (e.g., frequency tables for each independent or exposure variable). For example, if information collected for cases and controls or noncases includes age, gender, hospital ward, attending physician, and surgical procedure performed, the frequency of all of the values of those variables should be examined for the study population. This type of descriptive information is

TABLE 8-3

Frequency Distribution of Attending Physicians for Cases and Controls, Outbreak of Unknown Disease, Hospital X

Physician	*Number of Cases*	*Number of Controls*
A	14 (93%)	7 (47%)
B	0 (0%)	0 (0%)
C	1 (7%)	8 (53%)
Total	15 (100%)	15 (100%)

very useful to direct further analyses. For example, if the study population was exposed to attending physicians A, B, and C as shown in Table 8-3, further analyses might be conducted around events associated with attending-physician A.

Univariate Analysis: Categorical Variables Categorical variables (i.e., variables with values that can be sorted into categories such as ill or well, yes or no, male or female) are compared using the 2×2, or cross-tabulation, table. If a case–control study design has been used, ORs should be calculated by using the following formula:

$$\text{OR} = ad / bc$$

The OR is the odds that a person with the disease/adverse event was previously exposed to the risk factor of interest compared with the odds that a person without the disease/adverse event was not previously exposed to the risk factor of interest. Usually, the further away from 1.0 in either direction, the stronger the association between the variables. The OR estimates the RR (see later) when a case–control study design has been used. To continue with the previous example, if exposure to physicians A and C is compared with case or control status, exposure to physician A is associated with illness (Table 8-4).

When using a cohort study design, RR estimates can be calculated for the population, using the following equation:

RR = probability of being exposed divided by probability of being nonexposed or

$$\frac{a/(a+b)}{c/(c+d)}$$

TABLE 8-4

Two-by-Two Table Comparing Physicians A and C to Case–Control Status, Outbreak of Unknown Disease, Hospital X[a]

	Cases	*Controls*	*Total*
Physician A	14	7	21
Physician C	1	8	9
	15	15	30

[a]Odds ratio = ad/bc = (14)(8)/(7)(1) = 16.

The RR is the risk of development of the disease/adverse event if the exposure has occurred compared with the risk of development of the disease/adverse event if the exposure has not occurred. As with the OR, the further away from 1.0 the RR is, the stronger the association is between the variables. This calculation assumes that the study subjects have been selected on the basis of exposure; therefore, this calculation can only be used with a cohort study design.

Most statistical software packages also calculate 95% confidence limits (95% CI) around the OR or the RR. This calculation indicates that if the population were resampled a number of times, the OR or RR would fall within the calculated confidence limits 95% of the time. If the confidence limits surround 1.0, it is likely that for any given sample of the population, the real odds of disease/adverse event or RR could equal 1.0, indicating no association between the variables. Thus, 95% CIs are one indication of the significance of the OR or RR (see also Chapter 2).

Most statistical software packages also calculate a chi-square test from the 2×2 table to test the association between the variables. More commonly reported in the scientific literature than the chi-square value is the *p* value, which is based on the chi-square value. If the expected value in any of the cells of the 2×2 table is <5, the Fisher's exact test (FET) is calculated instead of the chi-square value. The *p* value for the FET is calculated directly from the 2×2 table in this instance, rather than by using chi-square tables. For either the chi-square test or the FET, the *p* value indicates the level of certainty one has that the association between the variables is not occurring by chance alone. Both the chi-square test and the FET require that the variables be mutually exclusive and independent.

Univariate Analysis: Continuous Variables Continuous variables, such as age or severity of illness measurement, are compared among the case- and control-patients or noncases by using measures of central tendency, most frequently the mean or median. If the data are normally distributed (i.e., plotting the values on a graph yields a bell-shaped, or normal, curve), the mean and its standard deviation should be calculated. If the data are not normally distributed, the median and range of the data values should be used.

Stratified and Multiple Variable Analysis Because many HAI are multifactorial, often it is necessary to control for one or more variables while testing another. For instance, SSIs frequently are related to the surgeon's skill (usually measured as the duration of surgery), the condition of the surgical site at the time of the operation (measured by a standard surgical site classification score), and the patient's underlying health status (measured by a variety of risk factor scores).

Analytic techniques to control for all of these factors usually start with simple stratification of the data. Other techniques include logistic or linear regression models (for categorical and continuous outcome variables, respectively), which require advanced statistical software and training. In some outbreaks, the number of case-patients may be too small to do either stratified or regression analysis. Furthermore, two or more variables may be linearly

associated so that the independent importance of each risk factor cannot be determined. Details on the use of univariate, stratified, and multivariate statistical techniques can be found in Chapter 3.

Use of Microcomputers The analytic techniques described in this section can be accomplished with the use of microcomputers. Statistical software packages, such as Statistical Analysis System (SAS Institute Inc., Cary, NC), EpiInfo Software (Centers for Disease Control and Prevention [CDC], Atlanta, GA), and others, offer a wide variety of features. Particularly useful is the Statcalc feature of EpiInfo. It allows calculation of the necessary sample size to find significant associations; direct input of data into cross-tabulation tables for calculation of ORs or RRs and their respective chi-square, FET, and *p* values; and direct input of data into a trend analysis model for continuous variables (*37*). Calculation of the power of the study or the sample size necessary to detect significant associations is essential before embarking on any outbreak investigation or epidemiologic study. Details on the use of microcomputers in hospital epidemiology can be found in Chapter 15.

MICROBIOLOGY LABORATORY ASPECTS OF THE INVESTIGATION

Once a potential outbreak has been identified, the microbiology laboratory should be notified immediately, so that all appropriate specimens and positive cultures can be saved. Because of the ubiquitous nature of microorganisms in the healthcare facility environment, typing of microorganisms thought to be related to an outbreak may be essential to determine if the infected patient is indeed part of the outbreak. The first line of typing of microorganisms is species identification. This is followed by biotyping and then antimicrobial susceptibility testing. For example, during an outbreak of SSIs caused by MRSA, a patient thought to be involved in the outbreak would be excluded as a case-patient if antimicrobial susceptibility testing revealed that he or she was infected with a methicillin-sensitive strain of *S. aureus*.

When antimicrobial susceptibility testing is insufficient to determine the relatedness of two microorganisms, other methods of typing can be used, including serotyping, phage typing, isoenzyme electrophoresis, and genetic fingerprinting techniques (e.g., pulsed-field gel electrophoresis, plasmid analysis, or restriction fragment polymorphism). These methods are further detailed in Chapter 94.

Although some research-oriented hospital laboratories may be capable of very sophisticated typing techniques, most infection control professionals require assistance in typing microorganisms from an outbreak. University, state health department, the CDC, or other laboratories may be able to assist with typing of isolates from an outbreak. It should be remembered that genetic or other typing of isolates can determine whether the isolates are the same strain (clonal) or not (nonclonal), but it cannot tell whether there is an outbreak or not. Outbreaks can be caused by clonal (common source) or nonclonal (intermittent person-to-person transmission because of inadequate hand hygiene) isolates.

ENVIRONMENTAL INVESTIGATION

A thorough investigation of an infectious disease/adverse event outbreak should include some inspection of the environment, particularly if an inanimate object is epidemiologically implicated as a possible means of transmission. For example, investigation of an outbreak of *Serratia marcescens* SSIs following breast reconstruction revealed that expandable breast implants were associated with a greater risk of infection than were nonexpandable implants. Furthermore, infections were more likely when the expansion procedure was performed in the surgeon's office (*38*). This led the investigators to sample solutions, water sources, and personnel from the surgeon's office that was involved in the expansion procedure. Positive cultures were obtained only from a specimen of saline taken from a partially used bag in the procedure room, allowing investigators to remove the contaminated solution and other bags with the same purchase date. Environmental cultures should not be taken randomly, because many surfaces are contaminated with numerous microorganisms, perhaps including the microorganism being investigated. Positive culture results from such random sampling may be misleading, difficult to interpret, and often confusing to investigators. Similarly, the first step in any outbreak investigation should not be widespread personnel or environmental culturing; rather such culturing should be based on the epidemiologic data identifying a potential source.

In addition to environmental cultures, outbreaks of diseases/adverse events caused by airborne microorganisms such as *M. tuberculosis* or *Aspergillus* spp. merit a thorough inspection of air-handling systems, isolation room airflow patterns, and infection control techniques. Again, neither routine environmental culturing nor selected culturing of the air or room is indicated; these should only be done when epidemiologically directed. Without epidemiologic direction, such culturing usually either misses the source or leads to uninterpretable results.

INTERPRETING RESULTS

The most important part of the investigation is the interpretation of results. Meaningful associations between exposures or risk factors and the development of disease depend on numerous factors: the quality of the study design and the study population, biologic plausibility (i.e., the measured association makes biologic sense), and the exposure's preceding the onset of the disease/adverse event (*39*). Other qualities that lend confidence to a significant association are the statistical strength of the association, consistency with other studies, and the presence of a dose–response effect (*39*).

INSTITUTING CONTROL MEASURES

Control measures can be instituted as soon as a potential outbreak is discovered. For example, increased attention to hand hygiene and other infection control techniques may halt transmission. In addition, published guidelines from the CDC, Association for Professionals in Infection Control

and Epidemiology, the Society for Healthcare Epidemiology of America, Joint Commission, World Health Organization, or other organizations may lend guidance for specific situations (*40–51*). If the investigation implicates a particular HCW or item of patient-care equipment, specific measures should be taken to rectify the situation.

EXAMPLE OF A HOSPITAL INVESTIGATION

An excellent example of an outbreak investigation in a hospital is the investigation of SSIs caused by an unusual human pathogen, *Rhodococcus bronchialis*, after open-heart surgery (52). This outbreak provided an opportunity to assess risk factors for infection with *R. bronchialis*, mode of transmission of the microorganism, and potential sources for this unusual HAI pathogen. Logical hypotheses for the source of SSIs after open-heart surgery included preoperative (e.g., nurses, physicians, or wards), intraoperative (e.g., operating room environment or personnel), or postoperative (e.g., recovery room or intensive care unit personnel) exposures. The investigators analyzed both categorical and continuous variables as measures of potential risk for infection and possible exposures as the source of infection (Table 8-5). The only factor significantly associated with infection was the presence of one operating room nurse, nurse A, during the operative procedure. Examination of nurse A's intraoperative practices revealed that she could have contaminated the sterile field after performing an activated clotting time (ACT) test that involved the use of a water bath for incubation of a tube of the patient's

TABLE 8-5

Categorical and Continuous Variables as Measures of Potential Risk for Infection

Potential Risk Factor	*Case-Patients (n = 7) (%)*	*Controls (n = 28)*	*Odds Ratio*	*p Value*
Categorical variables				
Male sex	7 (100)	24 (86)	NC	.6
Underlying conditions	6 (86)	22 (79)	1.6	1.0
Diabetes	1 (14)	6 (21)	0.6	1.0
Obesity	3 (43)	4 (14)	4.5	.1
Smoking	4 (57)	9 (32)	2.8	.4
Cancer	1 (14)	0 (0)	NC	.2
Renal insufficiency	0 (0)	0 (0)	—	—
Treatment with steroids	1 (14)	1 (4)	4.5	.4
Chronic lung disease	2 (29)	3 (11)	3.3	.3
Presence of nurse A	7 (100)	6 (21)	NC	.0003
Coronary artery bypass graft	7 (100)	28 (100)	—	—
Saphenous vein	6 (86)	26 (93)	0.5	.5
Mammary artery	6 (86)	25 (89)	0.7	1.0
Transfusion	4 (57)	13 (46)	2.2	1.0
Continuous variables				
Preoperative stay (d)	1.8 ± 1.3[a]	1.9 ± 1.8	—	.7
Postoperative stay (d)	6.2 ± 1.3	7.5 ± 3.7	—	.4
Age (year)	59.4 ± 5.4	58.5 ± 11.0	—	.9
Number of underlying conditions	2.2 ± 1.9	1.1 ± 0.9	—	.2
Duration of operation (min)	284 ± 64	292 ± 87	—	.9
Duration of bypass (min)	119 ± 38	128 ± 44	—	.7
Duration of aortic clamping (min)	67 ± 23	70 ± 27	—	.8
Amount of blood reperfused (mL)	903 ± 236	901 ± 317	—	1.0
Cardiac index[b]	2.8 ± 0.6	3.0 ± 0.5	—	.6
Duration of treatment (d)				
Stay in cardiac intensive care unit	2.2 ± 0.4	2.9 ± 2.2	—	.8
Swan–Ganz catheter	1.8 ± 0.4	2.2 ± 1.0	—	.6
Arterial line	2 ± 0	2.3 ± 1.0	—	.6
Mediastinal drains	2 ± 0	2.2 ± 0.8	—	.6
Pacer wires	4.8 ± 0.4	5.0 ± 1.6	—	.8
Ventilation	1 ± 0	1.6 ± 2.7	—	.6
Antimicrobial prophylaxis	4.2 ± 2.2	3.7 ± 1.0	—	.9

[a]Plus/minus values are means ± SD. ICU, intensive care unit; NC, not calculable.
[b]Cardiac index was defined as cardiac output in liters per minute per square meter of body surface area.
(From Richet HM, Craven PC, Brown JM, et al. A cluster of *Rhodococcus (Gordona) bronchialis* sternal wound infections after coronary artery bypass surgery. *N Engl J Med* 1991;324:104–109, with permission.)

blood. A revised hypothesis was that nurse A contaminated the sterile operative field after performing the ACT test; this would account for all of the cases of *R. bronchialis* SSIs during the epidemic period.

To prove that nurse A was responsible for all of the cases of *R. bronchialis* SSIs at the hospital, the investigators performed numerous cultures indicated by the epidemiologic data. These included cultures of nurse A's and nurse B's hands before and after each performed the ACT test; nasal swabs from all cardiac operating room personnel; swabs from nurse A's scalp, pharynx, vagina, and rectum; and swabs from environmental sites while nurse A was present in or absent from the operating room. Only cultures of nurse A's hands after performing the ACT test, nurse A's nasal swab, settle plates from the operating room while nurse A was present, and nurse A's scalp and vaginal cultures were positive for *R. bronchialis*. To identify the ultimate source of the microorganism, nurse A's operating room locker and her home were examined and selectively cultured. The neck-scruff skin of nurse A's dog and air vents at her home (where the dog would lay) were positive for *R. bronchialis*. Antimicrobial susceptibility testing and molecular typing showed that all of the outbreak isolates (i.e., patient, HCW, environment, and dog) were identical and distinct from nonoutbreak stock strains of *R. bronchialis*.

The role of the water bath used to incubate blood samples for the ACT test was analyzed by simulating what the scrub nurses would do during surgery and by using a colorless fluorescent dye in the water bath. After simulating the beginning of an open-heart procedure (e.g., performing an ACT test and opening sterile packs for the procedure), 8/11 circulating nurses contaminated the sterile field with fluorescent dye from the water bath. Also contaminated with fluorescent dye were all of the nurses' hands; some of the nurses' wrists, forearms, and scrub suits; the outer surface of the water bath container; the table surface; and the floor around the water bath. This simulation showed that although the bath water was culture-negative for *R. bronchialis*, the bath water, by wetting the hands of nurse A, provided the mechanism for the microorganism to be spread from nurse A's hands to the sterile field. Because nurse A was epidemiologically implicated in the investigation, cultures were obtained from a variety of sources highly likely to yield positive results. Random culturing of the operating room environment and other personnel earlier in the investigation would have been unfocused, increasing the work load on the laboratory without aiding the investigation, and most likely would have missed the source of the outbreak. Additional selected surgical personnel and environmental sources were included in the culture survey to avoid identification of nurse A as the probable source before confirming culture evidence could be obtained.

FINAL STEPS

After instituting control measures, assessing the efficacy of the introduced control measures is essential. Occasionally, more than one mode of transmission is present, and prevention interventions eliminate only one of the modes of transmission (*53*). In other situations, it is essential to ensure that previously accepted control measures really are adequate to terminate transmission (54,*55*).

Once an investigation is concluded, it is imperative that all of the concerned parties in the hospital and state or local health department, consultants, and other involved persons be told of the results of the investigation. In addition, if patient-care devices or products are implicated in the investigation, the appropriate divisions of the Food and Drug Administration or CDC should be alerted. Finally, during the course of the investigation, answering inquiries from the public and press may be necessary. It is good practice to have one person, usually from the public relations, risk management, or legal departments of the healthcare facility, respond to these inquiries. That person should be kept informed of all developments in the investigation.

Although the investigation of outbreaks is an interesting and challenging endeavor, it may be beyond the capability of a given infection control or epidemiology department because of financial or personnel resource constraints or lack of expertise in analytic and epidemiologic techniques. In such instances, assistance is available from state or local health departments, the CDC, university infection control or epidemiology departments, other facility infection control personnel, or private consultants.

RESULTS USING THIS APPROACH

From July 1987 through December 2005, the previously described approach to investigation of outbreaks was consistently applied by Epidemic Intelligence Service officers in the Investigation and Prevention Branch, Hospital Infections Program (currently the Prevention and Response Branch, Division of Healthcare Quality Promotion), CDC. In nearly 150 outbreak investigations, the source was identified and the outbreak was terminated (*4*,*16–18*, 20,*21,22*,*25*,*27*,*29*,*33–35*,*38*,54,*55–83*,84,*85–93*,94,*95–98*, 99,*100*,*101*,102,*103*,104,*105*,*106*,107,*108*,*109*,110,*111–114*,115,116,*117–127*,128,*129–140*,141,142,*143–155*, 156,*157*,*158*,159,*160–167*,168,*169–184*) (Table 8-6). The use of this approach has led to the identification of intrinsic product contamination [*Yersinia enterocolitica* from packed red blood cells (*58*), *Pseudomonas cepacia* in povidone-iodine disinfectant (*71*), aseptic peritonitis associated with peritoneal dialysis (*132*), gram-negative bloodstream infections associated with serum albumin (*137*), sepsis and death in neonates associated with contaminated glucose infusates (*138*), pyrogenic reactions associated with once daily administration of gentamicin (*154*), and *Mycobacterium gordonae* pseudoinfections traced to culture additive contamination (*26*)]. Many episodes of extrinsic product contamination involving either pyrogenic reactions and/or infection were detected that were associated with reprocessing of hemodialyzers (56,*60*,*63*,*85*,*93*,94,*96*, *103*,110,*111*,*118*,128,*139*,159). New modes of transmission were identified, such as *R. bronchialis* SSIs or *Malazessia furfur* infections in neonates traced to the HCWs' dogs (52,115); hepatitis A from prolonged excretion of the virus by premature neonates (*70*); many microorganisms from extrinsic contamination of the anesthetic propofol (20); anaphylactic reactions in patients and HCWs traced to latex exposure (*21*,84), aluminum, microcystin, or fluoride

TABLE 8-6

On-Site Healthcare-Associated Infections Outbreak Investigations, Hospital Infections Program/Division of Healthcare Quality Promotion, CDC, July 1987–December 2005

1987 [Outbreak name—state/country (reference number)]

1. Pyrogenic reactions in hemodialysis patients—Illinois (56)
2. *Malassezia furfur* infections in neonatal intensive care unit patients—Washington, DC (*57*)
3. *Acinetobacter* spp. bloodstream infections in intensive care unit patients—New Jersey (*18*)
4. *Yersinia enterocolitica* sepsis associated with red blood cell transfusion—Wisconsin/Texas (*58*)
5. *Pseudomonas cepacia* infection/colonization in attendees at a cystic fibrosis summer camp—Michigan (*59*)
6. Human immunodeficiency virus knowledge and compliance with CDC recommendations (NP)

1988

1. *Aspergillus flavus* pseudofungemia in bone marrow transplant patients—North Carolina (NP)
2. Methicillin-resistant *Staphylococcus aureus* surgical site infections in cardiac surgery patients—Tennessee (NP)
3. *Mycobacterium chelonae* infections in hemodialysis patients—California (*60*)
4. *Aspergillus fumigatus* surgical site infections in cardiac surgery patients—Tennessee (*61*)
5. Epidemic hemolytic anemia in hemodialysis patients—Pennsylvania (*62*)
6. Gastroenteritis in a retirement facility—California (*33*)
7. Pyrogenic reactions and/or bloodstream infections in hemodialysis patients—Arizona (*63*)
8. Hemolysis in pediatric hemodialysis patients—Texas (*64*)
9. Invasive candidiasis in hematology–oncology patients—France (*65*)
10. Disseminated intravascular coagulation in open heart surgery patients—California (*66*)

1989

1. *Serratia marcescens* bloodstream infections in intensive care unit patients—Illinois (*67*)
2. Surgical site infections in patients undergoing hip replacement procedures—Maine (*68*)
3. Hypotension in hemodialysis patients—New York (*69*)
4. *Rhodococcus broncialis* surgical site infections in cardiac surgery patients—Washington (52)
5. Hepatitis A infections in neonates in a neonatal intensive care unit—Hawaii (*70*)
6. *Pseudomonas cepacia* pseudobacteremia in infants—Texas (*71*)
7. *Xanthomonas maltophilia* infections in intensive care unit patients—Utah (*72*)
8. Group A streptococcal surgical site infections—California (NP)
9. *Salmonella* spp. gastroenteritis in patients and healthcare workers—Tennessee (NP)
10. *Pseudomonas cepacia* infections in cystic fibrosis patients—Pennsylvania (*73*)
11. Multidrug-resistant *Mycobacterium tuberculosis* infections in human immunodeficiency virus infected patients—Puerto Rico (*74*)
12. *Tsukamurella* spp. pseudoinfections traced to laboratory contamination—South Carolina (*27*)
13. *Mycobacteriun gordonae* pseudoinfections traced to intrinsic product contamination—Connecticut/Georgia (*26*)
14. Nosocomial infections in long-term care facility residents—California (*75*)
15. *Serratia marcescens* surgical wound infections following augmentation mammoplasty—North Dakota (*38*)
16. Allergic reactions in hemodialysis patients—Virginia (*76*)

1990

1. Group A streptococcus bacteremia in residents of a long-term care facility (*77*)
2. *Clostridium difficile* enteritis in a hospital—New York (*78*)
3. Drug-resistant tuberculosis in hospitalized AIDS patients—New York (*34*)
4. *Staphylococcus aureus* infections following clean surgical procedures—Michigan (*20*)
5. *Candida albicans* infections following clean surgical procedures—Illinois (*20*)
6. *Staphylococcus aureus* infections following clean surgical procedures—Texas (*20*)
7. Endotoxin reactions during clean surgical procedures—Maine (*20*)
8. Nosocomial transmission of drug-resistant *M. tuberculosis*—Florida (*35*)
9. *Enterobacter agglomerans* sepsis and bacteremia in postsurgical patients—Alabama (*20*)
10. *Enterobacter cloacae* bacteremia in emergency room and outpatient clinic patients—New Mexico (*29*)
11. Carbon monoxide poisoning in surgical patients—Georgia (*22,79*)
12. Inadvertent injection of HIV-contaminated material during nuclear medicine procedures—California and New Mexico (*80*)
13. Scleritis following cataract surgery—Florida (*81*)
14. Gram-negative meningitis and bacteremia in neonates in a neonatal intensive care unit—Guatemala (*82*)

(*Continued*)

TABLE 8-6

On-Site Healthcare-Associated Infections Outbreak Investigations, Hospital Infections Program/Division of Healthcare Quality Promotion, CDC, July 1987–December 2005 (*Continued*)

1991

1. Tuberculosis in renal transplant patients—Pennsylvania (*83*)
2. Anaphylactic reactions in pediatric patients—Wisconsin (*21*,84)
3. Pyrogenic reactions and bacteremia in hemodialysis patients—Ohio (*85*)
4. Multidrug-resistant *Mycobacterium tuberculosis* in New York City—New York (*25*)
5. *Aspergillus* spp. infections in immunocompromised patients—California (*16*)
6. Anaphylactic reactions in patients with spina bifida—Pennsylvania (NP)
7. *Klebsiella* sp. sepsis in neonates in a neonatal intensive care unit—Saudi Arabia (*86*)
8. Bacterial sepsis associated with pooled platelet transfusions—Ohio (*87*)
9. Anaphylactic reactions in pediatric patients—Oklahoma (NP)
10. Fungemia in neonatal intensive care unit patients—Louisiana (*88*,*89*)
11. Invasive aspergillosis in oncology patients—Pennsylvania (*90*)
12. Hepatitis A in healthcare workers in a bone marrow transplant unit—Florida (*91*)
13. Polymicrobial bacteremia in postcardiac surgery patients—Washington (*17*)
14. Bacteremia in hemodialysis patients—Texas (NP)
15. Hepatitis B among nursing home residents—Ohio (NP)

1992

1. Nosocomial transmission of multidrug-resistant *M. tuberculosis*—New York (*92*)
2. Pyrogenic reactions in hemodialysis patients—California (*93*)
3. Aluminum toxicity in chronic hemodialysis patients—Pennsylvania (94)
4. Nosocomial transmission of *M. tuberculosis*—Georgia (*4*,*95*)
5. Gram-negative bacteremia in patients undergoing hemodialysis—Maryland (*96*)
6. *Aspergillus fumigatus* sternal wound infections following open heart surgery—Pennsylvania (*96*)
7. Multidrug-resistant *M. tuberculosis*—New Jersey (NP)
8. Nosocomial transmission of multidrug-resistant *M. tuberculosis*—New York (*55*)
9. Nosocomial transmission of multidrug-resistant *M. tuberculosis*—New York (*98*)
10. Nosocomial transmission of multidrug-resistant *M. tuberculosis*—Florida (54)
11. *M. fortuitum* infections/pseudoinfections associated with bronchoscopy—Kentucky (99)
12. Nosocomial transmission of multidrug-resistant *M. tuberculosis*—New York (NP)
13. Complications of Lyme disease treatment—New Jersey (*100*)

1993

1. Endotoxin reactions during surgical procedures—Arizona (*20*)
2. *Serratia marcescens* infections in surgical patients—Arizona (*20*)
3. Invasive aspergillosis in cardiac transplant patients—New York (NP)
4. Nosocomial coagulase-negative staphylococcal bacteremia in neonatal intensive care unit patients—Kentucky (NP)
5. *Enterobacter hormaechei* bloodstream infections in neonatal intensive care unit patients—Pennsylvania (*101*)
6. *Norcardia farcinica* surgical wound infections after open heart surgery—Montana (102)
7. Adverse reactions and death during hemodialysis—Illinois (*103*)
8. Bloodstream and surgical site infections due to vancomycin-resistant enterococci—New York (104)
9. Surgical site infections due to methicillin-resistant *Staphylococcus aureus*—Tennessee (NP)
10. Nosocomial vancomycin-resistant enterococcal infections—Maryland (*105*)
11. Intravascular catheter complications in intensive care unit patients—Arizona (*106*)

1994

1. Bloodstream infections associated with outpatient infusion therapy—Rhode Island (107)
2. Pulmonary complications associated with total parenteral nutrition—Hawaii (*108*)
3. *Acremonium kiliense* endophthalmitis following cataract surgery—Pennsylvania (*109*)
4. Possible HIV transmission in a dialysis center—Colombia (110)
5. Acute hepatitis B infections in hemodialysis patients—Texas (*111*)
6. Acute hepatitis B infections in hemodialysis patients—California (*111*)
7. Bloodstream infections in pediatric oncology patients—California (*112*)
8. Methicillin-resistant *S. aureus* (MRSA) infection colonization in wrestlers—Vermont (NP)
9. *Clostridium difficile* gastroenteritis in hospitalized patients—Canada (*113*)
10. Postoperative *Ochrabactrum anthropi* meningitis in pediatric patients—Utah (*114*)

(*Continued*)

TABLE 8-6

On-Site Healthcare-Associated Infections Outbreak Investigations, Hospital Infections Program/Division of Healthcare Quality Promotion, CDC, July 1987–December 2005 (*Continued*)

1995

1. Nosocomial transmission of *Malassezia pachydermatis* in neonatal intensive care unit patients—New Hampshire (115)
2. Bloodstream infections in home infusion therapy patients—Texas (116)
3. *Salmonella sundsvall* infection in neonates in a neonatal intensive care unit—Oklahoma (NP)
4. *Serratia marcescens* infections in neonatal intensive care unit patients—Massachusetts (*117*)
5. *Enterobacter cloacae* bloodstream infections in hemodialysis patients—Canada (*118*)
6. Pyrogenic reactions in patients undergoing cardiac catheterization—Colorado (*119*)

1996

1. *S. marcescens* infection in cardiac intensive care unit patients—Pennsylvania (*120*,*121*)
2. Vancomycin-resistant enterococcal infections—Indiana (*122–124*)
3. Bloodstream infections associated with needleless devices—Indiana (*125–127*)
4. Fatal illness in a hemodialysis center—Brazil (128)
5. *E. cloacae* bloodstream infections in neonatal intensive care unit patients—Puerto Rico (*129*)
6. Hepatitis C infections possibly associated with intramuscular immune globulin—Texas (NP)
7. *S. aureus* bloodstream infections among patients undergoing electroconvulsive therapy at a psychiatric hospital—Mississippi (*130*)
8. Bloodstream infections in pediatric intensive care unit patients—Georgia (*131*)
9. Bloodstream infections in pediatric outpatients—Georgia (NP)
10. Aseptic peritonitis in peritoneal dialysis patients—Pennsylvania (*132*)
11. Vancomycin-resistant *S. epidermidis* bloodstream infection in a patient—Virginia (*133*)
12. Invasive aspergillosis in rheumatology patients—Maryland (*134*)
13. *Acinetobacter* species bloodstream infection in neonatal intensive care unit patients—Bahamas (*135*)
14. Neurologic (loss of hearing and vision) symptoms after hemodialysis—Alabama (*136*)
15. Bloodstream infections associated with serum albumen—Kansas (*137*)
16. Overwhelming sepsis and death in newborn nursery patients—Brazil (*138*)

1997

1. Bloodstream infections in hemodialysis patients—Maryland (*139*)
2. Nosocomial vancomycin-resistant enterococcus colonization/infection—Indiana (NP)
3. Vancomycin-resistant enterococcus colonization/infection in patients in hospitals and long-term care facilities in a region—Iowa, Nebraska, South Dakota (*140*,141)
4. Nosocomial bloodstream infections in sickle cell anemia patients—Georgia (NP)
5. *S. aureus* with reduced susceptibility to vancomycin—Michigan (142)
6. *S. aureus* with reduced susceptibility to vancomycin—New Jersey (142)
7. Pyrogenic reactions in cardiac catheterization patients—Brazil (*143*)
8. Dementia in solid organ transplant recipients—Maryland (NP)
9. Creutzfeldt–Jakob disease possibly associated with a dura mater transplant—Florida (*144*)
10. *Microbacterium* spp. bloodstream infections in oncology patients—Maine (*145*)
11. *Pseudomonas aeruginosa* infections in neurosurgical patients with external ventricular devices—Arizona (*146*)
12. Infections in pediatric oncology patients with indwelling central vascular catheters—California (*147*)

1998

1. Red eye syndrome associated with red blood cell transfusion—Michigan, Washington, Oregon (nationwide) (*148*)
2. Corneal degeneration after ophthalmologic surgery—Missouri (*149*)
3. *Malassezia pachydermatis* infections in neonates in a neonatal intensive care unit—Kentucky (NP)
4. Postcoronary artery bypass graft sternal wound infections—Wisconsin (*150*,*151*)
5. Hemolysis in hemodialysis patients—Nebraska, Massachusetts, Maryland (nationwide) (*152*)
6. Vancomycin-resistant enterococci in a long-term care facility setting—Illinois (*153*)
7. Pyrogenic reactions in hospitalized patients receiving parenteral gentamicin—California (nationwide) (*154*)
8. Vancomycin-resistant enterococcal infection/colonization among residents of acute and long-term care facilities—Iowa, Nebraska, South Dakota (141)
9. Gram-negative bloodstream infections in bone marrow transplant patients—Washington (*155*)

1999

1. *S. marcescens* bloodstream infections in surgical intensive care unit patients—Pennsylvania (156)
2. Cellulitis, sepsis, and death in neonates in a neonatal intensive care unit—Indonesia (NP)
3. *Klebsiella pneumoniae* bloodstream infections in neonates in a neonatal intensive care unit—Colombia (*157*)

(*Continued*)

TABLE 8-6

On-Site Healthcare-Associated Infections Outbreak Investigations, Hospital Infections Program/Division of Healthcare Quality Promotion, CDC, July 1987–December 2005 (*Continued*)

4. *S. marcescens* bloodstream infections in cardiac catheterization patients—California (NP)
5. Nosocomial sepsis and meningitis in neonates in a neonatal intensive care unit—Brazil (*158*)
6. *S. liquefaciens* bloodstream infections and pyrogenic reactions in hemodialysis patients—Colorado (159)
7. Nosocomial transmission of extended spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in long-term care facility patients—Illinois (*160*)
8. Vancomycin-resistant enterococcal infection/colonization among residents of acute and long-term care facilities—Iowa, Nebraska, South Dakota (141)

2000

1. Transmission of hepatitis C virus among patients at a hemodialysis center—Ohio (NP)
2. Investigation of possible nosocomial transmission causing relapse in TB patients (NP)
3. Adverse reactions associated with transfusion of leukocyte-reduced red blood cell units—multistate outbreak (*161*)
4. Postcoronary artery bypass graft surgical site infection (NP)
5. Community-acquired methicillin-resistant *S. aureus* and *S. aureus* with reduced susceptibility to vancomycin—New Jersey (*162*)
6. Pyrogenic reactions and death in renal dialysis patients—Ohio (*163*)
7. Transmission of hepatitis C virus in a hemodialysis center—Wisconsin (NP)

2001

1. Methicillin-resistant *S. aureus* infections among a college football team—Pennsylvania (NP)
2. Outbreak of skin infections with methicillin-resistant *S. aureus* in a state correctional facility (NP)
3. Possible nosocomial transmission of *M. tuberculosis* by contaminated fiberoptic bronchoscope—Pennsylvania (NP)
4. Catheter-related bloodstream infections in hemodialysis patients (NP)
5. Methicillin-resistant *S. aureus* infections in an American Indian community—Washington (NP)
6. Outbreak of invasive aspergillosis among renal transplant patients (NP)
7. Outbreak of *E. cloacae* bloodstream infections in a pediatric inpatient population—Missouri (*164*)
8. Outbreak of saline-filled breast implant contamination with *Curvularia lunata* among women who underwent cosmetic breast augmentation surgery—Alabama (*165*)
9. Adverse events and deaths associated with laboratory errors at a hospital—Pennsylvania (*166*)
10. Outbreak of sepsis and death associated with *Klebsiella pneumoniae* in neonatal intensive care unit patients—Cairo, Egypt (*167*)

2002

1. Hospital outbreak of *Candida parapsilosis* bloodstream infections—Mississippi (NP)
2. Multistate investigation of postoperative clostridial infections in patients undergoing knee surgery and allograft implantation—Minnesota (168)
3. *Enterobacter sakazakii* meningitis in a neonatal intensive care unit (NP)
4. Postoperative surgical site infections in patients who underwent orthopedic procedures and allograft implantation—California (*169*)
5. Outbreak of vancomycin-resistant *S. aureus* infections—Michigan (*170*)
6. Nontuberculous mycobacteria soft tissue infections associated with cosmetic injections—New York (NP)
7. Hospital outbreak of *Candida parapsilosis* bloodstream infections (*171*)

2003

1. Outbreak of vancomycin-resistant *S. aureus* infections—Pennsylvania (*172*)
2. *Mycobacterium tuberculosis* associated with nosocomial transmission in a hospital—Guatemala (NP)
3. *Phialemonium* infections among renal dialysis patients—Illinois (*173*,*174*)
4. Community-associated methicillin-resistant *S. aureus* skin and soft tissue infections—Hawaii (*175*)

2004

1. Postoperative group A streptococcal infections following allograft implantation—Colorado, Oklahoma (*176*)
2. Nosocomial transmission of *M. tuberculosis*—Taiwan (NP)
3. Fatal rabies in organ transplant recipients—Texas (*177*)
4. Outbreak of *Acinetobacter baumannii* infections—Maryland (*178*)
5. Outbreak of *Burkholderia cepacia* associated with contamination of albuterol and nasal spray (*179*)

(*Continued*)

TABLE 8-6

On-Site Healthcare-Associated Infections Outbreak Investigations, Hospital Infections Program/Division of Healthcare Quality Promotion, CDC, July 1987–December 2005 (*Continued*)

2005

1. Investigation of *S. marcescens* infections in cardiac surgery patients—Kentucky (*180*)
2. Outbreak of *Burkholderia cepacia* infections in an oncology clinic—Georgia (*181*)
3. Investigation of *S. marcescens* infections in cardiac surgery patients—California (*180*)
4. Outbreak of community-associated methicillin-resistant *S. aureus* skin and soft tissue infections—Georgia (NP)
5. Recovery of *Ralstonia* spp. from neonates—Pennsylvania (*182*)
6. Multistate outbreak of *B. cenocepacia* colonization and infection associated with the use of intrinsically contaminated alcohol-free mouthwash (*183*)
7. Multistate outbreak of toxic anterior segment syndrome, 2005 (*184*)

NP, not published.

toxicity in hemodialysis patients traced to an aluminum pump (94,*103*,128), inadequate water disinfection (128), or exhaustion of a reverse osmosis filter (*103*), respectively; *Mycobacterium fortuitum* infection or pseudoinfections from inadequate bronchoscopy disinfection (99); *Nocardia* SSIs traced to a colonized anesthesiologist and his contaminated home environment (102); bloodstream infections traced to needleless devices used in home infusion therapy (107,*112*,116,*125–127*); the role of the nursing shortage on increasing infection rates (*106*,*120*); and others. In addition, risk factors for transmission of *M. tuberculosis* (*34*,*35*,*74*,*83*,*92*) to patients and HCWs in healthcare settings were identified, and interventions were implemented and documented to terminate such transmission (54,*55*,*98*). Similarly, risk factors for the emergence and transmission of vancomycin-resistant enterococci were identified (104,*105*,*122–124*); then interventions (including active detection and isolation including active surveillance testing and barrier precautions) were implemented and shown to be effective in reducing or eradicating transmission on a ward (104,*105*), in an entire hospital (*124*), or in an entire region of a state (all acute care and long-term care facilities) (141). In addition, new and emerging HAI pathogens were identified, such as *M. furfur* in neonates (*57*,115), *Y. enterocolitica* in red blood cell products (*58*), *P.* (now *Burkolderia*) *cepacia* in cystic fibrosis patients (*59*,*73*), multidrug-resistant *M. tuberculosis* (*4*,*25*,*34*,*35*,54,*55*,*74*,*83*,*92*,*95*,*98*), nontuberculous mycobacteria in hemodialysis patients (*60*) or bronchoscopy patients (99), *R. bronchialis* or *Norcardia farcinica* in cardiac surgery patients (52,102), *Enterobacter hormaechei* in neonates (99), *Akremonium kiliense* in surgical patients (*109*), *Ochrabactrum anthoropi* in pediatric patients (*114*), vancomycin-resistant enterococci (104,*105*,*122–124*,141), and *S. aureus* with reduced susceptibility to vancomycin (142).

This approach has worked well for infectious and noninfectious diseases/adverse events and in all types of healthcare settings and countries. The success of this approach illustrates the value of a combined epidemiologic and laboratory investigation; the power of using these tools together is much greater than using either one alone. When appropriately implemented, this outbreak investigative approach identifies the source and mode of transmission, assists in evaluating the efficacy of the interventions, and ultimately and effectively protects patients and HCWs by preventing further infection/disease/adverse events.

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CHAPTER 9

Pseudoinfections and Pseudo-Outbreaks

Cheston B. Cunha and Burke A. Cunha

From an infection control and clinical perspective, pseudoinfections are interesting and important. On a daily basis, there are many concerns confronting infection preventionists (IPs) in reviewing clinical and microbiologic data. Given the high volume of microbiologic data generated per day, it is understandable that IPs particularly take notice of common microorganisms cultured/demonstrated from unusual body sites (for the microorganism) (e.g., *Streptococcus pneumoniae* from a wound culture) as well as unusual microorganisms cultured/demonstrated from any body site (e.g., *Chromobacterium violaceum* from respiratory secretion cultures). Potential pseudoinfection should be suspected either when an unusual microorganism is cultured from a usual body site (e.g., *Alcaligenes [Achromobacter] xylosoxidans* cultured from the urine) or when a common microorganism is isolated from an unusual body site (for the microorganism) (e.g., *Bacteroides fragilis* cultured from the cerebrospinal fluid [CSF]). The clue to possible pseudoinfection is a discrepancy between clinical findings and the typical manifestations of the isolate at the body site cultured/demonstrated (e.g., *Pseudomonas fluorescens* cultured from the blood in a patient with pneumonia). IPs should then determine by epidemiologic investigation whether the isolate represents a *bona fide* infection or pseudoinfection.

An abrupt increase in incidence of a microorganism relative to its prevalence in an institution should suggest a potential outbreak. Outbreaks are clusters of the same infection occurring over a limited period of time but must be differentiated from pseudo-outbreaks. A pseudo-outbreak may be defined as a cluster of pseudoinfections due to the same microorganisms cultured/demonstrated from the same site in multiple patients. Whenever a pseudoinfection is suspected, infection control should conduct an appropriate epidemiologic investigation to try and determine the common source of microbial contamination and mechanism of specimen contamination.

Infectious disease clinicians deal with other problems trying to correlate microbiologic results with clinical findings. On a daily basis, physicians must differentiate colonization from infection not only for accurate record keeping/diagnostic purposes but also to avoid unnecessary treatment of colonization, which may predispose to antimicrobial resistance.

Some patients with pseudoinfections are empirically treated with antimicrobial therapy before the diagnosis of pseudoinfection is realized. The more potentially serious the infection (e.g., bacteremia, meningitis, pneumonia), the more likely pseudoinfections will be treated empirically with antibiotics. In some cases, whenever an isolate is clearly unrelated to the clinical presentation (e.g., *Bacillus subtilis* isolated from the CSF in a patient with altered mental status), pseudoinfection is likely and empiric antibiotic therapy is used less often.

Epidemiologic investigations associated with pseudoinfections are one of the most interesting aspects of infection control. Pseudoinfections and pseudo-outbreaks should be reported to guide others facing similar epidemiologic quandaries. The pseudoinfection literature provides a wealth of information that is instructive and useful to IPs in conducting a focused epidemiology investigation to determine the potential source of microbial contamination.

PSEUDOBACTEREMIAS

The first type of pseudoinfection described was pseudobacteremia, which remains the most frequently reported pseudoinfection. Microorganisms associated with pseudobacteremias have been varied, but the most frequently implicated microorganisms have been *Bacillus* species, *Pseudomonas* species, or *Streptococcus* species. The most common sources of pseudobacteremia have been contaminated culture media, contaminated antiseptic solutions, or contaminated blood culture vials. Inadequate needle sterilization of blood culture autoanalyzer parts has also been responsible for some pseudobacteremias. Less commonly, pseudobacteremias have resulted from contamination of blood specimens in the laboratory. Rarely, actual infections have occurred from accidental reflux of microbial contaminated blood into patients during venipuncture (1,*2*,3,*4–31*,32,*33–50*,51,*52–72*) (Table 9-1).

PSEUDOMENINGITIS

Pseudomeningitis is the second most common type of pseudoinfection and should be suspected when nonneuropathogens are cultured from CSF in patients with altered mental

TABLE 9-1

Pseudobacteremia

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(1) 1969	*Escherichia coli*	7	0	7	Contaminated penicillinase in blood culture media
(*2*) 1972	*Acinetobacter lwoffi*	27	3	4	Contaminated penicillinase in blood culture media
(3) 1973	*Moraxella nonliquefaciens*	8	1	1	Contaminated tube holders of blood culture tubes
(*4*) 1974	*Bacillus* species	26	0	0	Contaminated blood culture media
(*5*) 1976	*Pseudomonas cepacia*	79	3	4	Contaminated benzalkonium chloride used for venipuncture
(*6*) 1976	*Flavobacterium Meningo-septicum*	6	0	0	Contaminated chlorhexidine solution used for venipuncture
(*7*) 1976	*Serratia marcescens*	40	0	0	Cross-contamination of blood cultures with nonsterile blood collection tubes
(*8*) 1977	*Acinetobacter lwoffi*	11	0	2	Improper blood culture technique in a mist tent heavily contaminated with bacteria
(*9*) 1978	*Pseudomonas maltophilia*	25	1	3	Cross-contamination of blood cultures with bacteria from nonsterile blood collection tubes
(*10*) 1979	*Staphylococcus aureus*	11	0	5	Blood cultures contaminated by a colonized (nasopharynx) laboratory technician
(*11*) 1980	*Clostridium sordellii*	11	0	0	Contaminated thimerosal solution/diaphragms of blood culture media
(*12*) 1980	*Acinetobacter lwoffi*	22	0	0	Blood cultures contaminated
(*13*) 1980	*Staphylococcus aureus*	5	0	0	Blood culture media contaminated by physician
(*14*) 1980	*Aerococcus viridans*	7	0	0	Inadequately disinfected blood culture bottle stoppers
(*15*) 1981	*Pseudomonas cepacia*	30	0	0	Contaminated povidone-iodine solution used for venipuncture/disinfection of blood culture bottle stoppers
(*16*) 1981	*Enterobacter cloacae*	7	0	1	Contaminated thrombin in blood culture collection vials
(*17*) 1981	*Klebsiella pneumoniae*	13	7	6	Contaminated sampling needle in automated blood culture analyzer
(*18*) 1981	Gram-negative bacilli	75	0	NK[a]	Improper blood culture collection technique
(*19*) 1981	*Pseudomonas cepacia*	16	0	2	Contaminated povidone-iodine solution
(20) 1982	*Klebsiella pneumoniae* *Streptococcus pyogenes* *Staphylococcus epidermidis*	2 1 1	0	1	Inadequate needle sterilization in automated blood culture analyzer
(*21*) 1982	*Bacillus* species	36	0	0	Contaminated syringes
(*22*) 1982	*Serratia marcescens*	17	0	NK	Improper blood culture collection technique
(*23*) 1982	*Serratia marcescens*	16	0	2	Cross-contamination with blood gas specimens
(*24*) 1982	*Pseudomonas aeruginosa*	17	0	0	Contamination of blood culture processing equipment
(*25*) 1983	*Bacillus* species	15	0	0	Contaminated cotton swabs used to disinfect blood culture bottles
(*26*) 1983	*Pseudomonas stutzeri*	24	1	21	Contaminated green soap solution
(*27*) 1983	*Enterobacter faecalis*	8	0	2	Cross-contamination in automated blood culture analyzer

(*Continued*)

TABLE 9-1

Pseudobacteremia (*Continued*)

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(*28*) 1983	*Pseudomonas maltophilia*	5	0	0	Contaminated sodium citrate solution, improper blood culture technique
(*29*) 1983	*Bacillus* species	15	0	0	Contaminated brain–heart infusion broth
(*30*) 1984	*Staphylococcus aureus* *Staphylococcus epidermidis* *Streptococcus* species *Escherichia coli*	11 10 1 1	0	3	Inadequate needle sterilization in blood culture analyzer
(*31*) 1984	*Streptococcus bovis*	1	0	1	Inadequate cleaning of needle in automated blood culture analyzer
(32) 1984	*Bacillus* species	26	0	1	Spore contamination of needle in automated blood culture analyzer
(*33*) 1985	*Streptomyces* species	7	0	0	Airborne contamination of clinical specimens 2° to construction
(*34*) 1985	*Pseudomonas cepacia*	2	0	NK[a]	Contaminated antiseptic handwash
(*35*) 1985	*Pseudomonas pickettii*	21	0	NK	Contaminated aqueous chlorhexidine solution
(*36*) 1985	*Pseudomonas fluorescens*	57	0	0	Cross-contamination from contaminated citrated blood collection tubes
(*37*) 1987	*Enterococcus species* *Staphylococcus aureus*	17 5	0 0	2 NK	Contaminated radiometric blood culture device
(*38*) 1987	*Ewingella americana*	20	0	14	Cross-contamination of blood culture bottles with bacteria from nonsterile tubes
(*39*) 1988	*Pseudomonas cepacia*	2	0	NK	Contaminated blood gas analyzer
(*40*) 1989	*Streptococcus viridans*	41	0	NK	Blood cultures contaminated by colonized laboratory technician with dermatitis
(*41*) 1989	*Streptococcus species*, *Staphylococcus aureus*	7	0	1	Blood cultures contaminated by a colonized laboratory technician with positive nasopharyngeal cultures
(*42*) 1990	*Bacillus* species	10	0	6	Blood cultures contaminated by nonsterile gloves used by phlebotomists
(*43*) 1991	*Candida guilliermondii*	17	0	2	Contaminated heparin vials used for blood culture collection
(*44*) 1991	*Enterobacter cloacae*	13	0	0	Nonaseptic processing of culture media
(*45*) 1993	*Pseudomonas pickettii*	27	0	0	Nonaseptic blood culture collection
(*46*) 1993	*Pseudomonas cepacia*	27	0	0	Contaminated EDTA in blood culture bottles
(*47*) 1993	*Alcaligenes xylosoxidans*, *Xanthomonas maltophilia*, *Klebsiella oxytoca*, *Corynebacterium aquaticum*	16	0	0	Nonsterile blood culture collection/processing
(*48*) 1994	*Mycobacterium avium-intracellulare*	30	0	1	Cross-contamination of culture media
(*49*) 1994	*Pseudomonas fluorescens*	11	0	0	Breakdown in aseptic technique
(*50*) 1994	Gram-variable bacilli	1	0	1	Contaminated culture plate
(51) 1994	*Enterobacter agglomerans*	37	0	0	Nonsterile blood collection tubes
(*52*) 1996	*Burkholderia cepacia*	13	0	4	Contaminated blood gas analyzer
(*53*) 1997	*Mycobacterium abscessus*	23	0	0	Probably due to contaminated lysis centrifugation tube

(*Continued*)

TABLE 9-1

Pseudobacteremia (*Continued*)

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(*54*) 1998	*Candida parapsilosis*	29	0	0	Contamination of blood culture bottles by laboratory technician
(*55*) 1999	*Pseudomonas fluorescens*	12	0	8	Contaminated lithium heparin bottles
(*56*) 1999	*Pseudomonas fluorescens*	53	0	0	Contaminated lithium heparin bottles
(*57*) 1999	*Serratia marcescens*	2	0	2	Contaminated blood glucose/lactate analyzer
(*58*) 1999	*Staphylococcus saccharolyticus*	6	0	NK	Inadequate venipuncture skin site preparation
(*59*) 1999	*Agrobacterium radiobacter*	15	0	NK	Contaminated blood culture tubes
(*60*) 1999	*Enterococcus faecium*	4	0	NK	Phlebotomist contaminated blood culture bottles
(*61*) 1999	*Pseudomonas fluorescens*, *Comamonas acidovorans*	7	0	NK[a]	Contaminated lithium heparin bottles
(*62*) 1996	*Burkholderia cepacia*	13	0	4	Contaminated blood gas analyzer
(*63*) 2000	*Bacillus megaterium*	1	0	0	Contaminated blood culture bottle tops
(*64*) 2001	*Paenibacillus macerans*	8	0	8	Contaminated blood culture bottles
(*65*) 2005	*Volvox globator*	1260	0	0	Contaminated blood culture media
(*66*) 2006	*Ralstonia pickettii*	6	0	2	Contaminated disinfectant solution
(*67*) 2007	*Achromobacter xylosoxidans*	58	0	8	Contaminated chlorhexidine containers
(*68*) 2007	*Ochrobactrum anthropi*	8	0	8	Contaminated ESR tubes
(*69*) 2007	*Candida guilliermondii*	149	0	8	Contaminated blood collection tubes
(*70*) 2007	*Bacillus* species	60	3	3	Dust contamination from ventilation system
(*71*) 2009	*Pseudomonas oryzihabitans*	4	0	0	None identified
(*72*) 2010	*Alcaligenes faecalis*	9	0	0	Contaminated blood collection tubes

[a]NK, not known.

status. The microorganisms most often implicated in pseudomeningitis are aerobic gram-negative bacilli/coccobacilli. The recovery of nonneuropathogens from the CSF in patients with altered mental status should suggest pseudomeningitis. As with other types of pseudoinfections, pseudomeningitis should be suspected when there is a discrepancy between the clinical presentation and the findings typical of the neuropathogen (e.g., *Candida albicans* isolated from the CSF in a neonate with fever and neurologic findings). Since *C. albicans* is a rare cause of fungal meningitis, the *C. albicans* cultured from the CSF should suggest the possibility of pseudoinfection. In pseudomeningitis, the source of specimen contamination is usually due to extrinsic contamination of lumbar puncture kit materials (e.g., slides, CSF tubes, CSF culture media). Alternately, contamination of CSF has occurred during specimen processing in the laboratory. Because of the mortality/morbidity associated with bacterial meningitis, patients with pseudomeningitis are likely to be given empiric antimicrobial therapy (73,*74–76*,77,*78*,79,*80–88*,89,*90–94*) (Table 9-2).

PSEUDOPNEUMONIAS

Mycobacteria, fungi, or, less commonly, aerobic gram-negative bacilli are microorganisms most often responsible for pseudopneumonias. Pseudopneumonias and pseudopneumonia outbreaks have frequently been associated with contaminated bronchoscopes. In practice, due to suboptimal cleaning/disinfectation, microbiologic contamination of bronchoscope parts (e.g., biopsy forceps, brushes), the stage is set for potential pseudopneumonias. Contaminated aqueous solutions used in respiratory therapy as well as topical anesthetics not uncommonly have been implicated in pseudopneumonias/pseudopneumonia outbreaks. Because most pseudopneumonias have been caused by mycobacteria or fungi, empiric antibacterial therapy for pseudopneumonias has been less frequent than with pseudobacteremias or pseudomeningitis (95,*96–114*,115,*116–132*,133,*134–142*,143) (Table 9-3).

TABLE 9-2

Pseudomeningitis

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(*73*) 1973	Gram-negative cocci	4	0	0	Contaminated specimen tubes
(*74*) 1974	Gram-positive cocci	1	0	1	Contaminated slides
(*75*) 1976	*Flavobacterium meningosepticum*	1	0	1	Contaminated skin preparation soap
(*76*) 1978	Gram-negative bacilli	10	0	5	Contaminated slides
(*77*) 1979	Gram-negative bacilli	2	0	2	Contaminated transport media
(*78*) 1983	*Salmonella typhimurium*	2	0	1	Contaminated pipette
(*79*) 1985	Gram-negative bacilli	0	0	1	Contaminated specimen tubes
(*80*) 1985	*Acinetobacter* CDC group VE-1	1	0	1	Extrinsically contaminated culture media
(*81*) 1986	*Sporobolomyces salmonicolor*	3	0	0	Extrinsically contaminated culture media
(*82*) 1987	*Aspergillus species*	1	0	0	Extrinsically contaminated culture media
(*83*) 1988	*Bacillus* species	16	0	3	Contaminated culture broth
(*84*) 1989	*Bacillus* species	1	0	1	Contaminated culture media
(*85*) 1990	Fungal elements	1	0	1	Airborne contamination of staining reagent
(*86*) 1991	*Pseudomonas paucimobilis*	1	0	0	Contaminated culture media
(*87*) 1994	*Gram-positive diplococci*	0	0	1	Contaminated culture media
(*88*) 1995	*Neisseria lactamica*	1	0	1	Contaminated culture media
(89) 1997	*Bacillus* species	1	0	1	Contaminated culture media
(*90*) 1998	Viridans streptococci	1	0	0	Contaminated culture media
(*91*) 1999	*Acinetobacter baumannii*	1	0	1	Contaminated culture media
(*92*) 2002	*Acinetobacter lwoffi*	1	0	0	Contaminated culture media
(*93*) 2002	*Acinetobacter baumannii*	1	0	1	Contaminated culture media
(*94*) 2003	*Flavimonas oryzihabitans*	1	0	1	Contaminated culture media

PSEUDOHEPATITIS AND PSEUDODIARRHEA

Recently, pseudohepatitis has been reported as another type of pseudoinfection due to cross-contamination of pipettes. Pseudodiarrheas, like pseudopneumonias, have been associated with contaminated endoscopes/endoscope cleaning solutions (*144–150*,151) (Table 9-4).

PSEUDOURINARY TRACT INFECTIONS

Urinary tract infections (UTIs) are a relatively uncommon cause of pseudoinfection. Potential mechanisms for pseudo-UTIs are either contamination of the urinary drainage collecting system in catheterized patients or contamination during urine specimen processing in the laboratory. A pseudo-UTI should be suspected if the urinary isolate cultured is not a usual uropathogen or pyuria is not present (*152–157*) (Table 9-5).

OTHER PSEUDOINFECTIONS

Various other pseudoinfections have been associated with contaminated transport media or contaminated disinfectants/soap solutions. Specimen contamination by laboratory technicians has also been reported (*158–163*,164, *165*,166,*167–169*) (Table 9-6).

EPIDEMIOLOGICAL ASPECTS OF PSEUDOINFECTIONS AND PSEUDO-OUTBREAKS

IPs, infectious diseases clinicians, and healthcare epidemiologists should be alert for potential pseudoinfections/pseudo-outbreaks. IPs are often the first to suspect a pseudoinfection. Pseudoinfections should be considered when there is a discrepancy between clinical findings and the usual manifestation of the isolate (at the body site from which specimens have been stained/cultured). Pseudo-outbreaks are clusters of pseudoinfections due to the same isolates from the same body site in different patients (Tables 9-7–9-9).

TABLE 9-3

Pseudopneumonia

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(95) 1999	*Pseudomonas cepacia*	22	0	1	Contamination of topical anesthetic used during fiberoptic bronchoscopy
(*96*) 2002	*Mycobacterium gordonae*	7	0	0	Sputum contaminated by tap water from patients rinsing their mouths prior to specimen collection
(*97*) 2002	*Pseudomonas aeruginosa*	103	0	1	Contaminated fiberoptic bronchoscopes
(*98*) 1978	*Serratia marcescens*	89	1	0	Contaminated fiberoptic bronchoscopes
(*99*) 1979	*Mycobacterium gordonae*	52	0	1	Bronchoscopy specimens contaminated with topical anesthetic dye
(*100*) 1980	*Penicillium*/*Trichosporon* species	8	0	0	Contamination of bronchial washings with topical anesthetic (cocaine)
(*101*) 1982	Coccidioidomycosis	7	0	0	Spore-contaminated slides
(*102*) 1983	*Mycobacterium gordonae*	100	0	0	Bronchoscope contaminated by water/glutaraldehyde
(*103*) 1983	*Penicillium* species	21	0	0	Contaminated bronchoscope biopsy forceps
(*104*) 1984	*Mycobacterium marinum*	5	0	1	Specimens contaminated by laboratory personnel
(*105*) 1977	*Bacillus* species	17	0	2	Contaminated fiberoptic bronchoscopes
(*106*) 1989	*Rhodotorula rubra*	30	0	0	Contaminated brushes used to clean bronchoscopes
(*107*) 1985	*Pseudomonas pickettii*	5	0	NK[a]	Contaminated respiratory therapy solution
(*108*) 1985	*Serratia marcescens*	4	0	NK	Bronchoscopes contaminated by water
(*109*) 1992	*Methylobacterium mesophilica*	7	0	NK	Contamination of fungal culture tubes
(*110*) 1994	*Mycobacterium xenopi*	21	0	0	Contaminated tap water used to disinfect bronchoscopes
(*111*) 1994	*Pseudomonas aeruginosa*	8	0	0	Contaminated bronchoscope cleaning solutions
(*112*) 1994	*Mycobacterium tuberculosis*	3	0	0	Contaminated staining solution
(*113*) 1995	Nontuberculous mycobacteria	9	0	8	Inadequate sterilization of culture system
(*114*) 1996	*Mycobacterium tuberculosis*	12	0	0	Laboratory specimen contamination
(115) 1997	*Legionella pneumophila*	3	0	0	Contaminated tap water
(*116*) 1997	*Mycobacterium chelonae*, *M. avium-intracellulare* *M. gordonae* *M. fortuitum*	28 3 2 1	0	0	Contaminated tap water
(*117*) 1998	*Mycobacterium tuberculosis*	9	0	0	Contaminated laboratory pipettes
(*118*) 1998	*Mycobacterium abscessus*	16	0	NK[a]	Contaminated distilled water used to clean bronchoscopes
(*119*) 1999	*Mycobacterium tuberculosis*, *M. avium-intracellulare*, *Pseudomonas aeruginosa*	12	4	NK	Contaminated bronchoscope biopsy port
(*120*) 1999	*Ralstonia pickettii*	34			Contaminated saline solution used in respiratory therapy
(*121*) 2001	*Mycobacterium gordonae*	5	0	4	Sputum staining solution contaminated by refrigerator water
(*122*) 2001	*Mycobacterium chelonae*, *Methylobacterium mesophilicum*	22	0	3	Contaminated automated endoscope washer
(*123*) 2002	*Mycobacterium szulgai*	31	0	NK	Contaminated water storage tank
(*124*) 2002	*Mycobacterium fortuitum*	19	0	1	Contaminated ice machine

(*Continued*)

TABLE 9-3

Pseudopneumonia (*Continued*)

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(*125*) 2002	*Mycobacterium fortuitum*	47	0	1	Contaminated ice machine
(*126*) 2002	*Mycobacterium simiae*	62	0	NK	Contaminated water supply
(*127*) 2002	*Mycobacterium gordonae*	16	0	NK	Contaminated automated endoscope washer
(*128*) 2002	*Mycobacterium tuberculosis*	6	0	2	Laboratory contamination of specimens
(*129*) 2002	*Pseudomonas aeruginosa*, *Serratia marcescens*	41	0	0	Inadequate bronchoscope sterilization procedure
(*130*) 2004	*Burkholderia cepacia*	4	0	0	Cross-contamination
(*131*) 2005	*Pseudomonas aeruginosa*	16	4	4	Contaminated bronchoscopes
(*132*) 2006	*Mycobacterium gordonae*	18	0	0	Contaminated test reagents
(133) 2006	Influenza A (H5N1)	21	0	1	False-positive testing
(*134*) 2006	*Mycobacterium terrae*	12	0	1	Cross-contaminated clinical specimens
(*135*) 2007	*Acinetobacter lwoffi*	16	0	16	Testing errors
(*136*) 2007	*Bordetella bronchiseptica*	5	0	0	Cross-contaminated blood culture media
(*137*) 2008	*Fusarium solani*	5	0	0	Contaminated bronchoscopes
(*138*) 2008	*Mycobacterium abscesses*	143	0	0	Contaminated culture media
(*139*) 2009	*Legionella species*	4	0	2	Contaminated bronchoscopes
(*140*) 2009	RSV	7	0	6	Test cross reactions
(*141*) 2009	*Legionella pneumophila*	13	1	0	Contaminated bronchoscopes
(*142*) 2009	*Mycobacterium paraffinicum*	14	0	0	Contaminated ice water
(143) 2009	Influenza A (H1N1)	1	0	0	False-positive testing

[a]NK, not known.

TABLE 9-4

Pseudohepatitis and Pseudodiarrhea

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
		Pseudohepatitis			
(*144*) 1981	Hepatitis B virus	7	0	0	Contaminated pipettes
(*145*) 2006	Hepatitis B virus	12	0	0	Laboratory cross-contamination
		Pseudodiarrhea			
(*146*) 1995	*Salmonella hadar*	39	0	0	Contaminated culture media
(*147*) 1999	*Aeromonas hydrophila*	NK[a]	NK	NK	Contaminated endoscopes
(*148*) 1995	*Cyclospora/Cryptosporidia*	280	0	0	Contaminated laboratory equipment
(*149*) 2003	*Bacillus cereus*	3	2	0	Contaminated probiotic medication
(*150*) 2008	Norovirus	25	0	0	False-positive tests
(151) 2009	*Clostridium difficile*	16	NK	NK	False-positive tests

[a]NK, not known.

TABLE 9-5

Pseudobacteriuria (Pseudo-UTIs)[a]

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
(*152*) 1982	*Pseudomonas cepacia*	44	0	0	Contaminated disinfectant solution
(*153*) 1987	*Mucor circinelloides*	1	0	0	Contaminated specimen
(*154*) 1988	*Serratia marcescens*	1	0	0	Contaminated ultrasound jelly
(*155*) 1989	*Trichosporon beigelii*	15	0	4	Contamination of urinary catheter drainage system
(*156*) 1997	*Klebsiella pneumoniae*	6	0	0	Transducer contamination
(*157*) 1998	*Pseudomonas putida*	23	0	NK[b]	Contaminated urine culture kits

[a]UTI, urinary tract infection.
[b]NK, not known.

TABLE 9-6

Miscellaneous Other Pseudoinfections

(Reference) Year	*Microorganisms*	*Number Affected*	*Number Infected*	*Number Treated*	*Cause/Source*
		Pseudokeratitis			
(*158*) 2007	*Aspergillus species*	23	0	0	Dust contamination from ventilation system
		Pseudopharyngitis			
(*159*) 2007	*Streptococcus pyogenes*	10	0	10	False-positive rapid Strep test
		Pseudo-osteomyelitis			
(*160*) 1994	*Candida parapsilosis*	1	0	1	Contaminated bone graft
(*161*) 1994	*Pseudomonas aeruginosa*	7	0	6	Contaminated saline diluent
(*162*) 1995	*Enterococcus faecium*, *E. cloacae*	3	0	0	Contaminated culture solution tubes
(*163*) 1998	*Alcaligenes xylosoxidans*	2	0	0	Contaminated saline
		Pseudoresistance			
(164) 2003	Gram negative bacilli	120	0	0	Antibiotic management program
		Pseudopertussis			
(*165*) 2007	*Bordetella pertussis*	3,666	0	NK[a]	False-positive polymerized chain reactions
(166) 2010	*Bordetella pertussis*	42	0	27	False-positive polymerized chain reactions
		Pseudovaginitis			
(*167*) 2009	*Serratia marcescens*	30	0	0	Contaminated saline solution
		Pseudotracheitis			
(*168*) 2010	*Burkholderia cepacia*	178	0	0	Contaminated disinfectant solution
		Pseudotoxic shock syndrome			
(*169*) 2010	*Clostridium sordellii*	6	0	2	Contaminated anaerobic cultures

[a]NK, not known.

TABLE 9-7

Pseudoinfections: Clinical and Epidemiological Considerations

- *Specimen contamination*
  - Isolate *unrelated* to clinical infection due to blood specimen contamination by skin flora during blood collection (e.g., CoNS culture from blood in a patient with CAP)
- *Colonization vs. infection*
  - Isolate is a *potential* pathogen (at the site cultured) but *no clinical signs of* infection (e.g., *Staphylococcus aureus* cultured from nonpurulent wound [serous/serosanguineous drainage])
- *Possible outbreak*
  - Cluster of same microorganisms cultured from the same site in multiple patients
- *Possible pseudoinfection/pseudo-outbreak*
- Culture of a *usual microorganism from an unusual body site* (for the isolate) (e.g., *Streptococcus pneumoniae* from urine in a patient with a UTI)
- Culture of *an unusual microorganism recovered from a usual body site* (for the isolate) (e.g., *Hafnia alvei* from sputum in a patient with pneumonia)
- *Outbreak pseudoinfection/pseudo-outbreak*
  - The patient's clinical presentation is *concordant* with isolate's typical manifestations (at body site cultured) (e.g., *Serratia marcescens* in blood cultures from multiple patients)
  - Investigate epidemiological aspects and potential common denominators
  - There is a *discrepancy* between the patient's clinical presentation and the isolate's usual clinical manifestations (at the body site cultured) (e.g., *Bacillus cereus* cultured from the CSF)
  - Investigate potential common sources of specimen contamination

UTI, urinary tract infection; CoNS, *Staphylococcus epidermidis*/coagulase negative staphylococci; CAP, community-acquired pneumonia.

TABLE 9-8

Pseudobacteremia: The Clinical Approach

Bacteremia	***Pseudobacteremia***
• Fever/chills	• Fever/chills (if present) *may* be due to ◦ Another infection ◦ Noninfectious disorder ◦ Antipyretic therapy
• Differentiate positive blood cultures from bacteremia	• *Exclude* blood culture (skin flora) contaminants
• *High-grade (2/4–4/4) blood culture* positivity usually indicates bacteremia[a]	• Isolate is *unusual* regardless of site cultured
• *Low-grade blood culture* positivity (e.g., blood cultures with skin flora, e.g., staphylococci (1/4–1/2), *usually not* indicative of bacteremia[a])	• Isolate is *not unusual* but site is *unusual* • There is *discordance* between the patient's *clinical findings* and the isolate's usual manifestations (*at the site cultured*) (e.g., *Pseudomonas fluorescens* bacteremia in a patient with pneumonia[b])

[a]With certain microorganisms (e.g., *Brucella*, *Listeria*), a single positive blood culture is indicative of bacteremia.
[b]*Pseudomonas fluorescens* is not a cause of either community-acquired pneumonia or healthcare-associated pneumonia.

TABLE 9-9

Pseudobacteremia: Epidemiologic Investigation

Potential Sources	*Investigative Approach*	*Items to Culture*
• Skin disinfectants	• Try to find other contaminated lots with the same microorganism as the one involved in the outbreak	• Culture unused disinfectant fluids from lots involved in the outbreak looking for same microorganism cultured from the blood
• Vacutainers, syringes, or needles	• Look for potentially contaminated lots with the same microorganism involved in the outbreak	• Culture unused disposable syringes (inside lumen and plunger) vacutainer threads where needle is attached, and needle hubs involved in the outbreak looking for same microorganism cultured from the blood
• Intravenous fluids	• Look for turbidity in the infusate (turbidity may not be present). Determine which unused IV infusion solutions (bottles/bags) are involved in outbreak	• Culture infusate from bottles/bags of lots involved in the outbreak looking for same microorganism cultured from the blood
• Intravenous tubing/connectors/ filters and disposable IV devices (reused)	• Look for cracks/breaks in equipment (may be gross/microscopic). Collect reused disposable devices (e.g., pressure transducer domes for culture). Culture entry and exit ports and any removable parts	• Culture filters and interior of reused disposable devices involved in the outbreak looking for same microorganism cultured from the blood
• Blood culture autoanalyzers	• Check temperature of injecting needle; assess nearness to open window/ vents. Correlate work shifts with time of culture positivity to determine possible link between events and personnel. Inquire about technician activities/habits during shifts when positive cultures were processed	• Check temperature of injecting needle after heating; when cooled, culture needle tip for same microorganism cultured from the blood • Culture tops of rubber caps/gaskets of blood culture bottles before applying antiseptic to rubber caps/gaskets looking for same microorganism cultured from the blood • Culture transport/culture media from lots involved in outbreak looking for same microorganism cultured from the blood

CONCLUSION

Pseudoinfections probably occur more commonly than they are reported. IPs should undertake appropriate epidemiologic investigations when a potential pseudoinfection is suspected to try and determine the source of contamination during the process of specimen collection and processing. Pseudoinfections should be reported in the literature since reports may provide vital information to guide investigative efforts to determine the source and mechanism of microbial contamination. The early recognition of pseudoinfection is also important to avoid the needless expense and potential complications of unnecessary empiric antibiotic therapy.

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SECTION II
Healthcare Quality Improvement

CHAPTER 10

Creating a Culture of Excellence

Ulises Ruiz and José Simón

This chapter examines how the existing systems of healthcare fall short of what their quality should be, what the evolution of the concept of quality in healthcare has been. It also outlines what approaches are available for creating a culture of excellence that allows for improvement of the quality of care, patient safety, and risk management, through a renewed management approach focusing on the patient as primary customer. The existing challenges for creating a new culture and implementing new approaches are discussed. Integration of approaches for a comprehensive journey toward excellence is advocated.

THE NEED TO IMPROVE THE HEALTH SYSTEM MANAGEMENT FOCUS ON PATIENT SAFETY

There is evidence of an ever-increasing incidence of adverse events in healthcare delivery in many countries. The facts show an alarming reality.

A 1991 Harvard study in the United States found that 4% of patients suffer some kind of harm in hospital: 14% of the incidents lead to death and 70% of the adverse events result in short-lived disability.

In Europe, an "Atlas of Avoidable Death 1985–1989" following healthcare services intervention, carried out by the European Community Working Group on Health Services, was published in 1997. The atlas counts the existing *cases of "unnecessary disease and disability and unnecessary untimely deaths" as measures of the quality of medical care. An excessive number of such unnecessary events was taken as a warning signal of possible shortcomings in the healthcare system which warranted further investigation (1).*

In the year 2000, the Hospitals for Europe Working Party on Quality of Care found 10% of adverse events as a result of hospital admissions.

In its *The World Health Report 2000, Health Systems: Improving Performance,* WHO analyzes the deficiencies of health systems around the world and when dealing with *The Potential to Improve* it states that: *This report finds that many countries are falling short of their potential….There are serious shortcomings in the performance of one or more functions in virtually all countries (2).*

Along this line, the scientific literature has shown the existence of so-called medical errors and how they can be prevented. A large study found that adverse events occurred in 3.7% of hospitalizations, leading to death in 13.6%. Over half of these adverse events resulted from errors that could have been prevented *(3,4).*

Basic considerations about errors in medicine, comparison of the aviation model to the medical model, and offering system changes to be implemented following the Total Quality Management approach can be found in Leape's Special Communication: *Error in Medicine* (5). The number of deaths associated with adverse events was also quantified *(6).*

Facing the problem, the Institute of Medicine (IoM) sponsored a National Roundtable on Health Care Quality, which stated among its conclusions that: .. *Serious and widespread problems exist throughout American medicine. … Very large numbers of Americans are harmed as a direct result. Current efforts to improve will not succeed unless we undertake a major, systematic effort to overhaul how to deliver healthcare*

services, educate and train clinicians, and assess and improve quality (7). Similar findings about the gaps in US healthcare were published as a Final Report to the President *(8)*.

These findings about patient safety in US medical care prompted the IoM to examine this issue through a Committee on Quality in Health Care in America, which released its landmark report *To Err is Human: Building a Safer Health System* in November 1999, establishing for the first time the results of an in-depth study that names medical errors as the nation's leading cause of death and injury. The report indicates that medical errors kill more than 44,000 people in US hospitals each year, which is more deaths than from motor vehicle accidents [43,458], breast cancer [42,297], or AIDS [16,516], and the total national costs of preventable adverse events are estimated between $17 billion and $29 billion.

The IoM report states in its conclusions that the current rates of injury from care are inherent properties of current system designs rather than poor performance by individual providers and that safer care will require new designs, outlining a four-pronged approach to prevent medical mistakes and improve patient safety (9).

Following a direction by the U.S. Presidency, the Quality Interagency Coordination Task Force (QuIC) developed the report *Doing what counts for patient safety: Federal actions to reduce medical errors and their impact*, stating the strategy of identifying prevalent threats to patient safety and reducing medical errors. It provided an action plan to implement the administration's initiative designed to help prevent mistakes in the Nation's healthcare delivery system *(10)*.

A second report of the IoM's Committee on Quality in Health Care in America, *Crossing the Quality Chasm: A New Health System for the 21st century*, addressing additional quality problems focuses on how the healthcare delivery system as a whole can be designed to innovate and improve care in all its quality dimensions for all Americans, considering a basic premise: *The purpose of the healthcare system is to reduce continually the burden of illness, injury* and *disability, and to improve the health status and function of the people of the United States*.

The Committee proposed six aims for improvement: (a) safety, (b) effectiveness, (c) patient centeredness, (d) timeliness, (e) efficiency, and (f) equity. However in assessing the capacity of today's US healthcare system to achieve these six aims, the Committee considers that: *In its current form, habits and environment, American health care is incapable of providing the public with the quality health care it expects and deserves*. It also states that *The current care systems cannot do the job. Trying harder will not work. Changing the system of care will* (11).

Studies conducted in the past decade in several countries discovered the magnitude of such problems in developed countries. The percentage of adverse events attributed to hospital admissions is similar in the different countries: Australia 16.6%, Britain 10.8%, Canada 7.5%, Japan 11%, Denmark 9%, New Zealand 12.9%, and Spain 9.3%.

Consequently, patient safety has become a global issue, much of which is being aimed at designing new approaches for improving healthcare systems worldwide: IoM (USA) report of the Quality Interagency Coordination, to the president, February 2004, WHO: the International Alliance for Patient Safety launched in October 2004, European Union: patient safety as a specific theme within the UK's and Luxembourg's 2005 EU Presidencies, and a *Patient Safety Summit* in November 2005.

All around the world, the performance of healthcare systems is being questioned and approaches to improve their design and performance have recently been directed outside the health sector. This is so, even though traditionally the authority to define and interpret the meaning of healthcare practice has been located solely within the healthcare professions where, for a long time, the know-how of other industrial and service sectors has been considered not applicable.

QUALITY OF CARE—A LASTING ISSUE IN HEALTHCARE

Historically, quality of care has been a major concern for leading healthcare givers. In the Hammurabi code (2000 BC), the physician causing the death of a wounded warrior would have the fingers of his hand amputated. The Hippocratic Oath (IV c.b.c) established standards for medical ethics. In the Middle Ages, throughout Europe physicians and surgeons were organized as guilds and needed recognition to act as such. In the United States, authorization to practice medicine appeared in 1760 and the first medical association, the Medical College, was founded in 1787.

In the modern ages, Florence Nightingale's observations for improving the quality of care in military hospitals during the Croatian war in the 1860s, where varied outcomes puzzled her, are the first attempt for improving hospital care.

The Flexner report in 1910 established standards for medical education, and Codman, a surgeon at Massachusetts General Hospital, introduced the concept of End Result Follow-Up in the decade of 1910. The American College of Surgeons was funded in 1913 to translate Codman's idea into a Minimum Standard for Surgical care and established a Hospital Standardization Program by 1917.

The Joint Commision on Accreditation of Hospitals originated out of this program in 1951, now known as the Joint Commission (TJC), which revised, expanded, and updated the previously established American College of Surgeons standards of care in hospitals.

In the 1960s, both Donabedian and Williamson introduced each in their own way, approaches in healthcare similar to those used in industry for product quality assurance.

Avedis Donabedian established a common denominator framework for both explicit and implicit inspection, defining structure, process, and outcome for care *(12)*. In the early seventies, researchers started investigating the reasons for the large variation found in the process of care among the practitioners, the hospitals, and the geographical regions *(13)*. In the late seventies, research by the Rand Corporation established an experimental design for evaluating the effect of different healthcare insurances on the processes and outcomes of care *(14,15)*.

Also in the sixties, John W. Williamson introduced his *Health Accounting* approach. Unfortunately, it was not well known and not recognized as a valid approach to managing quality in healthcare.

Aware of these changes, the Joint Commission changed its policy and its approach through the Agenda for Change in 1986, establishing criteria beyond the Donabedian framework and looking for the effects of healthcare on the customers *(16)*.

In the early 1980s, a European Community (EC) Concerted Action Project on Health Services and "Avoidable Deaths" initiated research on results from a series of conditions for which mortality is considered largely avoidable, given timely and appropriate medical intervention.

More recently, using developed information systems, data bases have been established where individual professionals and healthcare organizations can search for resources utilization and adherence to care protocols. Reaction of professionals to these data has been mixed. A successful use of this kind of information system has been reported by Wennberg *(17)*.

It is noteworthy to mention that all these key issues are a common rallying point in modern quality improvement approaches and are being considered as such in the so-called Excellence Models (Baldrige and EFQM) and more recently in the 2008 version of ISO 9000.

TJC is applying the same key issues in its approach, but differs in the methodology and tools applied implementing it as organizational criteria. Paul M. Schyve, Senior Vice President, TJC states: "Successful mechanisms are also likely to provide more detailed information about performance … while creating evaluation processes … through incorporating aspects of the Baldrige and EFQM approaches … likely to create a special focus on the safety of care, incorporating aspects of the ISO 9000 approach to quality management" (18).

For the past two decades, the industrial and service sectors have been looking for new managing paradigms in order to improve their performance, and their methods and techniques are being increasingly translated and used in the health sector. At present, patient safety and risk management are the priority issues for all these approaches.

HEALTH PROFESSIONAL, QUALITY OF CARE, AND ORGANIZATIONAL QUALITY

In the past, errors in medicine were considered the responsibility of caregivers rather than addressing underlying system design faults. The blame and punish approach to errors has been prevalent and still is being considered valid in many health systems, services, and organizations. Licenses are lost and health professionals are sued for error-induced injuries. Yet only rarely are these so-called medical errors due uniquely to the carelessness or inappropriate conduct of an individual health professional.

In the health services sector, services provided by healthcare professionals to individuals are central to the professional responsibility of the staff in the provision of care/service. However, responsibility for care and responsibility for running the organization should be clearly differentiated, as well as the dual role of physicians when they are both care givers and administrators of their own clinical service as a unit of the whole organization. Thus, the traditional professional bureaucracy approach currently employed by most hospitals in the developed world is shifting to focusing on organizing rather than on organizational structures.

However, the traditional hospital's dual authority structure may represent a source of tension, stemming from a difference in cultural perspectives between hospital administration and medical staff.

The administrative arm of a hospital is built upon a bureaucratic structure and is therefore more mechanistic in nature, encouraging conformity and efficiency through standardized rules and regulations. The administrator's allegiance is to organizational goals and he/she prefers a proactive approach and long-term goal setting *(19–21)*.

The medical profession, on the other hand, is founded on collegiality. It thrives on clinical autonomy and self-regulation, adopting a more reactive, independent problem-solving approach, with a preference for immediate outcomes. The medical staff possess a strong allegiance to their patients and their profession. Their orientation is more technical in that it is rooted in the natural sciences. As a result, the medical culture has historically tended to resist administrative constraints *(19–21)*.

There is a need to break down the traditional boundaries that separate physicians, hospital administrators, pharmacists, technicians, and nurses by shifting away from a culture of blame and by working together to systematically design safer, more effective, and efficient systems.

Today's healthcare centers and services are complex organizations where the work of each professional is part of a system that has to be constantly in perfect running condition, ensuring an efficient, effective, and safe operation for the benefit and safety of the patient who enters such a system, looking for care (22).

Healthcare professionals, both caregivers and administrators, have been confronted for two decades with a most perplexing issue on how to improve the quality of the healthcare system without losing traditional roles and responsibilities *(23–25)*, while facing an increasing recognition that healthcare providers have to respond to the preferences and values of the patients as their customers *(26,27)*.

As a result, two different perspectives for quality issues in healthcare, currently considered complementary, developed. First was the classical Quality Assurance approach cherished by healthcare providers *(28)* and second, the more recent approach of Total Quality Management imported from the industry and service sectors *(29)*. The healthcare organization continuous quality improvement trade off (CQI) reconciles both approaches through participation and active commitment of both managers and caregivers in the search of quality (22,*30*).

The service perspective for health systems as a nuclear concept for CQI has been, for the past decade, the focus of extensive quality research studies *(31)*. Factors such as customer satisfaction *(32,33)*, return behavior *(34)*, recommendations to others *(35)*, choice behavior *(36)*, and interactions with employees *(37)* have been considered when analyzing quality in health systems.

In the health sector today, approaches such as Quality Control (QC), Quality Assurance (QA), Business Process Reengineering (BPR), Continual Quality Improvement (CQI), Total Quality Management (TQM), and tools/techniques such as ISO 9000:2000, Six Sigma, and Balanced

Scorecard (BSC) are complementary methodologies to achieve what is considered Organizational Excellence as per models such as the Baldrige model in the United States, the EFQM model in Europe, and the Deming model in Japan.

Presently, it is recognized that assuring the quality, safety, and social justice of the care provided to patient-customers is a requirement for both public and private health services, beyond the basic public health measures. Therefore, a new healthcare system has to be designed for the 21st century (11,*38*), recognizing that criteria set in some of the oldest European public health services are also falling short of their expectations.

This urgent call to action for healthcare entities to reengineer their work processes, placing safety as a paramount institutional objective, requires a marked change in healthcare sector thinking, since no substantive enduring changes can be made without successfully remaking the existing organization's culture and reshaping the way members think, behave, and approach their work *(39,40)*.

Culture and Organizational Change

Recognition is growing among healthcare leaders of the need for a culture change within their organizations. Culture change is not a program with a completion date, nor is it a quick fix. It is an ongoing journey—a journey that requires leaders to understand the current state of the organization, establish a clear vision, align behaviors, and instill accountability.

Organizational culture is considered as a manifestation of internalized assumptions or "taken-for-granted" understandings that are shared by an organization's members on such matters as the interactions between humans, institutions, and their environment; therefore, members must find meaning in their professional and personal existence *(21)*. These assumptions are expressed through the values, beliefs, attitudes, behaviors, language, customs, goals, policies, and operations of an organization *(39,41)*.

Historically, in the healthcare sector, a "safety" culture has been one that integrates the Hippocratic maxim of "first do no harm" into the very fiber of its identity, infuses it into the norms and operations of an entire organization, and elevates it to the level of a top priority mission enshrined in formal corporate statements as a guiding principle that governs the work and is applied to its day-to-day practices.

Even though the "patient safety movement" is now clearly underway as generally accepted, "Improved safety must be our specific, declared, and serious aim, beginning at the top of our organizations" (42). It has to be emphasized that culture is at the very heart of an organization and plays a key role in helping organizations respond to the many challenges they now face when searching for a culture of safety as an organizational priority *(43–45)*. Specifically referring to the historical healthcare institutions accreditation culture, safety initiatives cannot be viewed just as a means of complying with yet another external mandate, but must be perceived by the entire membership as being integral to the organization's mission and vision.

Safety must be the dominant characteristic of all high-risk industries, including healthcare. The manner in which a healthcare organization balances the issue of safety with other organizational priorities will shift its culture toward or away from a safety orientation. Safety cannot be treated as an adjunct to the strategic decision-making process. As a general concept, a safety culture is what emerges as a result of a concerted organizational effort to move all cultural elements toward the goal of safety, including an organization's members, its systems, and work activities; it must be front and center and implemented at all levels of the organization *(46,47)*.

To this end, the organization must set safety goals and objectives that apply across the institution and down to the departmental level. Patient safety issues should appear as regular agenda items for discussion and implementation at all levels of the organization in order for safety to be sustained as a priority. Given the sweeping changes that will be necessary to bring about organizational safety in healthcare institutions, now more than ever, good leadership from both clinical and nonclinical arenas is an essential prerequisite to transforming an organization's culture. According to experts in the field of organizational change, no substantive transformations will take place within an organization without the skill, visible commitment, and guiding example of a recognized leadership. Effective leadership sets the expectation and tone for an organization by articulating the institutional vision through empowering messages and by reinforcing "doing the right thing" as a corporate priority *(45)*.

However, healthcare organizations have unique structures and are subject to societal expectations that must be accommodated within an organizational value system. But actually, they share many common challenges and objectives with large corporations in the industrial and service sectors. They all hire people with goals and ambitions, and with expectations as to how they will be treated, accepted, rewarded, and promoted.

All too often, however, employee expectations and those of the organization are not fully aligned. This may be true despite what the organization professes as its objectives. For employees, it is the culture of the organization that is the reality, not the mission statement that hangs on the wall.

Leaders must redefine the meaning of shared responsibility and accountability. Organizational cultures and the training and socialization of the numerous professional groups in healthcare also add to the considerable heterogeneity of value systems within healthcare organizations. These contribute to another challenge confronting healthcare managers—competing or conflicting values within a unit or the entire organization.

Four key elements of values-based leadership are required for healthcare managers who seek to develop as values-based leaders: (a) recognize your personal and professional values; (b) determine what you expect from the larger organization and what you can implement within your sphere of influence; (c) understand and incorporate the values of internal stakeholders; and (d) commit to values-based leadership.

A culture that is quality and safety oriented is characterized by a strong, broad-based working alliance that shares ownership of the organization's vision. The alliance is strengthened by the collaboration of "centers of power" within the organization, represented by critical segments of the hierarchy, including executive and medical staff.

The greater the solidarity and sense of ownership across the organization, the greater the willingness to

share responsibility and accountability for achieving the vision of safety *(48)*.

Everybody in the organization has a task, and all tasks can be considered as being a "process"; "process thinking" defines the new management paradigm.

Process Thinking

Modern health services constitute integrated processes. Care is delivered through core processes that follow the patient from the time of referral/request until after the discharge, including follow-up. Core processes, however, depend on a number of vital inputs in the form of supporting processes. Furthermore, achieving an integrated process approach is critical for assuring efficient healthcare risk management.

The identification of processes, their interaction, and their control and applying a system of processes within an organization are referred to as "the process approach."

A process is a unique combination of people, tools, methods, and materials that add value to an input to attain an output in goods and services.

Regardless of what their end products or services are, the concept of "process" can be applied to each and everyone.

When used within a quality management system, such an approach emphasizes the importance of:

1. Understanding and meeting requirements
2. The need to consider processes in terms of added value
3. Obtaining results from process performance and effectiveness
4. Continual improvement of processes based on objective measurement

Tasks (processes) link together to form systems that are aimed at achieving an end goal whose quality is prescribed in specified requirements and the goal of customer satisfaction. An individual task will have its own set of specified requirements to satisfy. Every task can be analyzed into the constituent elements that it needs or supplies.

The quality of task output depends as much on the quality of the inputs received at the workplace as it does on how well the task is actually performed or, as one might say, how well the process is system controlled. This basic fact has often been forgotten and people have been blamed for results not within their control.

In order to function effectively and efficiently, an organization has to identify and manage different linked activities where the output from one process becomes the input to another one.

The application of a system of processes within an organization, together with the identification and interactions of these processes, and their management, referred to as the "process approach" is the required foundation for establishing a quality management system.

Quality Management Systems

Quality management systems are the basis for the successful operation of an organization; it allows for systems control and systematic management, and process thinking is the nuclear concept for assuring its implementation.

The concept of a quality management system in healthcare emerged in the last century as a new paradigm in the healthcare improvement arena, where concepts such as quality of care, adverse events, cost of care, cost management, customer satisfaction, patient empowerment, and evidence-based practice established a new glossary for healthcare professionals.

Therefore, in the health services sector, requirements for quality management have to be interpreted differently than in industry and other types of business for the following reasons:

- Healthcare services are characterized by the physical and mental involvement of the patient in the process of care provision. Thus, the provision of care is based on the continuous interaction between healthcare professionals (providers) and customers.
- The customer may have little knowledge of the professional aspects of the service delivered. The relationship between the patient and the professional is an unequal one considering the professional input; choices will be highly influenced by the professional.
- Commonly, the purchase and the receipt of health services are separated (so-called third-party payment). Thus, the provider may have to satisfy different quality demands from its two main customers: the patient and the purchaser.
- Healthcare services are characterized by complexities such as relations and interactions between patients, healthcare professionals, health suppliers, insurers, industry, and governmental bodies. In addition, health services are subject to constant change introduced by evolving technologies.

Nevertheless, by the use of a quality management system, processes that are directly or indirectly related to the health services provided can be controlled to meet these requirements.

This new approach to healthcare management has required finding an acceptable methodology for measuring, assessing, and comparing organizational performance through valid standards and recognizing self-assessment and accreditation results, and has been, consequently, a high priority in technically developed countries *(49)*.

Even though the efficacy of quality management as a strategic orientation of the organization that impacts on the immediate and future performance and sustainable competitive advantage appears important, more data are still needed; the findings of a study on small and large hospitals in the United States has reinforced past anecdotal claims of success *(50)*.

Furthermore, the realization of total quality management in everyday practice required the availability of preexisting technologies, standards procedures, and numerical representations on where to anchor the new "customer"-oriented focus culture that confronts the traditional medico-scientific "patient" concept of quality healthcare (51).

Healthcare is more than a decade behind other high-risk industries in its attention to ensuring safety, and safety is the first critical step in improving quality of care considering management of risk a priority.

Patient safety has become a priority issue after the IoM report, and it appears that sectors such as that of aviation

can be a good benchmark for safety and risk management within the healthcare sector (52). It seems, therefore, that healthcare organizations can benefit from learning from other sectors that have implemented risk management in an integral approach toward a continuous improvement culture. Management of risk should be an integral part of any healthcare sector reform.

Risk Management in Healthcare

Traditionally, risk management in healthcare has been driven by insurance and litigation rather than the "holistic" approach that has evolved since the mid-1950s out of the manufacturing and insurance companies. This more formal approach to effective risk management is being accepted as a required management practice both in the private and public sectors and has led to the development of professional risk management associations in many countries *(53)*.

Increased interest in risk management in healthcare has developed since the 1960s when it originated in the United States, and spread to other English-speaking countries like the United Kingdom, Australia, and New Zealand. The growing recognition of the importance of a holistic risk management process has led to the development of generic standards for the healthcare sector in these countries and in some European countries *(54–56)*.

It has been generally accepted that health services is a high-risk business, and even though, at present, management of risk in health services is far behind other high-risk industries such as the aviation industry, management of risk should be considered an integral part of any health services management reform.

Unfortunately, in health services, even though risk is managed continuously, it is not yet managed as systematically as it could be, and therefore, all health services managers and staff should recognize the importance of effective risk management for becoming a modus operandi in any health service institution *(57)*.

Risk management follows a series of process steps, but it is also a system with a culture of consultation and communication. It requires a logical analysis of facts and data, and management structures so that the culture is understood and the process is followed *(58)*.

It also requires a proactive approach. In any system where safety is critical, as in health services, it is not acceptable to wait for loss before identifying the need for improvement. Risk management involves identifying potential problems in advance of the problem becoming critical. Risk should be managed continuously since all decisions involve risk of some kind or another.

The generic risk management process can be applied at all levels of an organization—strategic, operational, and tactical, and it involves the following steps *(59)*:

- *Identification of risks*, involves examining all sources of risk from the perspective of all stakeholders, both internal and external.
- *Analysis of risks*, in order to separate the minor acceptable risks from the major risks, and to provide data to assist in the evaluation and treatment of risks.
- *Evaluation of risks* requires comparing the level of risk found during the analysis process with previously established risk criteria, and establishing priorities for action.
- *Treatment of risks* considering acceptable and the nonacceptable risks.
- *Risk recovery* after an adverse event has occurred.
- *Continuous monitoring and review* are closing the loop steps essential for keeping the process updated.

Risk management should be an integral part of any health service system and should cover risk management activities related to patient care, personnel, documentation, data and communication, management, departmental procedures, and environment (60).

Besides taking accountability of the environment, risk management includes the realization of opportunities for introducing new approaches where a lack of action exposes the organization to unnecessary risks *(61)*.

Risk can arise from both internal and external sources and might include an adverse event during the care process, occurrence of an avoidable complication to the current health issue, occurrence of an avoidable side effect that is not categorized as an adverse event, failure of equipment, a threat to physical safety, a breach of security, a breach of legal or contractual responsibility, and fraud.

Therefore, management of risk and patient safety should be addressed at all levels of the healthcare institution, from the organization's top management to all the process owners. It includes the organization's CEO, the medical, nursing, general administration, and other directors, as well as the intermediate management, that is, heads of administration, clinical departments or services, and technical units.

Total Quality Management

It can be said that the successful implementation of this new quality management approach requires a conceptual break with the traditional interpretation of medical practice quality located solely within the medical profession. The total quality management approach involves every single component and every single person of the healthcare organization, that is, the totality of the organization. Everybody in the organization has a task, and all tasks can be considered as being a "process"; "process thinking" defines the new management paradigm.

Once the quality management systems are operating, the organization is managed according to the established requirements that are set from whatever managing approach the organization has chosen to follow.

OPTIONS FOR IMPROVING HEALTH SYSTEMS

Traditionally, healthcare organizations in the United States and other English-speaking countries have adopted an operating model based on an assessment approach that originated with the American College of Surgeons in 1917 and was further developed by the Joint Commission for Accreditation of Hospitals in 1954, today's JCAHO. Similar approaches for local accreditation of healthcare organizations have evolved in the UK and the Netherlands, and in some other European countries, as well as in Canada, Australia, and South Africa.

However, today there is a movement toward convergence of traditional approaches and managerial approaches for operating and assessing healthcare organizations. Their standardization and comparability within a country and among different countries are becoming a requirement for improving healthcare systems around the world. Political, commercial, and social forces also favor this convergence (18).

At present, healthcare organizations can follow several managing approaches and tools or methodologies that have been useful in industry and service sectors and have shown their promise when applied in the healthcare sector. We will consider the following:

- ISO International Standard for Quality Management ISO 9000:2000 series
- Baldrige National Quality Program: Criteria for Performance Excellence
- European Foundation for Quality Management Excellence Model
- Balanced Scorecard
- Six Sigma
- Lean Management
- Lean Six Sigma

ISO International Standard for Quality Management ISO 9000:2008 Series

Health services are increasingly becoming international markets. Over the past years, there has been a growing awareness that quality management systems may be applied to the health services sector to improve quality and safety, and ultimately promote public accountability for healthcare providers and policymakers.

National approaches vary, and different organizations may choose different methods and approaches to quality management. The ISO standards provide an international standardization framework for quality management systems and their evaluation.

Recognition of quality on the basis of commonly held standards facilitates mutual recognition between organizations. Consequently, there is a strong case for ISO compatibility with national quality management systems in the health services sector, especially in cross-border contracting situations.

The International Organization for Standardization

Established in the manufacturing and engineering industries after the Second World War, the ISO is a worldwide federation with members in 176 countries, and it has awarded over 982,832 international certificates (62).

The ISO has developed over 12,000 standards, of which the ISO 9000 series on quality assurance released in 1987 and revised in 1994 and 2000 has been seen as the most applicable to healthcare *(63)*.

The revised ISO 9000:2000 series, published in December 2000, moved its focus from quality assurance to quality management systems in convergence with the Excellence Models.

The ISO 9000:2000 series comprises a harmonized pair of standards, 9001 and 9004, with the same approach, structure, and vocabulary. ISO 9001:2000 establishes the criteria for certifying quality management systems in organizations, and ISO 9004:2000 offers guidelines for process improvement once quality management systems are operative.

The ISO 9000:2000 series *promotes the adoption of a process approach when developing, implementing and improving the effectiveness and efficiency of a quality management system to enhance interested party satisfaction by meeting interested party requirements (ISO 9001:2000, 0.2 Process approach)*.

The ISO 9001:2000 was revised in 2008 as ISO 9001:2008; ISO 9001:2008 was developed in order to introduce clarifications to the existing requirements of ISO 9001:2000 and to improve compatibility with ISO 14001:2004 (Environmental Management).

ISO 9001:2008 does not introduce additional requirements nor does it change the intent of the ISO 9001:2000 standard. ISO 9001:2008 is intended to be generic and applicable to all organizations, regardless of type, size and product category. It is recognized, however, that not all the requirements of this standard will necessarily be relevant to all organizations. Under certain circumstances, an organization may consider the exclusion of the application of some requirements of ISO 9001:2008 from its QMS. ISO 9001:2008 makes allowance for such situations, through subclause 1.2 Application (http://www.iso.org/iso/home.htm).

The model of a process-based quality management system shown in Figure 10-1 (Quality Management Process Model) illustrates the process linkages covering all the

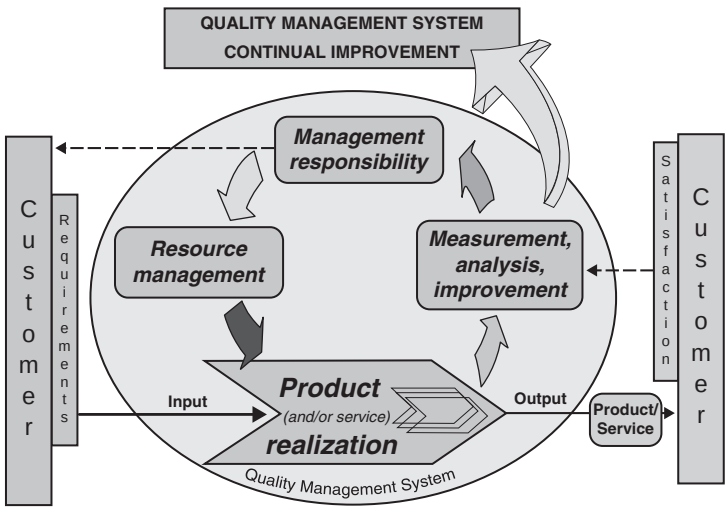

FIGURE 10-1 Quality Management Process Model. (Modified from ISO-9001:2008: Quality Management Systems Requirements, December 2008. http://www.iso.org/iso/home.htm.)

requirements established in the ISO 9000:2000 standard. This illustration shows that customers play a significant role in defining requirements as inputs. Monitoring customer satisfaction requires the evaluation of information relating to customer perception as to whether the organization has met the customer requirements.

ISO Guidelines for Healthcare Respected internationally as a credible system for addressing quality management issues, ISO 9000:2000 was written for industry, and so the language used is often inappropriate for healthcare services and can be confusing when healthcare personnel try to implement a quality system. The need for language clarification led to the US and EU initiatives described below.

USA: **IWA 1-The ISO-Industry Workshop Agreement 1, for Health Care, 2001** An *ISO 9004:2000 Guideline for process improvement in health service organizations* was published by ISO in September 2001 as IWA 1 (ISO's first Industry Workshop Agreement) to be used in defining the fundamentals of the healthcare organization's quality system and improvement methodology, not as a substitute for traditional accreditation (64).

The proposal for these guidelines was made jointly to ISO by the Healthcare Division of the American Society for Quality (ASQ-HCD) and the Automotive Industry Action Group (AIAG) representing the "Big Three" automotive companies: Ford, Chrysler, and General Motors.

The ASQ-HCD considered that the new series ISO 9000:2000, to be published in 2000, were easily applicable to the health sector as a way to implement quality management systems in healthcare organizations and improve the overall quality of care.

IWA 1 addresses the systems' deficiencies and the establishment of needed foundations for performance improvement in healthcare systems and organizations:

> *The goal of this document is to aid in the development or improvement of a fundamental quality management system for health service organizations that provides for continuous improvement, emphasizing error prevention, the reduction of variation and organizational waste, e.g. non-value added activities.*
>
> *(IWA 1 Introduction)*

These guidelines are not intended for use in third-party certification, although it could be used in the improvement of healthcare services through quality management systems in the health sector, certifiable to ISO 9001:2000.

EU: CEN/TS 15224:2005 (E) This *CEN/TS 15224-Guide for the use of EN ISO 9001:2000 in health services* has been published by CEN (European Committee for Standardization) in 2005 and was developed as a Technical Specification (TS) by a task force, CEN/BT/TF 142, of health experts including experienced physicians, nurses, and health administrators, representing different sectors and levels in the European health services sector.

Having identified the problem of language interpretation across many of the healthcare organizations across Europe that are implementing ISO 9001, the group brought together participants from the European Union to ensure the broadest range of experience, expertise, and engagement. The Swedish Standards Institute was nominated to chair the group.

The group's aims were to provide guidance for a more consistent approach to interpretation and consequently easier implementation of the ISO 9001 standard in healthcare, and to raise awareness among healthcare professionals of the importance of a systematic approach to quality management and how this can contribute to patient safety.

The guide provides an interpretation of each clause of the ISO standard intended to aid the healthcare professional when implementing a quality management system. The guide is not intended for certification purposes on its own.

This CEN/TS was limited initially to 3 years. In November 2007, the former task force decided to propose a revision of CEN/TS 15224, aiming at a Sector-specific standard as a European Norm (EN) to be developed by a Project Committee, CEN/Technical Committee 362 PC.

EU:CEN/TC 362 PC— *Healthcare Services—Quality Management Systems—Requirements Based on ISO 9001: 2008*

The task force, renamed CEN/TC 362 PC, agreed to produce a sector-specific standard, an EN, based on ISO 9001:2008 and EN/TS 15224:2005.

The requirements in this EN are based on ISO 9001:2008, with interpretations and specifications for healthcare organizations. The requirements have been modified according to the specific healthcare environment. New requirements have been added when considered relevant. This EN includes requirements related to clinical risk management but does not include requirements on environmental aspects according to ISO 14001.

> *This standard*
>
> *1. Gives requirements for systematic approaches for the organization's needs to produce health services with good quality*
>
> *2. Can be used by management on all levels in the health care organization, internal and external parties including certification bodies to assess the organization's ability to meet patients' needs and expectations*
>
> *3. Is applicable to all health care organizations regardless of structure, organization, owner, size or type of health service provided*

The EN will be ready for publication by the end of 2011.

US Malcolm Baldrige National Quality Program: Criteria for Performance Excellence

Created by the US Congress in 1987, the Malcolm Baldrige National Quality Award (MBNQA) criteria and processes (Fig. 10-2) are being reviewed every 2 years and improved so that they remain relevant and reflect current thinking.

The improvements made for the 1997 criteria are noteworthy. Improvements to the criteria's name, framework, wording, and rules have given them a new look, without changing their essence. Originally, the booklet describing the criteria was called Award Criteria; it is now called Criteria for Excellence.

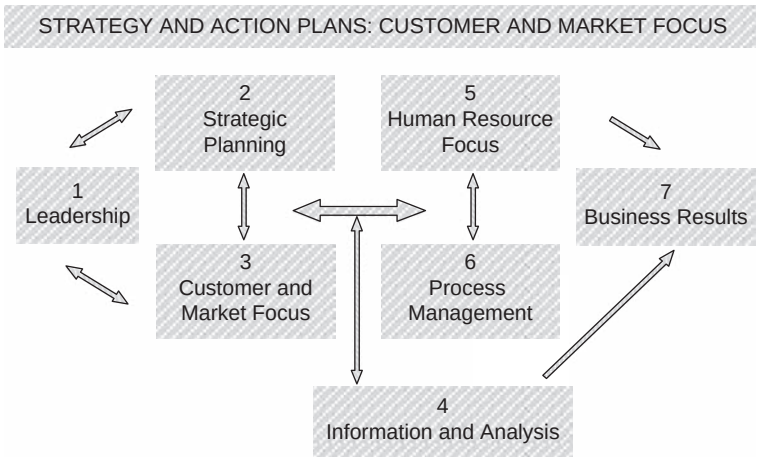

FIGURE 10-2 Malcolm Baldrige Excellence Model. (Redrawn from http://www.nist.gov/baldrige/publications/hc_criteria.cfm.)

The criteria are designed to help organizations use an aligned approach to organizational performance management that results in:

- *Delivery of ever-improving value to customers, contributing to marketplace success*
- *Improvement of overall organizational effectiveness and capabilities*
- *Organizational and personal learning*

The focus of the MBNQA is enhancing competitiveness. Its central purpose is educational; it should encourage the sharing of competitive learning and "drive" this learning, creating an evolving body of knowledge nationally. Its content reflects two key competitiveness thrusts:

1. Delivery of ever-improving value to customers
2. Systematic improvement of company operational performance

> *The criteria are built upon a set of interrelated core values and concepts. These values and concepts……. are embedded beliefs and behaviours found in high-performing organizations. They are the foundation for integrating key business requirements within a results-oriented framework that creates a basis for action and feedback (65).*

Overall, the MBNQA criteria provide an integrated, result-oriented framework for designing, implementing, and assessing a process for managing all operations.

For more than a decade, the healthcare community has been interested in applying the MBNQA criteria to healthcare. Its potential usefulness was advanced by Hertz and als *(66)*:

> *A Baldrige Award program in health care could facilitate and accelerate the extension of the knowledge base of important concepts and results measures for quality management and improvement and could greatly enhance the sharing of successful strategies.*

Since 1998, Baldrige Health Care Criteria have been available to healthcare organizations either to perform a self-assessment as an internal improvement effort or as the basis for an award application.

Self-assessment against all seven Categories of the Health Care Criteria allows the organization to identify strengths and to target opportunities for improving its processes and results.

Submitting an award application has other valuable benefits. Applicants receive a detailed feedback report based on an independent external assessment conducted by a panel of specially trained and recognized experts.

The framework of the Baldrige Business Criteria for Performance Excellence is adaptable to the requirements of all organizations including healthcare organizations. However, it is not assumed that these requirements are necessarily addressed in the same way.

The Baldrige Model in Health Care has been used in several healthcare organizations in the United States, and its implications have been discussed over the past decade.

Early experiences show that the Baldrige criteria can be used by healthcare organizations to conduct internal evaluations, resulting in improvement of the organization's effectiveness *(67,68)*. The Baldrige management framework was found to be useful for identification of areas of improvement and areas of achievement within a sample of VHA hospitals *(69)*.

Empirical evidence has been provided from 220 hospitals that the 19 dimensions of the Baldrige criteria lead hospitals to improvement on some dimensions of performance *(70)*.

Therefore, a specific way for addressing the Baldrige criteria has been developed as Health Care Criteria for Performance Excellence. This adaptation to healthcare is largely a translation of the language and basic concepts of business excellence to similarly important concepts in healthcare excellence.

According to the *2009–2010 Health Care Criteria for Performance Excellence:*

> *The Health Care Criteria for Performance Excellence have evolved significantly over time to help organizations address a dynamic environment, focus on strategy-driven performance, address concerns about governance and ethics, and, most recently, consider the key decisions driving both short-term success and long-term organizational sustainability.*

The Criteria have continually progressed toward a comprehensive, integrated systems perspective of overall organizational performance management

(http://www.baldrige.nist.gov/HealthCare_Criteria.htm).

Since 2002, the Malcolm Baldrige National Quality Award has been received by eight US healthcare institutions (http://www.baldrige.nist.gov/index.html).

EU EFQM Excellence Model

EFQM was founded in 1988 by presidents of 14 major Europeans companies, with the endorsement of the European Union. At present, more than 600 organizations all over Europe are involved. The main aim is to promote quality management through the external assessment of an award scheme (the European Quality Award and national awards, inspired by the example of the Baldrige Award in the United States). A reference model that could be used for self-assessment was established in 1989: the *European Foundation for Quality Management Excellence Model, 1989* (*www.efqm.org*).

The EFQM Excellence Model (Fig. 10-3) is the most widely used organizational framework in Europe and extends to global markets, reaching more than 30,000 organizations worldwide. Used as a tool for assessment, it delivers a picture of how well the organization compares to similar or very different kinds of organizations. Used as a management model, it can be used to define aspirations for the organization's capability and performance.

The EFQM Excellence model is a nonprescriptive framework for understanding the connections between what an organization does, and the results it is capable of achieving. It is used to structure a logical and systematic review of any organization, permitting comparisons to be made with a high-performing organization. It is also used to define what capabilities and resources are necessary in order to deliver the organization's strategic objectives. The model has its roots in the philosophy of total quality management and that recognizes that there are many approaches to achieving sustainable excellence.

The EFQM Model framework is structured on the following fundamental concepts:

- Customer focus
- Leadership and constancy of purpose
- Management by processes and facts
- People development and involvement
- Continuous learning, innovation, and improvement
- Partnership development
- Public responsibility

The premise on which the model is built is that excellent results with respect to performance, customers, people, and society are achieved through leadership driving policy and strategy, people, partnership, resources, and processes.

The enablers' dimensions ultimately lead organizations to excellent results: excellence in customer satisfaction, employee satisfaction, impact on society, and key performance results.

The EFQM Excellence Model is a practical tool to help organizations establish an appropriate management system and measure where they are in their path toward excellence, helping them to understand the gaps and then stimulating solutions.

The model has been revised periodically. The previous Excellence Model 2003 has recently been reviewed and revised to align the framework with current business needs and trends as the 2010 Model. All changes were presented at the EFQM Forum in September 2009 (http://ww1.efqm.org/en/EFQMForum2009/tabid/291/Default.aspx).

In the revised model, the emerging trends and topics that have more emphasis are "creativity and innovation," "sustainability," "corporate governance," "organizational agility," "risk management," "promoting products and services," and "supplier management.' Sustainability is now firmly on the agenda of management boards around the world. EFQM supports organizations in defining what sustainability means, providing approaches for its implementation and ensuring consistency between apparently conflicting responsibilities toward shareholders, employees, and society.

The model conceptualizes organizations by discerning five enablers' dimensions and four results dimensions in an operative structure.

Further information about the changes for the 2010 Model can be found through the Transition Guide at http://www.efqm.org/en/PdfResources/Transition_Guide.pdf.

In 1996, EFQM developed a specific guide for using the European Excellence Model in healthcare, but in 1999

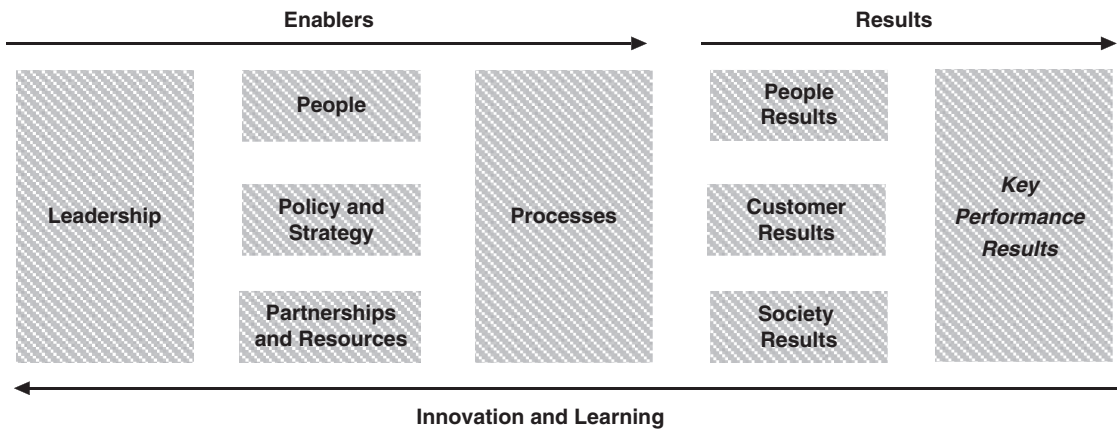

FIGURE 10-3 EFQM Excellence Model. (Redrawn from http://www.efqm.org/en/PdfResources/EFQM_Ex_Mod_Teaser.pdf)

the model was revised and a common framework is being applied to all sectors, industry as well as private and public service sectors, including healthcare.

Within the EFQM membership, there are about 40 members who are health practitioners, both from the public and the private sector communities, notably in Austria, the Netherlands, Spain, and Turkey among others, and there are a significant proportion of members who are linked in some way or other to the health sector.

The European Excellence Model is being used in healthcare organizations of different European countries (*71*,*72*,73,*74*,*75*).

Balanced Scorecard

The BSC, in combination with the Models of Excellence, is a useful tool to guide strategy development and implementation in healthcare organizations, bringing added value to the Total Quality Management approach (http://www.balancedscorecard.org/Home/tabid/36/Default.aspx).

The BSC (Fig. 10-4) is a framework proposed by Robert Kaplan and David Norton in 1992 to facilitate translation of strategy into action. It summarizes succinctly in a short document a set of leading and lagging performance indicators grouped into four different perspectives: financial, customer, internal processes, and learning and growth *(76–81)*.

The BSC has evolved from its early use as a simple performance measurement framework to a full strategic planning and management system. Kaplan and Norton describe the innovation of the BSC as follows:

> *"The balanced scorecard retains traditional financial measures. But financial measures tell the story of past events, an adequate story for industrial age companies for which investments in long-term capabilities and customer relationships were not critical for success. These financial measures are inadequate, however, for guiding and evaluating the journey that information age companies must make to create future value through investment in customers, suppliers, employees, processes, technology, and innovation."*

The BSC helps organizations translate strategy into operational objectives that drive both behavior and performance. It describes and helps implement and manage strategy at all levels of an organization by linking objectives, initiatives, and measures to that organization's strategy.

It is also a process that the organization uses to foster consensus, alignment, and commitment to the strategy by the management team and the people within the organization at large.

It provides an enterprise view of a healthcare organization's overall performance by integrating financial measures with other key performance indicators around customer (patient, physician, and payer) preferences, internal clinical and business processes, and personal learning, development, and growth (*82*,*83*,84).

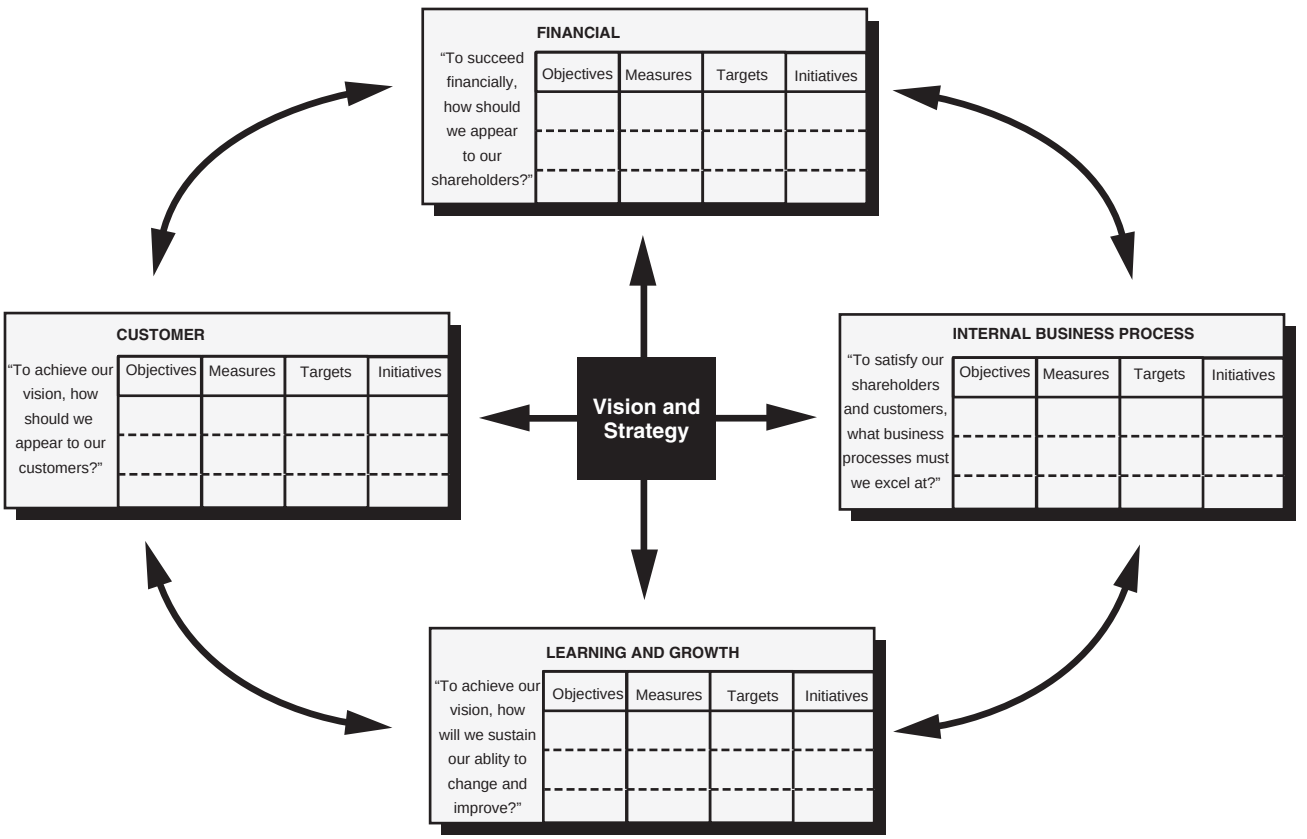

FIGURE 10-4 Balanced Scorecard framework. (Redrawn from Kaplan RS and Norton DP. "Linking the balanced scorecard to Strategy." *California Management Review*. 39/1 (Fall 1996): 53–79. ©1996, by The Regents of the University of California. Reprinted from the California Management Review, Vol. 39, No. 1. By permission of The Regents.)

A first Best Practices Conference on *Saving lives, saving money: and how healthcare organizations use the Balanced score card to achieve results* was held in Cambridge, Massachusetts, USA, in April 2002, and it focused on how healthcare organizations use the BSC to achieve results; it was organized by the Balanced Scorecard Collaborative (http://www.bscol.com).

The BSC is being used in healthcare institutions. It has been reported that the scorecard (a) is relevant to healthcare, but modification to reflect industry and organizational realities is necessary; (b) is used by a wide range of healthcare organizations; (c) has been extended to applications beyond that of strategic management; (d) has been modified to include perspectives, such as quality of care, outcomes, and access; (e) increases the need for valid, comprehensive, and timely information; and (f) has been used by two large-scale efforts across many healthcare organizations in a healthcare sector, which differ, namely, in the units of analysis, purposes, audiences, methods, data, and results (84).

Six Sigma

Six Sigma methodology was pioneered at Motorola Corporation in the 1980s. The methodology is based on rigorous statistical process control. It augments the traditional quality tools with exacting statistical analysis and a systematic problem-solving approach, targeting the root causes of variations, and redefining processes for long-term results. It strives to produce products and services with only 3.4 defects per million, meaning Six Sigma in statistical terms (http://www.isixsigma.com/).

Six Sigma can, thus, be considered a business quality improvement tool through improving process performance. It requires four steps, where data collection and analysis become the core of the Six Sigma projects. The Six Sigma methodology is known as DMAIC:

1. Define
2. Measure
3. Analyze
4. Improve
5. Control

It should be emphasized that Six Sigma is also a business culture approach, since the goal is to establish a culture of quality improvement at all levels of the organization by implementing improvement actions designed by specifically trained working teams.

In the healthcare sector, Six Sigma, as a philosophy seeking near-zero errors and being, somehow, an extension of failure mode and effect analysis, is ripe for its implementation by healthcare managers and practitioners concerned for patient safety and are already implementing a total quality management approach (*85*,*86*,87).

Six Sigma methodologies can help toward the abovementioned goals and can change the face of modern hospital and healthcare delivery systems. It can reduce variability and waste, translating to fewer errors; improve customer satisfaction; and provide better processes, greater patient satisfaction rates, and happier and more productive staff. The popularity of Six Sigma is growing in the healthcare industry.

At present, to reduce the errors and to move toward perfection, most of the hospitals are now pursuing Three Sigma or Four Sigma quality levels.

It is thought that the healthcare industry will not be able to achieve Six Sigma and should be aiming for Four or Five for most processes. However, Six Sigma is an achievable target for healthcare. There are multiple healthcare organizations that have currently achieved the Six Sigma level of performance, and certainly, it is not acceptable at many healthcare organizations to be at the Four to Five Sigma level, and they are striving to achieve the Six Sigma level of improvement. Errors in healthcare processes by sigma level are shown in Table 10-1 (Source: GE Healthcare).

Furthermore, figures in Table 10-2 illustrate that being 99% effective is just not good enough for appropriate patient safety in healthcare delivery.

Six Sigma is being increasingly used in healthcare (http://healthcare.isixsigma.com). Its use has been recently assessed through a national survey of Six Sigma programs in US healthcare organizations. The survey supplements the literature supporting the effectiveness of the Six Sigma methodology in healthcare (87).

Furthermore, a first 2-day conference on *Six Sigma for Health Care Providers* in San Francisco, in September 2001, up to the WCBF's 8th Annual Lean, Six Sigma and Process Improvement in Healthcare Summit in 2009 (www.wcbf.com/quality/5091) reflects the interest for this approach in healthcare.

TABLE 10-1

Errors in Healthcare Processes by Sigma Level[a]

Sigma Level	*Patients with Misplaced Personal Items*	*Coding Errors Requiring Correction*	*Phone Calls Exceeding the 2-min-on-Hold Limit*	*Defects/Million Opportunities*	*Percent Yield*
3 Sigma	3,660 every day	770/d	257 each day	66,800	93.32000
4 Sigma	340 every day	72/d	24 each day	6,210	99.34900
5 Sigma	12 every day	13/wk	5 each week	230	99.97700
6 Sigma	6 every month	10/y	3 each year	3.4	99.99966

[a]GE Healthcare.

TABLE 10-2

99% Error Free Is Not Enough for a Patient Safety Policy

3.8 Sigma: 99% Error Free	*6 Sigma: 99.99966 Error Free*
(10,700 error opportunities/ million)	(3.4 error opportunities/ million)
Wrong prescriptions 200,000/y	Wrong prescriptions 68/y
Incorrect surgery 5,000/wk	Incorrect surgery 1.7/wk
Wrong landing approach 2/d	Wrong landing approach 1/5 y

Lean Management

Similar to Six Sigma, the Lean approach focuses on process performance, making it possible to achieve dramatic improvements in cost, quality, and time. However, whereas Six Sigma is focused on reducing variation and improving process yield by following a problem-solving approach using statistical tools, Lean is primarily concerned with eliminating waste and improving flow by following the Lean principles and a defined approach to implement each of these principles.

Lean is a thinking process more than a simple to-do list of tools; the role of the leaders within the organization is the fundamental element of sustaining the progress of lean thinking. Lean thinking can be described as a closed loop, as shown in Figure 10-5.

The core idea of lean involves determining the value of any given process by distinguishing value-added steps from non–value-added steps, and eliminating waste (or *muda* in Japanese) so that ultimately every step adds value to the process.

Many of the key principles were pioneered by Henry Ford, under the termed "flow production." Following World War II, the Toyota Motor Company adapted Ford's principles as a means of compensating for its challenge of limited human, financial, and material resources. They, therefore, revisited Ford's original thinking and invented the Toyota Production System (TPS), which was one of the first managerial systems using these principles throughout the enterprise to produce a wide variety of products at lower volumes and with many fewer defects than its competitors.

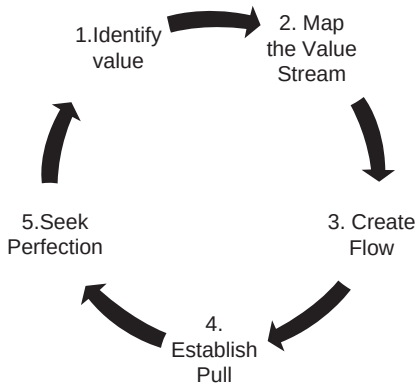

FIGURE 10-5 Lean thinking. (Redrawn from http://www.lean.org/WhatsLean/Principles.cfm.)

For Toyota, TPS was not just a production system; it was also a business system, incorporating all aspects of bringing a product to market, including design, supplier management, production, and sale. As such, it means organizing and managing product development, operations, suppliers, and customer relations using principles, practices, and tools to create precise customer value—goods and services with higher quality and fewer defects—with less human effort, less space, less capital, and less time than the traditional system of mass production.

The basic principles of TPS development have been:

- Add nothing but value (eliminate waste)
- Center on the people who add value
- Flow value from demand (delay commitment)
- Optimize across organizations

Much of the TPS way of thinking is based on the work of W. Edwards Deming, his philosophy of Total Quality Management and his interpretation of the original Shewhart *control chart*. He taught, among other things, that managers should stop depending on mass inspection to achieve quality and, instead, focus on improving the production process and building quality into the product in the first place.

The term *Lean* was first coined in 1988 at the MIT Sloan School of Management and the thought process of Lean was described by Daniel T. Jones, James P. Womack, Daniel Roos, and members of the International Motor Vehicle Program at MIT (*88*). In a subsequent publication *Lean Thinking*, James P. Womack and Daniel T. Jones described what are considered the five Lean principles *(89)*.

The five-step thought process for guiding the implementation of Lean techniques is easy to remember, but not always easy to achieve (http://www.lean.org/):

1. Specify value from the standpoint of the end customer by product family.
2. Identify all the steps in the value stream for each product family, eliminating, whenever possible, the steps that do not create value.
3. Make the value-creating steps occur in tight sequence so the product will flow smoothly toward the customer.
4. As flow is introduced, let customers pull value from the next upstream activity.
5. As value is specified, value streams are identified, wasted steps are removed, and flow and pull are introduced, and then begin the process again and continue.

The Lean methodology has a bias for action to rapidly improve processes and drive results and is used to accelerate the velocity and reduce the cost of any process (be it service or manufacturing) by removing waste.

Lean implementation is therefore focused on getting the right things, to the right place, at the right time, and in the right quantity to achieve perfect work flow while minimizing waste and being flexible and able to change.

Lean methodology is founded on a mathematical approach known as Little's Law:

$$\text{Lead time of any process} = \frac{\text{Quantity of things in process}}{\text{Average completion rate / unit of time}}$$

The lead time is the amount of time taken from the entry of work into a process (which may consist of many

activities) to the time the work exits the process. Lean contains a well-defined set of tools that are used to control and then reduce the number of things in process, thus eliminating the non–value-added cost driven by those things in process. Lean also contains tools to reduce the quantity of things in process.

Lean Healthcare System Leaders today in a wide range of industries, nonprofit organizations, government agencies, healthcare, and other areas are finding ways to apply the principles of Lean as a means of producing goods and delivering services that creates value for the customer with the minimum amount of waste and the maximum degree of quality.

Lean thinking is not typically associated with healthcare, where waste—of time, money, supplies, and good will—is a common problem. But the principles of Lean management can, in fact, work in healthcare in much the same way as they do in other industries *(90)*.

Proper implementation of the five simple Lean tools and techniques—5 Whys, 5S, Kanban, Visual Controls, and Standard Work—can help any organization launch its Lean transformation.

Hospitals cannot continue to operate as they have in the past. Some hospitals started experimenting with Lean methods in the 1990s and, at present, there are many examples of the positive impact Lean is having in hospitals throughout the world reflected in diverse worldwide networks such as, among others, *Australasian Lean Healthcare Network; Agency for Healthcare Research and Quality Innovations Exchange; Institute for Healthcare Improvement; NHS Confederation; Lean Enterprise Institute, United States;* and *Lean Enterprise Academy, United Kingdom*.

To maximize value and eliminate waste, leaders in healthcare must evaluate processes by accurately specifying the value desired by the user; identifying every step in the process (or "value stream") and eliminating non–value-added steps; and making value flow from beginning to end based on the pull—the expressed needs—of the customer/patient *(90)*.

By reducing the percentage of non–value-added work and thereby increasing the percentage of value-added work through a Lean transformation, hospital quality levels can improve significantly, and huge cost savings can be realized. Cost savings can then be redistributed to other QI initiatives. By concentrating efforts on identifying, acknowledging, and eliminating non–value-added work or waste, hospitals can realize their most fundamental goal of providing superior quality healthcare to their patients *(91)*.

It follows to redesign the patient journeys through their hospital. The results include eliminating unnecessary waits for patients, a drastic reduction in length of stay, no longer wasting staff time, freeing up emergency and elective capacity, and slashing the overtime and agency burden. Focusing on the patient journey and effectively synchronizing all the support activities also provide the essential context for delivering higher quality and safer care for patients (*92*,*93*,94,*95*).

It has to be emphasized that Lean Thinking in healthcare is neither about cost, nor about "efficiency" or staff cuts; it is about improving the safety and quality of healthcare by applying a series of continuous incremental improvements. Therefore, a hospital's Lean transformation cannot be an overnight success story, as changing old mindsets and organizational cultures takes time.

Lean Six Sigma

A combination of Lean and Six Sigma has synergy and creates a win–win situation. Both approaches require a process focus, and both include customer drivers, either to define what needs to be improved (Six Sigma) or to define value (which then drives process improvement).

Lean seeks to improve flow in the value stream and eliminate waste, doing things quickly. Six Sigma uses the DMAIC framework and statistical tools searching root causes to understand and reduce variation. It is about doing things error free.

A combination of both provides an over-arching improvement approach incorporating powerful data-driven tools to solve problems and achieve rapid process improvement with added value at lower cost. Potentially, this could increase productivity, improve quality, reduce costs, improve speed, create a safer environment for patients and staff, and exceed customer expectations *(96)*.

The key is to find the optimal combination of both approaches, adopting the Lean idea of focusing on what adds value and then using Six Sigma tools to help understand and reduce variation when the value stream is established.

The philosophy of Lean provides the strategy and creates the environment for improving flow and eliminating waste. Six Sigma helps to quantify problems, makes evidence-based decisions (this prevents wasting time on anecdotal evidence), helps to understand and reduce variation, and identifies root causes of variation to find sustainable solutions.

The UK NHS Institute for Innovation and Improvement has found Lean Six Sigma a promising improvement methodology that incorporates the best of Lean and the best of Six Sigma.

INTEGRATED APPROACH

Healthcare institutions have not been generally considered up to now as companies that might be managed efficiently. They have been administered rather than managed. The healthcare organizational structure requires nuclear changes so that modern accepted managerial approaches to excellence can be successfully applied. Therefore, it seems that finding the appropriate management systems for healthcare organizations in technically developed countries is becoming a high priority.

It seems that taking time to find an acceptable methodology for measuring, assessing, and comparing organizational performance through valid standards, as well as recognizing self-assessment and accreditation results in valid measures of performance *(97)*.

The traditional approach to external evaluation of healthcare organizations was a breakthrough when the American College of Surgeons established the Hospital Standardization Program in 1917. In 1950, a growing number and complexity of hospitals required revision of the standards and support of the entire medical and hospital field, resulting in the establishment of the JCAHO in 1951 *(98)*. However, the performance of the healthcare

organizations in the United States was challenged by the 1999 report of the IoM in the United States.

Accepting the fact that voluntary certification and accreditation represent a necessary recognition by service payers of healthcare organizations as suitable providers, self-assessment driving solely to certification or accreditation by an external organization should not be the only way to manage the knowledge gathered from this exercise.

The most important drivers of breakthrough improvement are leadership, creativity, and innovation. Executives must lead and mentor their people in the right directions and assure that their actions are linked to strategic performance. They need to deploy limited resources to the highest impact areas and not try to solve every problem in the hospital.

To accomplish this, they need to understand the existing improvement methodologies and how to integrate their approaches into an overall business improvement strategy.

However, generally, through the last half of the past century, the debate for identifying the best quality management approach in healthcare systems has focused on the their differences and benefits and hardly on their potential synergies *(99,100)*. Recently, **s**imilarities and differences among TQM, Six Sigma, and Lean as effective quality management models in healthcare systems have been discussed (101).

Piece-meal application of quality control methods, quality assurance schemes, and quality management philosophies, and their assessment through diverse external evaluation approaches has proved their insufficiency for dealing successfully with quality management systems and with patient safety.

Integration of the diverse methods, schemes, philosophies, and approaches for establishing a culture of self-assessment and continuous quality improvement in a journey toward excellence seems to be an alternative to be explored.

To move from the old organizational structures of healthcare institutions to a new organizational and managerial design, deliberate transitional steps are necessary. If carefully designed and well placed, these transitional measures will permit policy to evolve along consensual lines and can signal the overall direction of change, reassuring stakeholders that change is taking place smoothly and that the most immediate problems are being dealt with. It also helps to ensure that longer term systematic objectives are not compromised by short-term political imperatives *(102)*.

It has been shown that interactive integration of some of the best accepted quality management approaches can be carried out successfully according to the following scheme (103):

1. The initial step implies the early implementation of process thinking as the basic stepping stone for the continuous quality improvement journey toward excellence. It means that in order to function effectively and efficiently, an organization has to identify and manage all its linked activities, or processes, since the output of one is generally the input of another.
   The system of processes within the organization has to be defined and managed. The new ISO 9000:2008 promotes the adoption of a process approach, and therefore, at present, ISO 9000:2008 is the best tool for implementing "process thinking" and quality management systems in an organization.
   Understanding, systematizing, and controlling processes is the best way available today for preventing processes and system failures as well as human errors, as it is done in the high-risk sector of aviation. It could be a reliable approach for increasing patient safety in the healthcare sector.
2. As a second step, once the quality management system is in place, the healthcare-specific standards like those offered in the traditional healthcare accreditation approaches, should be implemented.
3. Once the organization is working effectively, efficiently, and safely, an excellence model can be established as a reference for the organization's pursuit of excellence.
   Initially, using an Excellence Model for self-assessment, an organization will have a good understanding of its own strengths and weaknesses at the process level. Scoring according to the model will offer a reference point for internal comparisons for periodical self-assessments and improvement actions and also for external benchmarking.
4. The BSC can be used at this point to provide the strategic focus needed to prioritize action and allocate resources.
   The Six Sigma approach can be easily integrated into existing quality management efforts through detailed data analysis, becoming part of the strategic plan, so that benefits such as reduction in costs of poor quality and improved profitability will be obtained.
5. Lean Management seems to be, up to now, a very effective scheme for managing healthcare systems and can be implemented as an alternative single approach for identifying, acknowledging, and reducing the percentage of non–value-added work, so that hospitals can realize their most fundamental goal of providing superior quality healthcare to their patients and redistributing the resulting cost savings to other quality of care and patient safety initiatives.

CONCLUSIONS

1. In general, all over the world, the performance of the healthcare systems falls short of acceptable requirements.
2. These shortcomings are not related to the economic health of the country or to its expenditure in healthcare.
3. Adverse events during healthcare focus priorities on patient safety and risk management.
4. In order to improve, approaches used in other sectors such as the service sector and the industrial sector can be applied to the healthcare sector, where, in fact, the concept of quality management systems has emerged as a new paradigm for managing healthcare systems and organizations.
5. Process thinking is the nuclear concept for the quality management systems and is the focus of most of the recognized approaches to quality improvement.

6. All of the existing approaches aim at continuously improving the organization, and many can integrate synergistically in a stepwise journey in pursuit of excellence. Therefore, integration of ISO 9000, Excellence Models, BSC, Six Sigma, and, more recently, Lean Management approaches, together with traditional accreditation, offer a logical stepwise journey toward excellence.

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CHAPTER 11

Selecting Improvement Projects

David Birnbaum

Epidemiology, as a process for logical inquiry, has much in common with systems analysis or industrial engineering (also known as management engineering) (1). Similar perspectives and complementary methods shared by these disciplines make them ideal for managing healthcare quality improvement (2). However, to succeed, these disciplines must be applied in a supportive setting and on worthwhile quality improvement projects. There are underlying principles and precedents of both successes and failures; these can serve as important guides to anyone contemplating extension of epidemiologic skills from familiar areas of infection control to less familiar areas of quality improvement. Healthcare as a business sector has lagged far behind the cutting edge of other industries in advancing its methods to assure and improve service quality. Healthcare organizations have generally failed to use the full potential of epidemiology in discerning alternative strategies and informing consensus on best practices; exploring the natural course of conditions; performing cost-benefit and effectiveness analyses; surveying patient preferences; measuring organizational effectiveness; establishing indicators, criteria, and other measures; and designing and evaluating surveillance systems (3,4). Although it is noteworthy and unfortunate that epidemiology is not listed among team leadership in seminal reference books and motivating reports (5,6), this reflects the simple fact that relatively few healthcare epidemiologists rose to embrace challenging new opportunities.

Although some of the language in general underlying principles for selecting improvement projects might introduce foreign concepts, the principles are not complicated. Mozena and Anderson (7) list the following essential criteria to consider:

- Impact on patient care or external customer
- Impact on favorable patient outcomes
- Magnitude of potential cost savings
- Cost of implementation
- Difficulty of implementation
- Ability to measure performance of process
- Potential benefits outweigh cost of the project
- Deals with key business issue
- High error rate
- Availability of data
- Impact on profitability
- Potential for success
- Impact on ongoing quality
- Ability to quantify results
- High visibility to customers or patients
- Elimination of rework
- High risk to patients or employees

A National Demonstration Project on Quality Improvement in Health Care reported that nomination and selection of projects often are run by steering committees (a quality council) but that the best ideas come from "listening to the voice of the customer" (in which external customers are patients who receive services and internal customers are staff members who collectively provide and support service delivery) (8). Surveying customer opinion is an active way to listen; design and conduct of surveys are familiar grounds in epidemiology. Epidemiologists also may be more aware than most about the distinction between measuring patient satisfaction, patient safety, and service quality of healthcare (9). Relating service attributes to customer expectations may involve less familiar but still simple techniques such as Quality Function Deployment matrices (a simple two-dimensional matrix in which the strength of association between specific items and categories of customer expectations is summarized) (10,11). However, all of these criteria and methods are disjointed considerations. What is needed to bring efficiency and acceptance is an effective system for their implementation.

GUIDANCE FROM HISTORICAL PRECEDENTS

Three precedents bear consideration as effective systems to select improvement projects. Although two were successful quality improvement systems, they failed to persist and become today's North American gold standard models. Williamson's Achievable Benefits Not Achieved (ABNA) system to identify and prioritize potential projects (12) has a remarkable track record among alternatives (13). Similarly, the so-called Denver Connection of the same era is a story of successful amalgamation and reorganization of two hospitals in a way that put quality improvement supported by real-time performance data

analysis as the centerpiece of medical staff departmental meetings and continuing medical education (encouraged by board-level involvement while the usual array of advisory committees was eliminated) (14). Finally, the Institute of Medicine's (IOM's) Model Process for semiquantitatively ranking alternative projects is instructive for its mathematical approach (15).

Dr. John W. Williamson developed systems for health accounting and ABNA during an impressive body of work that spans decades on the faculty of the Department of Health Services Administration at the Johns Hopkins University School of Hygiene and Public Health, Medicine and Medical Informatics at the University of Utah School of Medicine, Regional Medical Education Center of the Salt Lake Veterans Affairs Medical Center, and service on government commissions. Health accounting, conceptualized in the early 1960s, is "a management model to integrate continuing education and patient care research into an ongoing cyclic function to systematically improve the quality of medical care" (16). It is an evidence-based outcome-focused approach that selects project priorities through ABNA, a formal, efficient process refined in the 1970s. Although proven effective and cost-effective in a wide range of applied research and demonstration projects at the American National Institutes of Health, Veterans Administration, and elsewhere, Williamson acknowledges that the most successful application of his system to enhance national quality is in the Netherlands (16). The fact that Williamson's name and work are unfamiliar to so many throughout North American hospitals and healthcare leadership is hauntingly reminiscent of the history of W. Edwards Deming. Deming's influence took decades to return to North America, heeded by American manufacturers only after Japan capitalized on Deming's leadership to outperform their American counterparts (and later heeded by health service organizations decades after that!) (17). Williamson stresses the following:

1. The importance of applying principles of epidemiology, sampling, and simple statistical testing to QA-focused reviews
2. The necessity of a multidisciplinary team approach to QA, in which the consumer was the most important member of the team
3. The need to use structured group judgment methods for establishing priorities, criteria, and standards as well as QA action decisions under the usual conditions of factual uncertainty
4. The need for a unique set of statistical methods for QA that allowed comparison of measured results against consensus standards that reflected reasonably achievable projected outcomes

Consistent with concurrent surveillance methods that have become a mainstay of contemporary infection surveillance programs, Williamson recognized long ago that chart-based audits as a basis for quality assurance may be misleading and severely limit the potential impact of programs to improve quality (16). His ABNA process consists of selecting a team (ideally 7–11 persons, including "at least four knowledgeable and respected staff physicians" and representatives of other functional areas and the lay public) and then supporting that team through two 2-hour meetings 3 to 4 weeks apart. The first meeting is a training session simulating the later priority-setting session. A master list of potential topics developed during the training session, together with team recommendations on additional "data, literature, or consultation" required, provides an indication of support materials that will be needed at the second session. Ideally, these are gathered during the 3- to 4-week hiatus. There are seven tasks in the priority-setting meeting:

1. Introductory remarks by the moderator clarify meeting purpose, tasks, and timing of the 2-hour session and review the ABNA framework (5 to 10 minutes).
2. A simple four-column form is distributed so that individual team members can each list as many topics as they wish, listing along one row for each topic:
   a. exactly who (what group) will benefit
   b. for what health problem
   c. from what action(s)
   d. by which provider(s)

   A cue sheet is provided to give examples of various patient characteristics, health problem characteristics, provider characteristics, and (inter)action types that might be considered. Time is given to work individually (10 minutes).
3. Each team member, sequentially, is then asked by the coordinator to nominate one problem from their list. The coordinator develops a summary chart; in addition to the four columns identified in step two, when acting as coordinator, I found it helpful to list in two additional columns an indication of whether the intervention is known to work (nature of evidence for efficacy or effectiveness) and whether it is feasible (information on cost, cost-effectiveness, case study, etc.). Discussion is limited to clarification at this stage, and the process repeats until all the most promising ideas from each member's list are presented (30 minutes).
4. Individuals then vote in an "initial weights" column on their form to assign a priority rank (high to low on a five-point scale) for each project nominated (5 minutes).
5. The coordinator then collects the votes, anonymously recording both initial individual weights and their sum for each nominated project. This information, superimposed on the summary chart, is projected back to the group (10 minutes).
6. Discussion of results, one topic at a time, then examines whether priority ranking is tightly or widely dispersed, the strength of evidence, and other detailed considerations. On completion of comprehensive discussion, members are then asked to vote again on every topic, in a "revised weights" column on their form. The coordinator again collects and records votes anonymously (50 minutes).
7. The highest-ranked ABNA topics are then forwarded as recommendations from the team, along with any further recommendations for additional data or evidence required for any of the topics. The meeting is adjourned, the team thanked for completing its work, and special teams of qualified individuals then take responsibility for moving approved projects forward.

Meanwhile, also in the 1970s, radical changes under the amalgamation of the medical staffs at Denver's Swedish

Medical Center and Porter Memorial Hospital occurred. Radical change was needed because as Dr. William Robinson, Director of Medical Education, noted, "In spite of the hundreds of physician hours devoted to medical staff activities, little actually was accomplished. It was almost impossible to demonstrate that quality of care was in any way influenced by the physicians' repetitive, duplicative, unrewarding medical staff activities." The usual litany of committees was reduced to just three (executive, professional activities, and credentials). A reduced number of subcommittees composed of small numbers of individuals, the bulk of whom were not physicians, served these committees, and much of the quality-related work was shifted from committees to medical staff departments supported by the work of subcommittees or research and education department employees. Medical staff members were strongly encouraged to ask questions at their departmental meetings about quality issues, and then make policy decisions based on evidence delivered soon thereafter (answers supplied through real-time research capacity in their own institution) (14).

Although successful into the 1980s, by the turn of the 21st century, the Denver Connection was so far dismantled that it no longer even existed in the institutional memory of Porter Hospital's present administration! Porter and Swedish, partners of the so-called Denver Connection formed in 1972, went their separate ways in 1992. These two hospitals serving health needs of southeast Denver had remained separate corporate entities, yet collaborated successfully for many years following formal merger of their medical staff organizations. That merger was initiated by the doctors, not by the administrators, for the purpose of improving quality of care. Administrative support grew following demonstrated successes, and the hospitals cooperated in division of complementary health services, instead of duplication of what the other offered solely to compete. That was before big business entered sickness. Ultimately, poor quality of management in emerging, large, managed-care corporations led to unexpected deficits in profitability of operations, and corporate vision shifted to preoccupation with that debt. A grass-roots anticompetitive way of serving the community's health needs could not sustain itself in the face of powerful market forces and growing business empires awash in corporate debt. Personal ideologies in administrative leadership compounded the difficulty of making effective alliances, and mistrust grew where open communication once thrived. Key participants later interviewed conveyed a sense of loss and regret, a realization they participated in something very unique and beneficial that was lost for illogical reasons ("nobody had any appreciation what we were doing was special or unique … only in retrospect we came to appreciate the specialness of what we were doing."). The influence of accreditation programs in this saga was noteworthy only for its lack of influence (18). It is tempting to speculate that this visionary effort thrived because it followed characteristic principles that seem to distinguish great companies from others (19) and that the Denver Connection ultimately fell when it strayed from core values and these fundamental principles.

The IOM Model Process to set priorities in health technology assessment addresses similar dimensions as ABNA, but in a more quasinumeric than nominal group consensus manner. The IOM priority score for each technology, instead of being assigned by consensus ranking, is calculated as $\Sigma W_1 \ln S_1 + W_2 \ln S_2 + \ldots + W_7 \ln S_7$, where W_i represents the criterion weight and S_i the criterion score for ($i = 1$–7).

1. Prevalence (e.g., cases per 1,000 persons)
2. Burden of illness (e.g., difference in quality-adjusted life years of individuals with vs. without the condition under consideration)
3. Cost (total direct and indirect costs per person with the condition)
4. Variation in rates of use of the technology (coefficient of variation)
5. Potential to change health outcome (subjective assessment on a five-point scale)
6. Potential to change costs (subjective assessment on a five-point scale)
7. Potential of assessment result to inform ethical, legal, or social issues (subjective assessment on a five-point scale)

The first three criteria are objective measures; the remaining four are subjective and are addressed by one or more expert panels. Criterion weighting values are arbitrary choices; the process described has an expert panel select one criterion as least important, which then is assigned weight of one. Mean weights given by panel members for each of the remaining criteria, relative to the least important one, then determine the other six weights. After discussion of results to resolve any wide disagreement, results of a second vote are final. Pilot test results with small conventional and mailed response panels are examined in the IOM report, which gives the following values: $W_1 = 1.6$, $W_2 = 2.25$, $W_3 = 1.5$, $W_4 = 1.2$, $W_5 = 2.0$, $W_6 = 1.5$, and $W_7 = 1.0$. Logarithms of criterion scores are used to make the model multiplicative rather than additive, thus responsive to relative rather than absolute differences in scores (algebraically, the formula can be restated as $\Sigma W_i \ln S_i$, which equals the product ΠS_i^{wi} for $i = 1$–7). Subjective item scales, therefore, run from a value of one for least likely to five for most likely.

Health accounting provided a philosophy, the Denver Connection a forum, and ABNA a method all consistent with today's emphasis on evidence-based practice and continuous quality improvement (CQI). What lessons should one take from these all-but-forgotten precedents? Williamson reflects on lessons learned from 25 years of experience (16), naming three premises on which quality assurance or improvement is based and five principles that evolve from it:

- Because it is an inherent management function encompassing both effectiveness and efficiency of any healthcare activity, the main issue is not whether but how well it is conducted.
- As a healthcare management function, it involves the same clinical problem-solving principles whether applied at an individual, institutional, regional, national, or international level.
- As a scientific endeavor, it must be built on a foundation of the health sciences integrated with other disciplines

(including philosophy, quantitative disciplines such as epidemiology, education, social sciences, business and management, economics, and informatics).
- It must start with clarification of individual and organization values, must be supported by management of incentives, and will be successful to the extent that it is internally motivated.
- Although it must be organized along sound management and administrative principles, it will be successful to the extent that responsibility for excellence moves closer to the bedside.
- It is inherently interdisciplinary, so it will be successful to the extent that it is comprehensive in membership and vision.
- Attention should be focused on carefully targeted problems selected by consensus methods, not dispersed in shotgun approaches or restricted to narrow problems defined by audit of single data sets.
- It must be subjected to ongoing analysis of costs and accomplishments to ensure that it maintains effectiveness and adapts to changing times.

Clearly, these premises and principles are not consistent with chart audits conducted behind closed doors, at accreditation-mandated intervals, by discipline-specific advisory committees that regarded patients or their families as recipients of care rather than members of a team. They also are not consistent with quality being viewed as a destination (viz., no evidence of negligent care) rather than as a journey, or with centralizing authority in a quality council. The Denver Connection clearly represented a journey outside the map of externally mandated routes and vaguely defined directions. It decentralized autonomy, predated by decades the Health Care Financing Administration (HCFA) (subsequently renamed the Centers for Medicare and Medicaid Services, CMS) instigated removal of infection control committees as a Joint Commission on Accreditation of Healthcare Organizations (JCAHO, subsequently renamed The Joint Commission, TJC) requirement, inspired one other hospital to disband that committee despite accreditation standards (20), and set a coordination role for administration in an era when command and control was the norm. In short, neither of these precedents was typical of conventional programs during their era, and they documented successes in their publications. Instructively, ABNA and the Denver Connection challenged but failed to change convention and in this one is warned about the importance of establishing protective legislative, board, and administrative political perimeters around vital programs (17,18).

SURVIVAL AS A MANAGER OF CHANGE

Discussion of timing and perception is not obvious in the previous list by Mozena and Anderson but is inherent in the ABNA process. Healthcare epidemiology often succeeds when implementing interventions that are motivated by frank outbreaks of disease, but may not be as successful in convincing administrators to adopt new programs during normal times when competing against business cases or political agendas of line departments. One can take lessons from the social policy cycle recognized in public administration and must recognize the importance of marketing to create a sense of need before attempting to satisfy that need ("deals with key business issue" criterion). Later steps recognized in the policy cycle are familiar ground to the evidence-based nature of epidemiology; however, an initial stage of creating shared understanding of any problem (because all parties can agree on the data but disagree on the theory or meaning explaining that data and, therefore, on direction of actions required) and, second, articulating that vision to ensure sufficiently widespread acceptance or readiness to act are politically astute *(21)*:

- Identify issues
  - Problem defined
  - Problem articulated
- Policy analysis
  - Collect relevant data and information
  - Clarify objectives and resolve key questions
  - Develop options and proposals
- Undertake consultation
- Move toward decisions
- Implement
- Evaluate

Healthcare must operate in a businesslike manner but must retain at its core the values inherent in principles underlying healthcare professions, because care cannot be viewed simply as a commodity to sell. "Patients do not value healthcare *per se*, they value health; "health care" is an intermediate good that people consume (based on expert advice) in hopes of deriving a health benefit. Many patients, and especially those under duress of serious illness, do not have the time, interest, or ability to gain sufficient knowledge to be equally informed as their healthcare provider. So, no matter how much information patients receive, choosing your surgery is never going to be like buying a car" *(22)*. Our primary focus should be on improving quality, not on cutting cost. If experience in other industries is any guide, improving quality will lead to cost reductions. To motivate change in a business environment, program managers should consider principles of economic application to recognize the diminishing effectiveness of different arguments (excellent arguments: improving operating costs, increasing production rates, and improving product quality; good arguments: improving customer relations, improving labor relations, and increasing job pride; fair arguments: reducing injury rate, giving legislative compliance, and reducing liability potential; and poor arguments: enhancing public relations or providing personal satisfaction) *(23)*. The experience of clinical microbiology laboratory directors who have been successful at proving cost-effectiveness as a new business skill is pertinent *(24)*. Administrators may be more interested in projects that promise to lower variable rather than fixed costs, work with cost rather than charge data, and show benefit using adjusted cost estimates. Adjusting cost estimates for a diagnosis-related group (DRG) probably is not familiar to most healthcare epidemiologists, but epidemiologists are aware of the "shifting base" bias potential that is inherent in an indirect adjustment (standardization)

calculation *(25)* that hospital administrators tend to apply to compensate for differences in severity of patients within DRGs. A stronger than ever emphasis on transparency and public reporting also is pertinent. The task today is to improve quality while also rebuilding public confidence in the safety of patient care—a task that requires honest, balanced reporting in context to explain what is being done well, what could be done better, why certain projects are given priority over others, and what progress is being made.

MANAGEMENT OF CHANGE TO ACHIEVE QUALITY MANAGEMENT

Quality management is a sustained, systematic approach to improving quality. Quality management requires an ability to chart the best courses (a task for which the technical skills of epidemiologists generically are well suited) and to help all workers pursue specific targets along those courses. The latter task requires communication and organizational development skills and methods complementary to epidemiology. Chapters in this section are integrated and meant to be read together, unlike chapters of other sections in this book. They offer complementary insights from experienced professionals of various backgrounds, and it is important to recognize that no one background likely offers all the attributes needed for successful improvement project management. A framework for considering roles, strengths, and weaknesses is provided in Figure 11-1.

STARTING ON A PATH THAT LEADS TO SUCCESS

When introducing CQI programs, it is essential to avoid early failures, because they are a dispiriting enemy of progress in promoting continuous improvement. Rather than lose momentum by failing at the start, it is better to begin with small yet meaningful projects, be successful, attract champions who sustain progressive projects, and mobilize new converts into groups that do more over the long term.

Two aspects identified in previous lists, *availability of data* and *collect relevant data and information,* are fundamental to decision criteria, policy cycles, and design of surveillance programs. Quality of healthcare data (in terms of precision, accuracy, and reliability) has been considered extensively by epidemiologists *(26–29)*. Therefore, this is an aspect in which the core "process" knowledge of healthcare epidemiologists can guide decisions about which noninfectious disease problems to study, whether to use available data sources, and which supplementary surveillance tools should be developed. Although other specialists probably have more "content" knowledge than the healthcare epidemiologist about a given noninfectious disease, interdisciplinary collaboration between process and content experts is more likely to lead to success.

Benchmarking often is mentioned as a source of guidance. Recent volumes describe successful and cost-effective improvement projects. Although the best way to select the right improvement projects for a given organization is to understand the needs, expectations, resources, culture, and values of that organization and its own customers, there also is merit in benchmarking the success of others. Early volumes of *Quality Profiles (30)*, for example, profile a selection from more than 1,100 quality improvement initiatives; these were chosen by an advisory board of experts in quality improvement from health plans, trade associations, government organizations, and individuals from National Committee for Quality Assurance (NCQA) and Pfizer (the sponsors of the volume). According to its authors, case studies selected for the second edition demonstrate more sophistication and more refined use of data than initiatives in the first edition (18 months earlier). Since then, additional volumes have been made available (at *http://www.qualityprofiles.org/index.asp*). Forum opportunities represent another source of research funding, benchmark information, and networking opportunities. A noteworthy example is the Breakthrough Series Collaboratives and Pursuing Perfection program *(http://www.ihi.org/IHI/Programs/StrategicInitiatives/PursuingPerfection.htm)* of the Institute for Healthcare Improvement. Clinical practice guidelines provide another basis for evaluating quality of care to identify opportunities for improvement *(31)*, an area in which the Agency for Healthcare Research and Quality (*http://www.ahrq.gov*) has a lead role, but it is important to remember that "listening to the voice of the customer" implies attempting to delight customers with unexpected extras of valued quality rather than focusing just on fixing deficient care. Comprehensive reference books devoted to this topic have now been produced by professional societies, such as the American College of Medical Quality *(32)*.

CHECKPOINTS ALONG THE JOURNEY

Ensuring that project teams have sufficient time, skill, and information to make critical assessment of data from internal or external sources is an obvious but often overlooked checkpoint. Another checkpoint is influence of those teams among peers and organizational hierarchy. Availability alone is not sufficient justification for allocating resources. Credibility, willingness, and readiness form a better basis for selecting team members for each project; processes for team activities must be efficient and effective; and training needs of teams must be met. If outside assistance is needed to bring in expertise with quality improvement methods, then a resource to consider is CMS-supported Quality Improvement Organizations (see *http://QIOSynergy.org*).

Last, but not least, the journey must be chronicled in ways that are meaningful to all stakeholders. Deming's famed 14 Points for Management and the enumeration of "Deadly Diseases" advocate driving out fear, shifting focus from short to long term, and eliminating recognitions based on essentially random chance allocations, or just doing well as an individual in the system at short-term

Focus	*Allied Health Care Professions*						*Quality Professionals from Other Industries*			
	Medical or Nursing Directors	Primary Providers		Clinical Support		Healthcare Epidemiologists	With Professional Degree		Without Degree	
		Doctors	Nurses	Laboratory Technologists	Respiratory, Physical, or Occupational Therapists		System Engineering	Other Engineering	Green or black belt course	Certified by exam
Leadership, Education, and Communication										
System Design & Innovation; Knowledge of Clinical Setting										
Process & Outcome Measurement (monitoring, surveillance)										
Process Improvement Technical Skills (eg: CQI, Lean, 6-Sigma)										
Other (content vs. process expertise)										

FIGURE 7-2 A Framework for Successful Improvement Project Management.

quotas rather than attempting to improve the system. Thus, Deming advocates eliminating practices such as traditional "employee of the month" and subjective annual employee performance rating *(33)*. In their place, CQI activities, supported by administrative models oriented toward building learning organizations and reinforced by team-building morale-boosting recognition for actual achievements, have merit. As part of your chronicle, an annotated inventory of current quality-related activities should be maintained. If quality assurance and improvement are viewed in the context of a surveillance system to detect and prevent adverse trends, then familiar methods to evaluate surveillance system performance readily apply. A three-part form developed for this purpose is shown in this chapter (Table 11-1A–11-1C).

Similarly, in each project, maintaining a newsworthy log of project progress and events should be an archivist's responsibility. This inventory and log can be used to promote interdisciplinary communication throughout an organization and its surrounding community, and to serve as a basis to continuously monitor the value and cost-effectiveness of current measures. In addition, as a gauge of institutional culture and readiness to change, these documents can provide insight into the types of projects likely to succeed or fail at any given period in an organization's journey toward quality. Since its inception in 1987, thousands of businesses have used the more structured Malcolm Baldrige Award (*http://www.quality.nist.gov/*) application process as a way to chart progress on that journey. Education and health categories were formally added to the award program in 1999; in recent years, healthcare organizations predominate among the types of applicants. The comprehensive Baldrige program provides a wide-ranging audit, as do other award programs patterned after it, but a less formal annotated chronicle of an individual institution's own history also has unique worth. We may have been slow to recognize the importance of sharing success stories in social and scientific exchanges *(34)*.

External review programs that acknowledge competence and reveal organizational deficiencies or other opportunities for improvement include familiar accreditation programs, International Organization for Standardization (ISO) certification, the American Baldrige Award, the Japanese Deming Award, and others. They are not identical; thus, it is important to appreciate the relative merits of the model that each establishes. It has been noted that "Baldrige and JCAHO standards are both based on the concepts of CQI but differ in so many ways that direct comparison is difficult" *(35)*. Baldrige criteria have tended to be more general; accreditation agency criteria have been more specific and prescriptive. The Baldrige Award also differs from ISO 9000:94 certification, but the new ISO 9000:2000 standard reportedly has the same focus as Excellence Models such as Baldrige or European Foundation for Quality Management (see Chapter 10 for more detail). As the Baldrige Web site described, "The purpose, content, and focus of the Baldrige Award and ISO 9000[:94] are very different. The Baldrige Award was created by Congress in 1987 to enhance US competitiveness. The award program promotes quality awareness, recognizes quality achievements of US organizations, and provides a vehicle for sharing successful strategies. The Baldrige Award criteria focus on results and continuous improvement. They provide a framework for designing, implementing, and assessing a process for managing all business operations. ISO 9000 is a series of five international standards published in 1987 by the ISO, Geneva, Switzerland. Companies can use the standards to help determine what is needed to maintain an efficient quality conformance system. For example, the standards describe the need for an effective quality system, for ensuring that measuring and testing equipment is calibrated regularly and for maintaining an adequate record-keeping system. ISO 9000 registration determines whether a company complies with its own quality system. Overall, ISO 9000 registration covers <10% of the Baldrige Award criteria." The Baldrige information Web pages also acknowledge that both the U.S. Baldrige Award and Japan's Deming award are based on the same purposes (to promote recognition of quality achievements and to raise awareness of the importance and techniques of quality improvement), but note that the Baldrige Award focuses more on results and service, relies on the involvement of many different professional and trade groups, provides special credits for innovative approaches to quality, includes a strong customer and human resource focus, and stresses the importance of sharing information (see *http://www.quality.nist.gov/* for more information about the award). Another recent development is HF-2 Business Operating Systems (BOS) for Health Care Organizations: Requirements for Process Improvements to Achieve Excellence *(36)*, which evolved from an Industry Workshop Agreement 1 effort to make ISO 9000 more specific to the healthcare industry.

LEADERSHIP

Epidemiology has long been recognized as providing the scientific foundation for public health and the evidence-based resource for health planning. Unfortunately, dissatisfied customers rather than healthcare epidemiologists have been leading recent movements to initiate change and improvement in healthcare. Although the automotive industry has quality problems of its own, it recognized 20 years ago that healthcare tops its list of direct costs in the construction of automobiles *(37)*. Now 20 years later, having not seen significant innovation and progress within healthcare, the automotive industry's division within the American Society for Quality (ASQ) became the driving force for radical redirection in healthcare leadership by demanding ISO certification of its suppliers and funding consensus meetings to support initiatives of ASQ's Health Care Division that led to ISO's Industry Workshop Agreement 1 (6). There is no reason for epidemiologists to take a back seat while others drive, for as Dr. John Millar, vice-president of the Canadian Institute for Health Information, observed to a room filled with healthcare epidemiologists and infection control professionals during a symposium on "Collaborations to Improve Health Care Quality," "you folks have more expertise than most people who could be in this game" *(38)*.

Quality Program Survey Form (TABLES 11-1A–C)

TABLE 11-1A

Section I: What Does Your Program Assure?

Quality assurance involves systems of monitoring to confirm that a specified level of quality is delivered, and systems of controls to maintain or adjust performance. As an initial step in designing an appropriate program, you need a clear understanding of current objectives and an inventory of existing activities. Section I should be completed, independently, by all participants (e.g., the manager, director, and administrator for each quality program).

Completed by: Date (dd/mm/yy): / /

1. Please attach a copy of your statement of program philosophy, purpose, or mission.
2. Please complete the following section to list your current goals and objectives; date of last review/revision; associated monitoring and/or control activities; and whether these are mandated by external requirements. Continue on the reverse side if necessary.

Goal/Objective #1:_____

Date Adopted (dd/mm/yy): / /

Monitoring Activities: Control Activities:

Circle as appropriate: STATUTORY, PROFESSIONAL, ACCREDITATION requirement

Goal/Objective #2:_____

Date Adopted (dd/mm/yy): / /

Monitoring Activities: Control Activities:

Circle as appropriate: STATUTORY, PROFESSIONAL, ACCREDITATION requirement

Goal/Objective #3:_____

Date Adopted (dd/mm/yy): / /

Monitoring Activities: Control Activities:

Circle as appropriate: STATUTORY, PROFESSIONAL, ACCREDITATION requirement

Goal/Objective #4:_____

Date Adopted (dd/mm/yy): / /

Monitoring Activities: Control Activities:

Circle as appropriate: STATUTORY, PROFESSIONAL, ACCREDITATION requirement

(Adapted from MMWR 1988;37(S5) By Applied Epidemiology)

TABLE 11-1B

Section II: How Is It Being Assured? Program Structure

For each of the Monitoring Activities listed in Section I, please answer the following questions. Use one page for each activity under each numbered Goal/Objective. Section II should be completed, independently, by the program manager (e.g., Infection Preventionist), the program director (e.g., Healthcare Epidemiologist), and the administrator to whom they report.

Completed by: Date (dd/mm/yy)://

3. This page relates to Goal/Objective #_____ Activity_____
4. Is there written documentation (policy, procedure, instruction, etc.) covering this activity?
   Yes *No* If yes, please attach a copy or indicate location.
5. How will this activity help to assure quality? (check all that apply)
   __ Establishes baseline levels/monitors trends
   __ Detects incidents to prevent recurrence
   __ Detects incident-producing conditions before injury or damage results
   __ Other (specify):
6. How will the information be used? By whom? Give examples
7. What information is requested or collected?
8. What sources of information are used (e.g., medical record, lab reports, incident reports, professional activity summary reports, committee records, etc.)?
9. Who has responsibility for reporting or collecting this? Describe the flow of information.
10. What percentage of actual events is detected?
    - Have program sensitivity and specificity been measured formally?
    - How are minimum sample sizes or sampling frequencies determined?
11. After data analysis, to whom are reports sent? How frequently? Who has authority to act on this information?
12. Have objectives for this activity changed over the past 2 years; if so, why?

TABLE 11-1C

Section III: How Well Does the System Work?

For each monitoring activity listed in Section II, please answer the following questions. Use one page for each numbered Goal/Objective activity. Section III should be completed by your program director; questions 19 and 20 should also be answered by your administrator.

Completed by: Date (dd/mm/yy)://

13. This page relates to Goal/Objective #_____ Activity_____
14. What method(s) is (are) used to analyze the data collected?
15. What are the time delays from actual incidence to
    - Detection: _____ (unknown)
    - Reporting: _____ (unknown)
    - Analysis: _____ (unknown)
    - Dissemination: _____ (unknown)
    - Action: _____ (unknown)
16. What problems or biases can affect the activity?
17. What are the costs (in dollars or hours per week) for data collection, analysis, and dissemination? Please indicate whether the figure is known (i.e., charted to a cost center), estimated, or unknown.
18. Does this cost include everyone involved?
19. What decisions or outcomes has the activity effected? Check and provide examples:
    - ___ Prompted review or corrective action:
    - ___ Validated good performance:
    - ___ Provided support for a (change in) policy or procedure:
    - ___ Influenced allocation of resources:
    - ___ Influenced educational priorities/programs:
    - ___ Other:
20. Is there a mechanism for ongoing evaluation of this activity's value? If yes, give details.

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CHAPTER 12

Conducting Successful Improvement Projects

Marisel Segarra-Newnham and Ronald G. Berglund

In the *Third Edition of Hospital Epidemiology and Infection Control* edited by C. Glen Mayhall, there are two chapters (Chapters 10 and 12) on quality methods and the selection of improvement tools to bring about effective healthcare changes (1,2). In Chapter 10, a basic improvement method using design, monitor, repair, and improve was reviewed and applied to a surgery center. As part of this method, root cause analysis (RCA), is/is-not analysis, benchmarking, brainstorming and affinity diagrams, and a plan-do-check-act (PDCA) cycle were utilized (1).

Chapter 12 on "Selecting Change Implementation Strategies" described the use of a PDCA cycle of improvement applied to a variety of projects including decrease in medication errors in the veterans affairs (VA) health system with the use of computerized physician order entry (CPOE) and bar-coded medication administration (BCMA) and the implementation of an outpatient intravenous antibiotic therapy program, among others. Issues that were handled particularly well and lessons learned from mistakes along the way were reviewed (2).

In this edition, we will combine Chapters 10 and 12 of the previous edition, will provide additional tools that can be utilized for improvement projects, and will describe potential applications for these tools. We hope to provide ideas on how to select the most effective tool to conduct a successful improvement project. We will review recent literature on BCMA and CPOE implementation. We will review PDCA and apply the method to the medication reconciliation process. The A3 process will be introduced and applied to patient transport within a medical center. A summary table will provide a listing of various tools and techniques along with potential applications.

THE VETERANS EXPERIENCE OF IMPLEMENTING BCMA

The impetus to create a paperless medication ordering system continues unabated since the late 1990s. CPOE systems are expected to affect the high proportion (56%) of medication errors that occur during prescribing *(3)*. A medication error is defined as "a failure in the process of treatment that leads to, or has the potential to lead to, harm to the patient" *(4)*. A goal of Institute of Medicine (IOM) was to have handwritten orders eliminated by 2010. However, currently only about 10% of hospitals have a CPOE system; nonetheless, this number had doubled in 10 years (5). The VA health administration is usually given as an example of a system that successfully implemented CPOE. Transition to a computerized medical record is not easy since old habits are hard to break. Consistency in enforcing the use of technology and having administrators and supervisors who themselves use and understand the system are key.

Designing good computerized systems should be a clear goal, because using automation that has been poorly designed and tested will only make it easier and faster to achieve undesirable results. Automation appears to work well for repetitive tasks while the human can spend their time with more complex tasks that require discernment, communication, cooperation, creativity, and flexibility *(6)*. Humans are still needed to make complex decisions *(7,8)*. These systems will avoid reliance on memory, recall, or vigilance. While the latter issues may not be totally eliminated, they should not be the main way to avoid errors and patient harm. In the planning process it is imperative to include as many end users as possible so that their opinions and desires can be incorporated into the process, and leave their "finger prints." This nurtures the sense of "ownership" giving incentive to participate in the new process despite the unknowns and frustrations.

While CPOE eliminates the hassles of trying to decipher a prescriber's handwriting, it can create new types of "problem orders." For instance, errors due to "typos," appearance of double dosing *(9)*, drop down menu errors by selecting the wrong drug or route or dosage *(3)*, and inflexible formats (10) may occur. Clinicians also may report "alert overload" if too many alerts are sent after an order is entered (11). Anecdotal evidence and reports show that the rate of ignoring or overriding these alerts increases with time (11). It is important to provide useful decision support information and to ensure that only clinically significant interactions or dosing errors require an override *(12)*. One way to decrease problems with ignoring critical drug interactions is to force the prescriber to specify a reason to "override" the order; however, that alone should not be used by the pharmacist as a reason to dispense a medication without further review. In some cases, providers just enter several characters to "bypass" this alert. The technology is not advanced enough to recognize the randomly entered key strokes as nonsense. The availability

of a clinical pharmacist specialist in patient care areas has been shown to decrease medication errors in the intensive care unit and other settings (*13*,14,*15*).

As discussed in Chapter 12 of the *Third Edition*, the VA launched a major change in the control of medication by instituting BCMA for all inpatient medications. It has been several years since the initial trials were preformed at several VA hospitals, and the data collected have been used to improve the ongoing processes. In 2009, Mims et al. (16) reviewed the BCMA system and the quality monitoring program that identifies and corrects the problems discovered when implementing it within the VA. Their research determined that major problems of using BCMA included:

1. No bar code labels on drugs, which is a supply chain problem
2. Missing doses, which is a process problem due to a lack of standardization for administration of medications
3. Labels that do not scan, which is both a supply chain and process error
4. The medication scans but issues a "Drug not Found" error caused by software and hardware problems
5. Misplaced medications caused by automated packer, process error, and design error
6. Mislabeling (medications or patient) errors caused by a lack of quality control

While the initial compliance data were as low as 91% for bar code accuracy (ability of scanner to read the bar code correctly), the data for the fourth quarter of fiscal year 2007 reported successful scans of 98% for the correct dose or correct patient. While the authors concluded that a quality-monitoring program that uses best practices had corrected the problems, a success rate of only 98% equals more that 40,000 errors per 1 million opportunities of identifying the wrong dose or wrong patient. This rate may be considered too high.

In an earlier article published by the Joint Commission (JC), 15 best practice recommendations for BCMA were listed to help non-VA hospitals to implement this system. The best practice list was the result of their study of nursing information specialists and 30 unstructured interviews with diverse stakeholders (17). Some of the recommendations are to create interdisciplinary committees, train all users, avoid double-documentation systems, and verify allergy information displayed in the computer prior to medication administration.

These recommendations were selected without the use of the models identified in Chapters 10 and 12 of the *Third Edition* of this book. The authors of this chapter suggest that it is important to verify the extent to which a problem is mitigated by following the recommendations provided by the JC article since these recommendations "might even create unintended consequences that generate new paths to failure" and that evaluation should be ongoing (17).

IMPLEMENTATION OF BAR CODING TECHNOLOGY

BCMA systems have been suggested as a way to decrease medication errors related to the administration phase by adding another system check to the ones already performed by the pharmacist and the nurse in a phase of medication use where errors may be less likely to be detected (18). The BCMA system incorporates the "five rights" that the nursing profession is familiar with right patient, right drug, right dose, right time, and right route. Nationally, the VA has reported a 75% decrease in the wrong medication being dispensed after implementation of BCMA *(19,20)*. The baseline error rate was not reported. The use of BCMA in the VA started in 1999 and is currently on version 3.0. There are several errors that are possible to be introduced in the process; some of the most common errors are process workarounds such as performing steps out of sequence, adding steps that are outside policy, or omission of steps (i.e., manually entering a bar code instead of using the scanner, scanning medications in advance) (17,18). In some instances, scanning of multidose vials may be a problem *(20)*. Similar to CPOE, education and testing by clinicians who will use the system are important steps in order to avoid underestimating the change that is required to adopt new technology *(20)*. Teams should be multidisciplinary, and duplicate systems should not be used for more than 2 weeks to avoid duplicate orders and dosing or facilitating providers who will not make the switch (17). It is important to have management involved and to provide examples to employees *(20)*.

In a recent article, a research team evaluated errors and outcomes related to implementation of CPOE *(21)*. One of their findings was that "inconsistent communication in CPOE poses a significant risk to safety." About 20% of the errors reported in this study could have resulted in significant harm if not caught by a pharmacist. Using the best sample from this study in which 99.8% of the orders were correct and the 2007 BCMA report in which 98% of the time the correct dose and correct patient were identified (16), we could infer that the combination of CPOE and BCMA could lead to a total compliance rate of 97.8%. Thus if the goal of BCMA and CPOE is to reduce medical errors, combining them could theoretically add to the problem. Many of the issues listed by Patterson et al. (17) are reported by this study group as well, using a different computer system.

It is apparent that attempts to fix separate parts of the medication system itself may not be the best method, especially if this is not done in a systematic way. In implementing these new technologies, there was no consistent tool used for project management. Using a tool such as PDCA or the more detailed A3 process could lead to greater user satisfaction of the computer systems and maximum efficiency and effectiveness. Next we describe the successful use of a PDCA cycle to improve medication reconciliation.

TOOLS FOR QUALITY IMPROVEMENT

PDCA Cycle Example for Medication Reconciliation for HIV Inpatients

Our *PLANNING STAGE* consisted of reviewing our system and the literature. Theoretically it would be easier to reconcile medications if a patient is followed in the same institution for all their healthcare needs; however, even with a computerized medical record shared between inpatient and outpatient providers errors can still occur due to loss of information upon transfer between settings *(22)*. While

teamwork and the goal of seamless coordination of care are important, they may be difficult to achieve if the information is not shared equally within an institution. Integrated systems are important. In some cases, different software programs are used within the same hospital, making communication more difficult. A review of hospital discharges for patients of the HIV clinic in 1999 at the West Palm Beach VA revealed that a high percent of patients were receiving incorrect doses or medications for treatment of HIV or related opportunistic infections. We learned that most of these admissions were not related to HIV, and a consult to the infectious diseases (ID) service was not always done. To improve education of inpatient internal medicine providers, who are not well versed in the treatment of HIV disease, the ID clinical pharmacy specialist was asked to follow patients admitted to the hospital if the ID service was not formally consulted to facilitate transfer between inpatient to outpatient setting and vice versa. For the majority of our clinic patients, the pharmacist was the professional most familiar with their history, besides their primary care ID physician.

The *DO STAGE* consisted of implementing a system whereby the pharmacist would receive an electronic-mail alert whenever an ID clinic patient is admitted to the hospital. When the pharmacist receives the e-mail, the patient is visited and their inpatient and outpatient medication regimens are reconciled. The review includes most recent clinic visits notes. Any discrepancies are reviewed with the attending physician and a "pharmacy admission progress note" is written to document any changes or recommendations. The information is then forwarded to the ID clinic staff for their information. The *CHECK STAGE* showed us that at least half of the recommendations provided were to avoid a potential medication error and the rest were to provide information to the inpatient provider, and we were able to publish this experience *(23)*.

The system continues 10 years later with a slight decrease in the number of interventions needed per patient. The *ACT STAGE* consists of ongoing evaluation, providing education, and making changes as needed. The process in our facility has improved information sharing between the inpatient and outpatient setting. Our experience shows that even if a computer system and facilities are shared, miscommunication can still occur due to lack of familiarity with current protocols. The pharmacist serves also as a source for medication information and education for providers and patients *(24)*.

The PDCA cycle is an excellent tool when the process to be improved requires minimal resources and involves one or two departments instead of larger projects such as introducing new technology (i.e., BCMA).

THE A3 PROCESS

It is obvious that implementing a system requires a process that starts at the beginning and finishes at the end. It sounds simple, but as can been seen from the paragraphs above, incomplete planning requires a lot of rework and creates many problems. One popular technique being used globally is the *A3 process*. This process is a structured problem-solving approach that uses a tool called the A3 problem-solving report. The report is adapted from Toyota Production Principles and has been applied in healthcare settings. We have adapted the approach by articulating 10 steps to proceed from problem identification to resolution in a fashion that fosters learning, collaboration, and personal development. The problem solver records the results of investigation and planning in a concise, two-page document (the A3 report) that facilitates knowledge sharing and collaboration. The term "A3" derives from the paper size used for the report, which is the metric equivalent to 11 inch × 17 inch paper. We have focused on the problem-solving report, because it is the most basic style, making it the best starting point. Why use it? Most problems that arise in organizations are addressed in superficial ways, what some call "first-order problem solving." That is, we work around the problem to accomplish our immediate objective, but do not address the root causes of the problem so as to prevent its recurrence. By not addressing the root cause, we encounter the same problem or same type of problem again and again, and operational performance does not improve. The A3 process helps people engage in collaborative, in-depth problem solving. It drives problem solvers to address the root causes of problems, which surface in day-to-day work routines. The A3 process can be used for many situations, and in our experience, when used properly (e.g., all of the steps are followed and completed), the chances of success improve dramatically.

Steps of the A3 Process

Step 0: Identify a problem or need
Step 1: Conduct research to understand the current situation
Step 2: Conduct a RCA (Root Cause Analysis)
Step 3: Devise countermeasures to address root causes
Step 4: Develop a target state
Step 5: Create an implementation plan
Step 6: Develop a follow-up plan with predicted outcomes

The results of steps 0 to 6 can be recorded on an A3 report.

Step 7: Discuss plans with all affected parties
Step 8: Obtain approval for implementation
Step 9: Implement plans
Step 10: Evaluate the results

The A3 report goes hand in hand with steps 0 to 6 of the A3 process. The purpose of the A3 report is to:

1. Document the learning, decisions, and planning involved with solving a problem
2. Facilitate communication with people in other departments
3. Provide structure to problem solving so as to maximize learning

Note that the A3 process is rooted in the more basic PDCA cycle and also incorporates an RCA. Steps 1 to 4 are the PLAN step of the PDCA cycle. Steps 5 and 9 are part of the DO step and steps 6 and 10 are part of the CHECK step. Based on the evaluation, another problem may be identified and the A3 process starts again (ACT). This process is a good match for projects that require multiple disciplines to interact and improve a program. We provide an example of applying the A3 process to solve long patient transportation times at a medical center.

A CASE STUDY IN A3 PROBLEM SOLVING

Long Patient Transportation Times

The Context At Community Medical Center (CMC), two types of patients are sent to the diagnostic departments for procedures: outpatients and inpatients. The outpatients come to the hospital, register, complete the procedure, and leave on the same day. The inpatients reside in the clinical departments overnight and are sent to the diagnostic departments for various procedures depending on the medical necessity. Once the procedure is complete, the patient is returned to the clinical department.

Some of the outpatients who come for the procedures are elderly and frail and therefore unable to walk to the diagnostic department. It is the responsibility of the transportation department to provide a transporter for the patient to get to the appropriate department for procedures. Similarly, it is the responsibility of the transporter to get inpatients to the diagnostic department when they are scheduled for a procedure. The diagnostic departments (i.e., Operating Room, Radiology, Nuclear Medicine, Cardiology, Endoscopy, and Emergency Room) in CMC regularly reported that patient transporters took an exceedingly long time causing delays in treatment and patient waits, and they blamed the transporters for the delays. Many thought that the transporters were having long coffee breaks and that transport was taking over half an hour to bring patients to their appointments. The transportation manager decided to address the issue with an A3 process and report.

A group of individuals representing the diagnostic departments (i.e., Radiology, Endoscopy, Special Procedures, Cardiology), Nursing, Transportation, and Quality Risk Management met to discuss the issue and initiated the A3 problem solving method. These individuals formed the core A3 problem-solving team. To understand the problem first hand, the transportation manager and four transporters observed the current process. They observed the process for requesting transportation for patients every day for 10 hours over 10 days. The manager also contacted and interviewed different individuals in the diagnostic departments and the clinical departments to get first hand information about the process. The transportation manager observed all nursing stations and procedure areas, and noted a process full of miscommunications. For example, a ward secretary said she would call a transporter right away, but she actually made the call 37 minutes later, 3 minutes before the procedure. This happened frequently. The procedure department and the nursing station never communicated as to the expected patient transport times or procedure times. The patient's nurse often was not aware that the patient was going to a procedure, so the patient medications were not always administered for the procedure. In addition, using a self-devised form, the manager of transportation completed a patient transportation survey. In his survey, he measured the time difference between the transporters receiving a request from the diagnostic department to the time the patient was transported to the diagnostic department or the procedure area. The results of 23 patients surveyed over a 3-day period (January 15, 2003–January 17, 2003) showed an average request to delivery time of 56 minutes. The actual patient transport time was only 5 minutes and the rest was preparation time and delays in communication. The communication delays caused additional delays in procedures, resulting in unhappy patients, clinical workers, and physicians. In the current state, somebody from the diagnostic department, usually a technician called or paged the transporter. At other times, somebody from the department called the ward secretary on the floors who then called the registered nurse (RN) and the transporter. The transporter did not know who was paging. Sometimes, the message the transporter received said, "Bring down John Doe to Radiology." There was no information on the room number, bed number, floor, or area. The transporter did not know from where the person was paging and did not always know whom to call to clarify. They only knew that a patient needed to be transported. A great deal of time was thus expended by the transporter on patient search. If the information was complete and the patient was ready for the procedure, the transporter reached the patient and transported him or her to the diagnostic department without delay. However, in many situations when the transporter reached the patient (usually inpatients), they were not ready and were in need of medications, bathroom break, IV change, or other needs. In those situations, as the patient was not ready for transport, the transporter contacted the nurse. The transporter left the room and waited for the call from the nurse when the patient was ready for the procedure. The transportation manager created a drawing of the current state (patient ready for transport) on the A3 report with appropriate icons and arrows to indicate the flow of information and patient through the system (see Fig. 12-1). On the current state drawing, he recorded the shortest (9 minutes), longest (177 minutes), and average transportation time (56 minutes) from the data collected earlier. The problems he identified were no written message to request a transporter and late arrival by the patients at the diagnostic departments. These are depicted as "storm clouds" on the current state diagram.

The A3 problem-solving team brainstormed the root causes to the problems using the "5-Whys" approach. The 5-whys tool is used to develop root causes for a problem. Brainstorm all the possible causes of the problem. Ask: "Why does this happen?" As each idea is given, the facilitator writes it as a branch from the appropriate category. Causes can be written in several places if they relate to several categories. Again ask "why does this happen?" about each cause. Write subcauses branching off the causes. Continue to ask "Why?" and generate deeper levels of causes. Layers of branches indicate causal relationships. When the group runs out of ideas, focus attention to places on the chart where ideas are few.

The analysis of the first "storm cloud" revealed that the staff members calling from the diagnostic department were often too busy to send written messages to the transporter or to the floors, and therefore, the message lacked complete information causing delays. The analysis of the second "storm cloud" revealed that because the RNs or the ward secretaries were sometimes not aware that a patient needed a procedure, they failed to prepare the patient on time, which eventually led to late arrival of the patient at the diagnostic department.

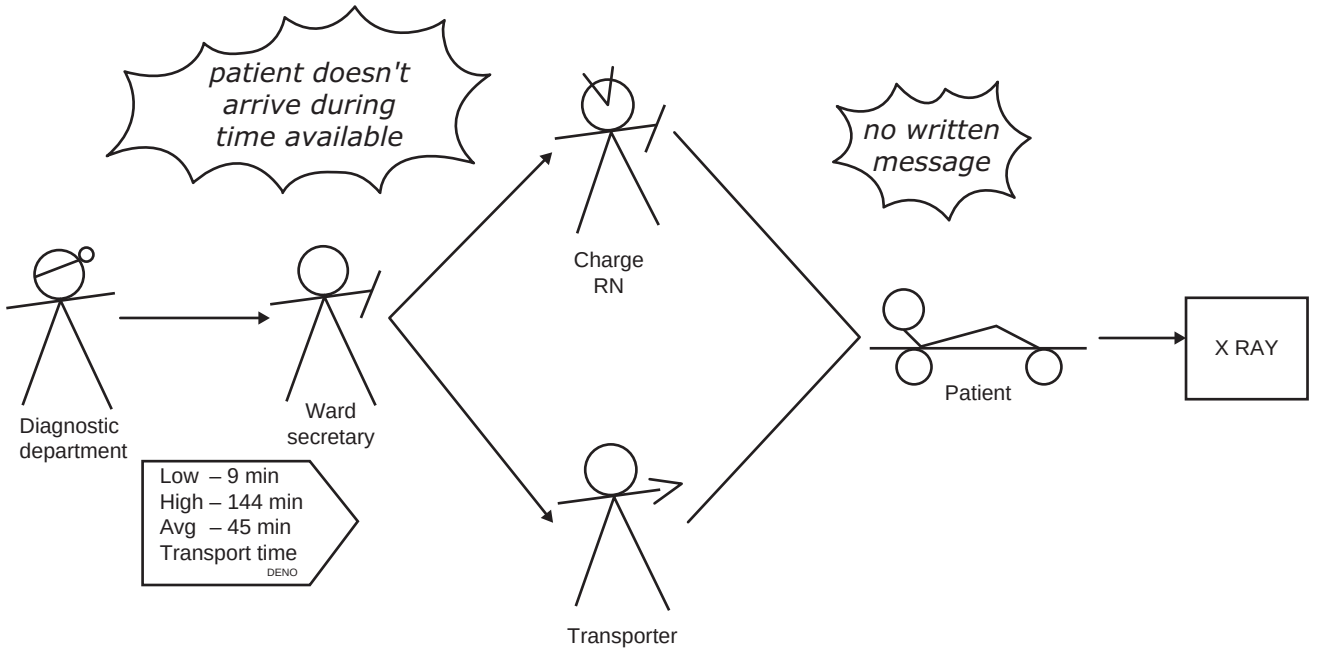

FIGURE 12-1 Current state of patient transport.

Based on the understanding of the current state and the associated root causes, the team embarked on devising the target state. The transportation manager termed the problem solving as "Road to Recovery." In the target state, the staff in the diagnostic department (usually a technician in Radiology or Endoscopy, or ward secretary in Surgery) would page both the charge RN and the transporter at the same time. The information included in the page would be complete information for effective transport of the patient to the diagnostic department (i.e., patient's first and last name, medical record number, room number, destination, etc.). The charge RN would attend to the nursing care patient needs and the transporter would attend to the comforts during transport such as shoes, blankets, chairs/stretcher, etc. If everything was found in order, the patient would be transported to the diagnostic department for the procedure. On completion of the procedure, the diagnostic department would page the transporter who will return the patient back to their room. The transportation manager drew the target state drawing on the A3 report as illustrated in Figure 12-2.

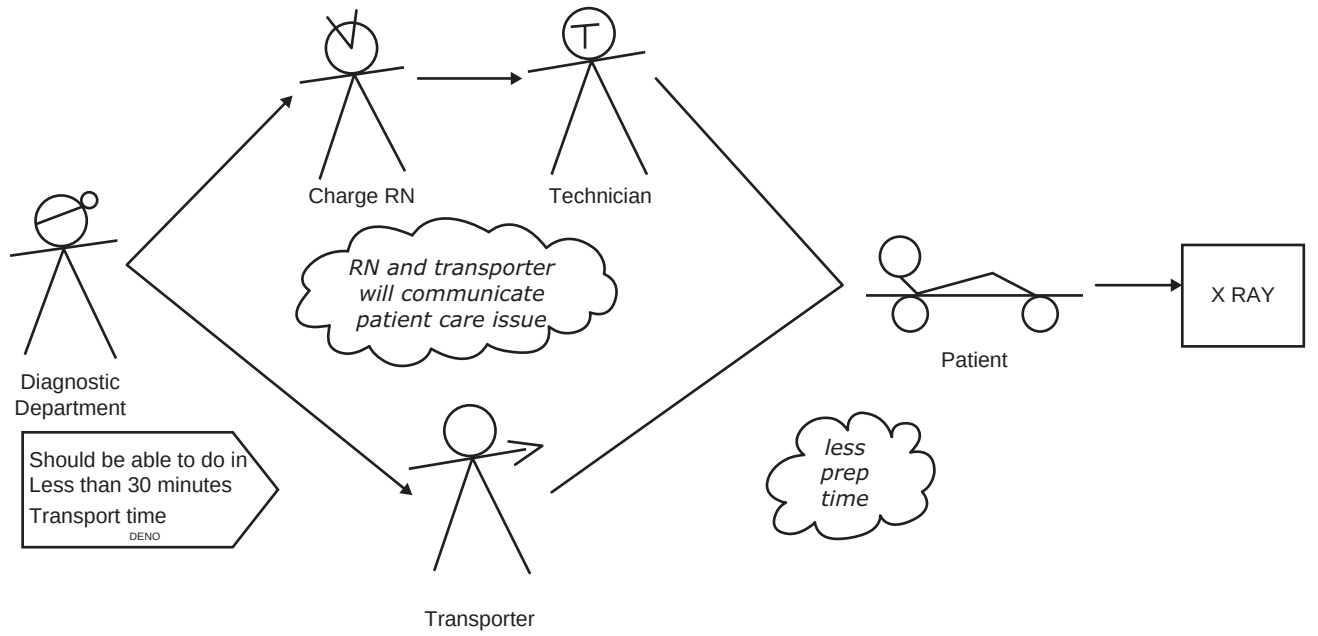

FIGURE 12-2 Patient transport procedure goal.

The specific countermeasures to achieve the target state were as follows:

- Diagnostic departments will beep the charge RN and the transporter at the same time.
- The page will include specific information, and a reference card.
- The charge RN (or designee) and the transporter would attend the patient, with specific responsibilities.
- Make the patient aware of the ensuing procedure.

As part of the implementation plan, the team created a specific action plan. First a designated transporter and a staff member responsible for communications in CMC developed a "group page" whereby two or more people could be paged simultaneously by the diagnostic departments. Second, the transportation manager and the charge RNs met and developed a patient tracking sheet (a log sheet for the floor staff to sign off when the patient is transported). Third, the transportation manager and the designated transporter developed a reference card that contained the pager numbers of the charge RNs of each clinical department and the transport pager number that the diagnostic departments should page. It also listed the information to be communicated by the diagnostic department when asking for a patient transport. This information includes:

- Name of the department from where the message is paged
- First and last name of the patient
- Patient's Medical Record No.
- Room No.
- Patient's destination

The reference card also contained the step-by-step procedure for requesting a transporter by the diagnostic departments. The transportation manager sent copies of the sheet to every department to ensure safe, accurate, and efficient transport of patients.

To ensure smooth implementation of the improved process, the transportation manager met with key individuals in all clinical departments on a one-on-one basis, explained to them about the necessity of the new process, and got their feedback on the new process and how it could be improved. He also had meetings with the house supervisors to get them on board with the new process.

The transportation manager set the target time from request to delivery at 30 minutes. The rationale was that most procedures are scheduled in 30 minutes increments. He carried out follow-up surveys at regular intervals to continue to assess transport time, and improvement in transport times was documented over 2 years, from average transport time of 15 minutes in March 2003 to 9 minutes in May 2005.

The transportation manager felt that the A3 process was very effective for problem solving in healthcare. He found the A3 process a very important tool for evaluating problems and/or processes. It allows a team to look at how a process flows and where the problem or work around area may be. It promotes team work on solving problems by giving a global and unbiased look into procedures. This process also incorporates other tools that quality managers are familiar with such as PDCA and RCA. Two other tools that could be used to solve these types of problems would be the Scribble Pad (a version of a RCA to solve existing problems) which could be deployed when problems of implementation are first discovered. The second tool is called TRIZ. This method is based on logic and data utilizing structured algorithms to solve problems and to facilitate "outside of the box" thinking. Additional information can be found on the Internet (25).

TABLE 12-1

Tools for Quality Improvement Projects and Potential Application

Tool	*Goal and Project Type*
PDCA	Small improvement in process already well established requiring minimal resources (i.e., medication reconciliation, home antibiotic infusion service)
RCA	Evaluation of causes for single or related events (i.e., medication errors)
A3 process	Introduction of new technology or redesign of a process involving significant amount of resources or multiple disciplines (i.e., patient transport, BCMA implementation)

PDCA, plan, do, check, and act; RCA, root cause analysis; BCMA, bar-coded medication administration.

SUMMARY

The A3 process along with PDCA and RCA are tools that can be used for improvement projects. Determining which one to use depends on the type of project, the familiarity with the tools by the persons involved, and the time available for problem solving. Most clinicians involved in quality improvement are familiar with the PDCA process; however, the A3 process, while having more steps can ensure a more complete evaluation of the process and can be useful for most projects. Table 12-1 provides a summary of possible applications for different improvement tools.

As healthcare organizations move forward to automate and improve medication processes, it should become an expected norm that many different "PDCA" cycles or A3 processes will be occurring simultaneously, and in fact every system will be continuously monitored and evaluated, and the question of "how can we further improve?" should continually be asked.

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CHAPTER 13

Public Reporting of Healthcare-Associated Infections

Ingi Lee and Patrick J. Brennan

BURDEN OF HEALTHCARE-ASSOCIATED INFECTIONS

In 2000, the Institute of Medicine (IOM) published "To Err is Human: Building a Safer Health System" *(1)*. This report documented the extent and impact of medical errors on patient quality and safety, and identified potentially preventable outcomes, including healthcare-associated infections (HAIs).

The Centers for Disease Control and Prevention (CDC) defines an HAI as "a condition resulting from an adverse reaction to the presence of an infectious agent or its toxin that occurs in a patient in the healthcare setting and is not present or incubating on admission" (2). Several reports have tried to estimate the prevalence and impact of HAIs on the US health system. Over the past decade, there has been a 36% increased incidence in HAIs *(1,3)*. The CDC estimates that 5% to 10% or 2 million of hospitalized patients develop HAIs annually *(4,5)*. HAIs are associated with approximately $28 to $45 billion in annual attributable costs and 90,000 to 100,000 in annual overall deaths *(5–7)*. The impact of HAIs on morbidity and mortality appears to vary based on the type of infection. Umscheid et al. (8) reported that catheter-associated bloodstream infections (CABSIs) and ventilator-associated pneumonias (VAPs) account for greater than 66% of HAI-related mortality and are associated with up to five times higher mortality rates compared to other HAIs. These figures regarding patients with HAIs are not only significant in themselves but notably higher than those found in uninfected patients. The 2007 statewide HAI surveillance data from the Pennsylvania Health Care Cost Containment Council (PHC4) reported that mortality rates (12.2% vs. 2%), lengths of stay (mean: 19.7 days vs. 4.4 days; median: 15 days vs. 3 days), and hospital charges (mean: $191,872 vs. $35,168; median: $87,655 vs. $19,748) were all higher in patients with HAIs *(9)*. However, it is unclear what proportion of these differences are directly attributable to infection, since these patients often have underlying comorbidities or have undergone more complex procedures that place them at increased risk for HAIs.

Although there is consensus that HAI rates can and should be decreased, estimates of the proportion of HAIs that are largely preventable vary. Clinical evidence supports the notion that substantially decreasing HAIs, at least for discrete periods of time, is possible. For example, the Pittsburgh Regional Healthcare Initiative, which comprises hospitals in southwestern Pennsylvania, initiated a multifaceted infection control intervention in 2001 with the goal of decreasing CABSIs in intensive care units. The intervention included five components: (i) promoting targeted evidence-based catheter insertion practices (e.g., maximum sterile barrier precautions, chlorhexidine for skin disinfection, and avoiding femoral site insertion), (ii) developing an educational module on CABSI prevention strategies, (iii) promoting standard tools for recording adherence to recommended practices, (iv) providing a standardized list of supplies in catheter insertion kits to adhere to recommended insertion practices, and (v) collecting and distributing data on CABSI rates to participating hospitals. CABSI rates decreased 68% over 4 years, from 4.31 to 1.36 per 1,000 central line days *(10)*. Using data from studies such as this, several overall reductions have been calculated. Reports issued from the CDC Study on the Efficacy of Nosocomial Infection Control calculated that a third of HAIs could be decreased by instituting appropriate infection control programs (*4*,11). A 2010 study by Umscheid et al. (8) estimated that the proportions of preventable HAIs may vary based on the type of infection. They calculated that catheter-associated urinary tract infections (CAUTIs) may be the most preventable (up to 65–70% or 95,483–387,550 CAUTI annually); followed by CABSIs (up to 65–70% or 44,762–164,127 CABSI annually), VAPs (up to 55% or 95,078–137,613 VAP annually); and lastly, surgical site infections (SSI) (75, 526–156,862 SSI annually) (8). They also estimated that CABSIs were associated with the highest number of preventable deaths and highest impact costwise (8).

HOW PUBLIC REPORTING MAY MOTIVATE A DECREASE IN HAIS

Since 2000, there has been growing public and media interest in calling attention to the burden of HAIs, with the emergence of several consumer organization–led efforts including the Consumer Union Stop Hospital Infections and the Reduce Infection Deaths campaigns *(12–14)*. This increased attention to the burden of HAIs combined with the IOM report, continued efforts to reduce healthcare costs, and public dissatisfaction with the quality of healthcare,

resulted in an increased call for public reporting and the implementation of state and nationwide initiatives mandating public disclosure.

Proponents, including the CDC, believe that making performance information publicly available is an important component of HAI elimination efforts. They advocate that public reporting could potentially decrease HAI rates, and in turn decrease HAI-related mortality and costs, via one of three potential pathways: the selection pathway, the change pathway, and/or the reputation pathway (*15*,16,*17*,*18*). In the selection pathway, consumers would use publicly available information to inform their selection of what they view to be the safest hospitals and providers. Therefore, protecting or improving market shares would motivate efforts on the part of the hospitals or providers. In the change pathway, providing feedback on existing problems or quality deficits would be sufficient in motivating hospitals and providers to implement evidence-based interventions that could decrease HAI rates. In the reputation pathway, maintaining or improving their public image would provide the motivation for hospitals and providers to change. Although each of these pathways may play a role, a study by Hibbard et al. *(18)*, which compared private confidential reporting, which would stimulate change via the change pathway, versus public reporting, which would stimulate change via the reputation pathway, found that the reputation pathway may be the strongest driver to change.

Public reporting is not limited to HAIs, but has also been used to measure other healthcare outcomes and processes of care. The Centers for Medicare and Medicaid Services (CMS) has several programs to publicly disclose healthcare information to consumers including the National Voluntary Hospital Reporting Initiative, the Premier Hospital Quality Incentive Demonstration Project, and the Nursing Home Quality Initiative.

IMPORTANT COMPONENTS OF PUBLIC REPORTING

Healthcare Infection Control Practices Advisory Committee

Due to the increased interest in public reporting, the Healthcare Infection Control Practices Advisory Committee (HICPAC), a federal advisory committee that provides infection control guidance to the Department of Health and Human Services and the CDC, convened in 2005 to provide guidance in helping policymakers in the creation of public reporting systems. This report enumerated the following principles that HICPAC believed were essential for successful public reporting: (a) identifying appropriate measures of healthcare performance, (b) identifying patient populations for monitoring, (c) case finding, (d) validation of data, (e) resources and infrastructure needed for a reporting system, (f) HAI rates and risk adjustment, and (g) producing useful reports and feedback (*19*,20).

Identifying Appropriate Measures of Healthcare Performance

HICPAC recommended a comprehensive approach to identifying an appropriate measure of healthcare performance. This would include measuring both process and outcome measures *(21–23)*. Process measures (e.g., adherence rates of central line insertion practices), which are currently recommended by the National Quality Forum and required by CMS and the Joint Commission on Accreditation of Healthcare Organizations, would potentially provide a simpler comparison than outcome measures. Appropriate process measures have an unambiguous 100% target, should be valid across a variety of healthcare settings, and do not require adjustment for a patient's underlying HAI risk. The outcome measures (e.g., CABSI) should be selected based on multiple factors including the prevalence, severity, and preventability of the HAI; and the ability to accurately detect and report the infection (*19*,20,*24*).

Identifying Patient Populations for Monitoring

Collecting hospital wide HAI rates is difficult at most hospitals due to resource limitations. Therefore, HICPAC recommended that monitoring be focused on populations where HAIs are more frequent and where prevention strategies would make the most meaningful impact.

Case Finding

HICPAC also advocated the use of standardized case-finding methods (e.g., review of medical records, administrative data sources such as the *International Classification of Diseases, 9th revision, Clinical Modification* [ICD-9-CM]). Standardization is important since differing merits and limitations may be associated with each method and the use of different methods may yield inconsistent results, resulting in potential surveillance bias (i.e., hospitals with more comprehensive case finding will report higher HAI rates due to their surveillance method).

The best methods to measure HAIs have not yet been clearly defined. Although using ICD-9-CM codes, which were developed for payment purposes, for HAI surveillance may be relatively facile, there appears to be significant limitations to this method. A study by Sherman et al. (25) reported that ICD-9-CM has a 61% sensitivity and 20% positive predictive value in identifying HAIs (i.e., CABSI, CAUTI, VAP, and SSI). Stevenson et al. (26) also reported that administrative coding alone may be insufficient for HAI surveillance. Stone et al. (27) performed a comparison of HAI identification using two different methods (i.e., Patient Safety Indicator vs. CDC definition for CABSI) and found that they resulted in discordant results.

Validation of Data

Validation of data was recommended by HICPAC to ensure that the information is complete, accurate, and comparable among hospitals.

Resources and Infrastructure Needed for a Reporting System

Hospitals are limited in the infection control resources that are available to them. Therefore, HICPAC recommended allocation of adequate resources (e.g., trained infection control personnel), in addition to an effective infrastructure (e.g., data collection forms and training manuals) to collect accurate data and to produce useful reports. HICPAC also stressed the importance of balance to ensure that the efforts used to comply with public reporting do not detract from necessary patient care and prevention efforts.

HAI Rates and Risk Adjustment

Reported infection rates should be adjusted for factors that may be associated with HAI risk to allow for reasonable comparison across hospitals. This would account for and not unfairly handicap those hospitals that treat higher-risk patients or perform higher-risk procedures that may be associated with increased risk.

Producing Useful Reports and Feedback

HICPAC recommended that the released reports need to be clear, interpretable, and useful to the public. The reports should also include limitations of the data and the methods used for risk adjustment. Lastly, future studies need to evaluate whether this additional information does help consumers make informed decisions, or whether it misleads or results in confusion.

Association for Professionals in Infection Control and Epidemiology

In addition to the guidance provided by HICPAC, the Association for Professionals in Infection Control and Epidemiology (APIC) released a position paper in March 2005 *(28)*. This document supported the public's right to know, but acknowledged that there were current limitations to the usefulness of public reporting. A few of the potential limitations included limited resources necessary to accurately capture surveillance data (which are often extracted manually), and that ensuring fair comparisons of HAI rates across hospitals may be difficult given the differing levels of complexity in the patient populations, treatments, and procedures offered. APIC listed the following nine recommendations, echoing the guidance from HICPAC, that they believed were necessary in public reporting of HAIs: (a) standardized surveillance monitoring of the same outcome (e.g., HAI) and process (e.g., evidence-based healthcare practices demonstrated to decrease HAI) measures; (b) standardized methods to collect, risk adjust, analyze, compare, and report data; (c) development and implementation of computer systems to help improve the efficiency, accuracy, and effectiveness of infection surveillance programs; (d) involvement of infection control experts in the design, implementation, and evaluation of systems for publicly reporting infection data; (e) mechanism to ensure that data reported will be useful and not misleading for consumers and to provide information back to hospitals to help implement changes in infection control programs; (f) consumer education on infection prevention strategies and the meaning of publicly released reports; (g) adequate support and resources to prevent infection control personnel and other healthcare resources from being diverted away from necessary infection prevention activities and toward data collection; (h) research to determine the impact of public reporting of HAIs; and (i) adequate funding and infrastructure to support public reporting.

STATE LEGISLATION ON PUBLIC REPORTING

In December 2006, the Consumer Union Hospital Infection Disclosure Act advocated for hospitals to collect and submit quarterly reports on SSI, VAP, CABSI, and CAUTI rates to their respective state health departments *(29)*. State agencies would then make the risk-adjusted data publicly available on their state websites. This document also required state health departments to create advisory committees that would include hospital representatives, healthcare professionals including physicians and nurses, epidemiologists, researchers, consumer organizations, health insurers and health maintenance organizations, and health insurance purchasers. A number of states have implemented reporting of HAIs based on this document within a range of varying frameworks *(30)*.

In 2004, Pennsylvania became the first state to require public reporting of HAIs. Pennsylvania instituted their public reporting requirement in phases. All acute care hospitals were initially required to submit data on cardiovascular, neurosurgical, and orthopedic SSIs. The list of reportable infections evolved over time until it encompassed all HAIs, including SSIs, CABSIs, CAUTIs, and VAPs. The PHC4, an independent state agency originally established in 1986 by the General Assembly and the Governor of the Commonwealth of Pennsylvania to promote control of healthcare costs, was tasked with collecting statewide HAI data and reporting this information annually. Surveillance data are not collected from billing data. Instead, HAIs are reported by individual hospitals with an increasing number of hospitals using a form of electronic surveillance (although not all hospitals utilize the same system). In addition to providing overall HAI rates, PHC4 then presents data categorized by "peer groups" comprised of hospitals that may be more similar in the patients they treat and the services they offer. PHC4's 2007 report included surveillance data for 1,578,600 patients from 165 general acute care hospitals in Pennsylvania *(9)*. They reported that 27,949 patients had acquired HAIs. This was the first year that PHC4 was able to compare infection rates to prior years. In comparison to 2006, the overall HAI rates decreased 7.8% from 19.2 per 1,000 cases to 17.7 per 1,000 cases, with decreased rates noted for CAUTIs, VAPs, CABSIs, and SSIs.

Over the past 6 years, additional states have followed and expanded upon the Pennsylvania experience. In 2005, Florida became the first state to release hospital-specific HAI rates through a website called Florida Compare Care (http://www.floridacomparecare.gov) created by the Florida Agency for Health Care Administration. Utilizing the data to make comparisons among hospitals, however, is difficult due to a lack of standardization in data collection. As of March 2010, 27 states have passed state legislation requiring public reporting of HAIs, 5 have allowed for voluntary or confidential reporting, and five have not formally passed legislation but have formed task forces or advisory committees to pilot programs for public reporting (Table 13-1). Of the remaining states that do not have state legislation, many have bills pending *(31)*. With a few exceptions, the agency responsible for reporting is typically the state's department of health; and both statewide as well as hospital specific statistics have been made available *(30)*. A majority of these hospitals have utilized NHSN for reporting with NHSN noting increased hospital enrollment from 300 to >2,400 hospitals at the end of 2009 (*9*,32). The remaining states have not mandated the source from which surveillance data should be obtained *(33)*.

TABLE 13-1

Public Reporting of HAI by State

States with legislation requiring public reporting of HAI (year)
- Alabama (2009)
- California (2008)
- Colorado (2006)
- Connecticut (2006)
- Delaware (2007)
- Florida (2004)
- Illinois (2003/amended 2005)
- Maine (2009)
- Maryland (2006)
- Massachusetts (2008)
- Minnesota (2007)
- Missouri (2004)
- New Hampshire (2006)
- New Jersey (2007)
- New York (2005)
- Ohio (2006)
- Oklahoma (2006)
- Oregon (2010)
- Pennsylvania (2004/amended 2007)
- Rhode Island (2008)
- South Carolina (2006)
- Tennessee (2006)
- Texas (2007)
- Virginia (2005)
- Vermont (2006)
- Washington (2007)
- West Virginia (2008)

States with confidential reporting of HAI to state agencies (year)
- Nebraska (2005)
- Nevada (2005)

States with voluntary public reporting of HAI (year)
- Arkansas (2007)
- Arizona (2006)
- Wisconsin (2009)

States with a task force or committees established to guide public reporting of HAI (year)
- Alaska (2006)
- Georgia (2006)
- Indiana (2005/amended 2007)
- New Mexico (2007)
- North Carolina (2007)

States with no legislation on public reporting of HAI
- District of Columbia
- Georgia
- Hawaii
- Idaho
- Iowa
- Kansas
- Kentucky
- Louisiana
- Michigan
- Mississippi
- Montana
- North Dakota
- South Dakota
- Wyoming

FEDERAL LEGISLATION ON PUBLIC REPORTING

Quality measurement initiatives including public reporting of HAIs have also been addressed on the federal level by the US Congress and CMS. The Healthy Hospitals Act of 2009, which requires public reporting of HAIs by hospitals or ambulatory surgical centers, was introduced to Congress and is currently in the first step of the legislative process. The CMS Hospital Quality Initiative was started in 2003 to provide healthcare-related information that would help consumers make informed decisions. Although the program started with voluntary reporting, data for certain medical conditions including pneumonia are now required for full Medicare reimbursement *(12)*.

IMPACTS AND CHALLENGES OF PUBLIC REPORTING ON HAIS

Although most states have mandated public reporting of HAIs, the impact of these efforts is unclear. In 2005, HICPAC requested that the CDC conduct a systematic review of existing literature to evaluate the effectiveness of public reporting on healthcare quality (*19*,20,34). The authors identified 10 studies for inclusion. However, there were no studies that addressed HAIs. In addition, most had methodological flaws including the study design used (none were randomized controlled studies), lack of adjustment for potential confounders, and suboptimal definitions of outcome measures. Highlighted findings from the selected studies are as follows. Two studies reported that improvements in outcomes noted from public reporting systems were likely due to secular trends *(35,36)*. Two other studies, however, did report an association between public reporting and decreased cardiac surgical mortality *(37,38)*. These studies adjusted for secular trends and utilized risk-adjusted mortality as the outcome measure. However, it remains unclear whether these surgical outcomes are generalizable to medical outcomes, including HAIs. McKibben et al. (34) argued that deaths or complications related to surgical procedures may be easier targets for improvement since the responsible healthcare organizations and surgical teams can be readily identified. In contrast, there are likely multiple factors that place a patient at risk for HAIs, and these factors may not be able to be well delineated. With the evidence review by the CDC, HICPAC concluded that there was insufficient evidence to recommend for or against public reporting of HAIs (*19*,20,34).

Since then, there have been a number of additional studies published evaluating the effect of public reporting. The most recent systematic review on this topic was performed by Fung et al. *(39)* and included 45 studies published from 1986 to 2006. Again, none of these studies evaluated HAIs. Overall, the authors reported that public reporting modestly affected consumer selection of health plans, but not hospitals. A synthesis of 11 studies, largely descriptive in nature, found that public reporting stimulated quality improvement efforts on the part of hospitals. However, there were inconsistent data regarding public reporting on improved effectiveness, patient safety, and patient centeredness.

Several additional studies published also found that publicly reported data did not meaningfully affect consumer selection of healthcare providers and/or hospitals *(40,41)*. They reported that the decisions, particularly more urgent treatment decisions, were largely influenced by recommendations from family and friends. A study by Mazor et al. *(15)* found that consumers preferred and were best able to compare hospitals when presented with short simple reports. However, this information was not sufficient in itself for decision making. Consumers also relied on additional factors including prior experience, reputation, and insurance coverage. The less-than-expected impact of public reporting on consumers' decision making may result from nonstandardization of reported data. Rothberg et al. *(42)* conducted a study comparing the results from five websites that ranked local hospitals in Massachusetts based on four diagnoses. They found that there were significant inconsistencies and a lack of correlation in the results available from these sites. This nonstandardization of data reporting and interpretation could decrease the usefulness of publicly available data.

SUMMARY

HAIs, infections that are acquired in the healthcare setting, are associated with significant morbidity and mortality. There has been growing healthcare, media, and public interest in decreasing HAI rates, many of which are believed to be preventable; however, the proportion of HAIs that are actually preventable is unclear with reported rates varying from 33% to 70%. Public reporting of HAI has been advocated as an important component in decreasing HAIs with legislation or regulations passed in a majority of states. Consumer organizations have argued that making this information publicly available is imperative for consumers to make informed decisions and could in turn, be a strong motivator for healthcare providers and hospitals to institute changes and make the elimination of HAI a top priority. Despite the increase in public reporting, there is wide variability in how this information is collected and reported, and there is inconclusive data regarding the impact of public reporting on patient safety and quality, particularly for HAIs. Further research will be important to evaluate whether these measures have been able to decrease rates of HAI, and to help identify limitations that may help to increase its effectiveness.

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CHAPTER 14

Working with the News Media in Public Communication

Marjorie Kruvand

Outbreaks. Pandemics. MRSA. E. coli. H1N1. Salmonella. C. diff. West Nile virus. Surgical-site infections. Mandatory infection reporting. These are some of the challenging topics that public health professionals, healthcare epidemiologists, and infection preventionists deal with in their efforts to protect the health of patients, employees, and the public. Increasingly, these topics have also captured the attention of the news media and the public. Communicating with the public is an increasingly important responsibility of hospitals and other healthcare facilities, government agencies, and healthcare organizations. Working with the news media is an essential way in which this occurs.

Your institution, organization, or agency may want to communicate proactively or reactively on a health issue in the hope that the public will become informed, take action, change their behavior, or be reassured. Or a reporter may contact you, seeking information or expert opinion on an issue involving your institution or community—or beyond. When a new "superbug" surfaces, every time there is an outbreak, whenever a journalist needs help deciphering the "alphabet soup" of pathogens or understanding the difference between causation and coincidence, you may be a logical resource for the news media because of your experience and expertise.

Yet many public health professionals avoid talking with reporters because they predict the story will be marred by misrepresentation, sensationalism, and inaccuracy (1). These fears are frequently overblown, however, and the outcome can be improved by an understanding of how the news media works as well as preparation and practice. Anyone can learn effective communication skills to help them become more confident and comfortable talking with reporters and improve the likelihood of a getting a story that is accurate and fair. And the more often you talk with reporters, the better you will become.

This chapter provides an overview of the news media and details how the media landscape has changed drastically over the last decade or so. It describes what guides the work of reporters and what they are looking for from you. It walks you through what to do after a reporter calls and before, during, and after an interview. It also introduces the practical skills and communication techniques that can make anyone a stronger communicator, and, hopefully, lead to long-term, mutually beneficial relationships with reporters. And finally, it suggests additional resources for information and training.

THE ROLE OF THE NEWS MEDIA IN PUBLIC COMMUNICATION

The public gets most of its information about health and science from the news media. The news media is a critical vehicle, as well as one of the most accessible, for communicating scientific and medical information *(2)* as well as the principal arena in which scientific issues and controversies come to the attention of decision makers, interest groups, and members of the public *(3)*. The news media serve as brokers between health, science, and the public, "framing social relationships for their readers and shaping the public consciousness about science-related events…. Through their selection of news, journalists help to set the agenda for public policy" *(4)*. The news media also forcefully shape how policy issues related to health and scientific controversies are defined, symbolized, and eventually resolved *(3)*.

Health and Science News

More than half of Americans get information about health and science from television, 22% from newspapers, 12% from the Internet, 8% from radio, and 3% from magazines *(5)*. Studies show that the public is interested in news about health and science: 35% of Americans surveyed in 2009 said they enjoy keeping up with science news "a lot" and an additional 41% said they enjoy keeping up with it "some" (6).

In another survey, 95% of Americans said they were "very interested" or "moderately interested" in news of medical discoveries and 92% said they were "very interested" or "moderately interested" in scientific discoveries—higher than the percentages who said they are "very interested" or "moderately interested" in the economy, agriculture, local schools, military and defense policy, or international and foreign policy *(5)*.

Public health news has all the ingredients for compelling stories, according to Maryn McKenna, a former public health reporter at the *Atlanta Journal-Constitution*:

> *Public health stories have urgency, drama and novelty. They are complex, what a public health scientist would call "multifactorial." Frequently they arise out of the near-universal dread of the new and frightening (7).*

Public Knowledge—and Why It Matters

Despite solid public interest in news of health and science, public understanding of complex health and scientific topics is quite low. In fact, surveys repeatedly show that ignorance, superstition, and irrational thinking often prevail over knowledge *(1)*. When US adults were quizzed in 2009, respondents correctly answered an average of eight of the 12 questions, or 65%; only 10% got all 12 questions right (6). Among the findings: 46% of respondents did not know that antibacterial antibiotics will not kill viruses.

Eighty-five percent of US scientists surveyed in 2009 said it was a major problem that the public did not know much about science (6). Lack of public understanding about health and science can help foster a society in which "science is often misrepresented and arguments about values are often presented as if they are legitimate scientific disputes" (1). Other arguments supporting the need for increased scientific literacy are being able to make better personal choices in everyday life, being encouraged to follow and participate in policy debates, and being more likely to support scientific and medical research (8):

> *We need an informed public if social policies are to be decided on reasonable and rational grounds. Everything from the future of health care and how it's paid for, to taxation on fuel, could benefit from a wider appreciation of the wider science (9).*

Stereotypes and Strained Relations

There has been considerable debate over the intellectual divide of science and the humanities into "two cultures," which was proposed in 1959 by C. P. Snow, an English physicist, civil servant, and novelist. Among its manifestations is a perceived gap between "scientists who don't speak English and reporters who don't speak science," which has kept the two professions "worlds apart" (10). Others contend that the gulf between scientists and journalists is neither as wide nor as unbridgeable as some suggest. As *Nature*, the British science magazine, editorialized:

> *Science and journalism are not alien cultures, for all that they can sometimes seem that way. They are built on the same foundation—the belief that conclusions require evidence; that the evidence should be open to everyone; and that everything is subject to question. Both groups are comprised of professional skeptics. And whether it's directed towards an experiment or a breaking news story, each can appreciate the other's critical eye (11).*

Still, there is an "enormous scope for mutual misunderstanding and suspicion" between journalists and scientists (8). Part of the reason is that the professions "demand two completely different standards of evidence" (10). Language use is another major source of tension: "What is for a scientist being precise is for a journalist splitting hairs. Necessary scientific qualifications translate as uncertainty or the hedging of bets in the media" (8). As Kathy Sawyer, a former science reporter for the *Washington Post*, put it:

> *Science is slow, patient, precise, careful, conservative and complicated. Journalism is hungry for headlines and drama, fast, short and very imprecise at times (10).*

The vast majority of scientists rarely talk with the news media. Forty-five percent of US scientists surveyed in 2009 said they never talk with reporters, 31% said they did so rarely, and only 3% said they did so often (6). A survey of more than 1,600 scientists in Britain by the Wellcome Trust found that only 29% had talked with the news media in the previous year *(12)*.

Yet neither profession can accomplish the task of communicating with the public without the other:

> *If reporters don't understand what a scientist is saying, how can they translate it for their audience? Or, put another way, if scientists aren't clear and concise, how can they expect reporters to get the story right? (13).*

How Scientists Perceive Reporters

Scientists view journalists as "imprecise, mercurial and possibly dangerous" (10). Scientists complain that reporters don't understand the basics of scientific methods, including the proper interpretation of statistics, probabilities, and risk. As a result, the news media oversimplify complex issues (10).

US scientists have negative views about news coverage of science (6). Seventy-six percent said they believe it is a major problem that the news does not distinguish between well-founded findings and those that are not, and 48% said oversimplification is a major problem. Only 15% of US scientists rated television coverage of science news as excellent or good, while 83% said it was fair to poor. In contrast, 36% of the US scientists rated newspaper coverage of science as excellent or good, while 63% rated it as fair or poor (6). In Britain, only 6% of scientists surveyed said they trusted journalists at national newspapers to provide information on scientific facts, and 11% were confident of journalists' ability to discuss the social and ethical implications of science *(12)*.

How Reporters Perceive Scientists

Journalists see scientists as "narrowly focused, self-absorbed, cold-eyed and arrogant" (10). Dan Fagin, a former environmental reporter for *Newsday*, put it this way:

> *Scientists now are more reluctant than ever to venture out of their ivory towers. Shunning messy public controversies, they tend to communicate only to each other and through the rarified language of peer-reviewed journals (14).*

British scientists surveyed by the Wellcome Trust acknowledged that the public sees them as doing poorly in public relations *(12)*.

Reporters contend that scientists don't appear to grasp that news is a perishable commodity that must be made relevant to readers and viewers. Journalists also complain that scientists are too wrapped up in esoteric jargon and are unable—or unwilling—to explain their work simply and cogently (10).

Quality of Health and Science Reporting

Even journalists acknowledge the imperfections of today's health and science reporting: it tends to be quickly produced, brief, superficial, and easy for the audience to digest *(15)*. Coverage is heavy on lifestyle and fitness

stories, profiles of desperate cases and "rescue medicine," and "disease-of-the-month" features. There is an increased reliance on news releases and fewer investigative pieces. Andrew Holtz, a former health reporter at CNN, contends that "much local TV health and medical news coverage looks like the media equivalent of a 99-cent drive-thru menu: quick, cheap, but ultimately unnourishing" *(16)*.

Part of the problem stems from journalists' uncertainty about their fluctuating role in society: should they be cheerleaders, interpreters, watchdogs, critics, or some combination? One science journalist describes the professional challenge this way:

> *Is our job to describe the bigger picture, or simply report what is 'new'? Should we present black-and-white versions of reality that lend themselves to stark headlines, rather than grayer complexities that are harder to distill into simple truths? (17).*

In addition, reporters tend to cover health and science as a series of disconnected events, dangers, or breakthroughs:

> *The unfortunate practice of treating science this way encourages the incorrect belief that scientific results are final, immutable end points. Thus, when new scientific research modifies prior findings, the public feels misled, as if scientists keep pulling the rug out from under them (13).*

Reporters believe more interaction and engagement is needed with scientists and public health professionals. But they contend that the onus has been placed squarely on themselves: While journalists are frequent visitors to hospitals, research labs, and offices of government agencies, they say it is rare to see a scientist in the newsroom (13).

WHY WORK WITH THE NEWS MEDIA?

Your first instinct might be to shun talking with reporters. You may have heard anecdotes about interviews gone wrong. You may think you are too busy, or believe your boss or colleagues would frown on it as self-promotion (10). You may think what you have to say is too esoteric for reporters to understand or too difficult to translate into everyday English. Or you may believe that the news media is an arena in which "important work is all too often misrepresented or hyped" (1). But these knee-jerk reactions are insular and ultimately counterproductive. As the editors of *Nature* asserted:

> *Science, with its inherent uncertainties, can be hard to put across to the public. But blaming 'sloppy' journalism is too easy. If researchers are to make their points effectively, they should learn more about how the media work (18).*

Some public health professionals refuse to talk to reporters yet are quick to criticize when the news media get the story wrong or miss the story entirely. Public health professionals, healthcare epidemiologists, and infection preventionists cannot have it both ways: they cannot criticize the media for the poor quality of information communicated to the public or leaving the public in the dark about important issues while refusing to talk with the news media. Dr. William R. Jarvis, who was an official at the U.S. Centers for Disease Control and Prevention for 23 years before becoming a consultant, says: "If you don't have experts talk to the media, people with much less expertise or no expertise will be talking and there could be a huge amount of misinformation out there."

Increased Reliance on Experts

The news media increasingly depend on experts for three main reasons: to offer facts, to increase credibility, and to provide objectivity *(19)*. Most often, experts are used to provide and verify facts and background information *(20)*. A study of *The New York Times, Los Angeles Times*, and *Washington Post* found that nearly twice as many experts were quoted in 1990 as in 1978 *(21)*. Research on Danish newspapers also found that the number of experts has increased dramatically over the last 40 years *(22)*. Reporters increasingly include more experts to make stories more interesting and relevant by highlighting conflict and tension:

> *… Since the requirement of maintaining professional objectivity precluded journalists from personally judging the statements or actions of those involved in news stories, persons having no part in the conflict—'persons of authority'—were brought in as referees and critics. Experts from academia and the research sector were perfect for this role (22).*

Several other factors have encouraged greater use of experts, including increased media competition. Reporters have also compensated for low levels of public trust in journalism by using experts to augment their own credibility *(22)*. Another factor is the growing complexity of the news; 60% of local television health reporters surveyed said they must frequently find a health expert to explain complicated information because of the technical nature of medical news *(23)*.

Reporters as Conduits

Reporters see themselves as conduits to the public. "As they see it, the job they are doing is to stand in for their audience, asking the questions that the general public wants answered" (8). Working with the media to provide important information to the public thus helps provide a public service.

Another reason to talk with reporters is that it can establish or reinforce your expertise and raise your profile. Being quoted in the media may contribute to funding opportunities, career advancement, and greater prestige. Examples of successful communication with the public are looked upon favorably in an era of increased competition for government and private funding. Thirty-seven percent of US scientists surveyed in 2009 said it was either very important or important for career advancement to have their research covered by the news media (6).

The institution, organization, or agency for which you work also benefits from media coverage because of increasing pressure to elevate its prestige, establish trust and credibility, attract funding, and preserve its viability *(22)*. Being mentioned in news stories can thus have significant practical value.

HOW THE NEWS MEDIA WORKS

In many democratic countries, media organizations are privately owned by families or corporations, including large chains and international media conglomerates. The news media serves more or less successfully as an independent "Fourth Estate," raising awareness of issues, interpreting events, keeping an eye on government and big business, and serving as advocate and critic. In other countries, such as China, media organizations are owned and operated by the government and used to help advance governmental aims and policies. In still other countries, the news media is nominally independent but subject to explicit or implicit state interference or pressure.

Types of media organizations include daily and weekly newspapers (national, regional, and local) and their websites, television stations and networks (including cable television), radio stations and networks, magazines, Internet news sites, blogs, and wire services such as the Associated Press and Reuters, which distribute news among member media organizations. Recent changes in the media landscape will be discussed later in this chapter.

Generalists and Specialists

Reporters are typically intelligent and inquisitive: "Journalists are no less professional than the scientists they deal with; all but a few want to report accurately and fairly" (8). The vast majority of reporters are college graduates, but their degrees tend to be in the liberal arts. Many reporters focused on subjects such as English and history and avoided mathematics and science. Reporters are likely to be knowledgeable about a variety of topics, but their knowledge tends to be a mile wide and an inch deep. This is especially the case with general-assignment reporters, so called because they are assigned to cover whatever stories the editor deems newsworthy that day. General-assignment reporters may cover a city hall meeting one day and report on sewer problems or a factory shutdown the next. This broad-but-shallow knowledge of many reporters is in stark contrast to public health professionals and epidemiologists, who are experts in a narrow field or subfield.

While most reporters are generalists, others are specialists assigned to cover a specific "beat," in which they are responsible for identifying and developing news in that subject area. Beat reporters have more specialized knowledge than general-assignment reporters and some receive specialized professional training. Reporting on public health requires a particular set of skills that differ from those of other journalists, including a basic familiarity with biology, lab science, and clinical medicine; the ability to decipher budgets and politics; and a lack of fear of math *(7)*. A handful of US reporters who cover health or science news have medical or doctoral degrees.

How do you assess a reporter's knowledge of a technical topic? How do you communicate without talking down to them or oversimplifying? If a reporter does not understand what you are saying, he or she will have no chance of translating the information and or communicating it accurately to their audiences. "*How much do you already know about… ?*" or "*Would like me to bring you up to speed on… ?*"are ways in which you can politely assess the extent of the reporter's knowledge at the beginning of the interview and offer to fill in any gaps. Reporters will appreciate this even if they claim to be the highly knowledgeable about the topic.

What Reporters Are Like

Reporters are skeptical, curious, and have a "seen-it-all-before" attitude. They are hungry for great stories, especially stories no other reporter has (called *scoops* or *exclusives*). Reporters are trained to follow a set of organizational routines that guide their work. As part of the newsgathering process, reporters are supposed to rely on credible sources and accurate information and to provide balance in their stories by including the viewpoints of both sides (or all sides). Reporters are driven by deadlines. By the time they contact you, they will probably have their story almost written. They may have a specific spot in the story in mind where they would like to insert a quote or two from you. While this may seem unnatural to you, it is an efficient way for reporters to work (13).

Selling the Story

Reporters first have to "sell" their editor on the merits of the story in the hope of getting prominent placement, such as the front page of the newspaper or the lead story on a television or radio newscast:

> *Journalists sometimes feel the need to play carnival barkers, hyping a story to draw attention to it. This leads them to frame a story as new or different—depicting study results as counterintuitive or a break from the past—if they want it to be featured prominently or even accepted by an editor at all (17).*

Reporters then try to "sell" the story to their audience through vibrant storytelling, human interest, compelling writing, colorful language, and relevant examples. Depending on the nature of the story, the goal may be to get the audience to pay attention, become informed, take action, become outraged, or feel reassured.

Constraints on Reporters

Reporters face a number of constraints that make their job more challenging. The first is time. Reporters are busy and overworked. Deadlines curb the amount of research reporters can do and the number of sources they can contact while limiting the time available for double-checking facts.

Space is another restraint. Increasingly, there is inadequate space and air time to tell complex stories. Glen Nowak, director of the division of media relations at the CDC, said scientists and physicians erroneously believe that they "should be providing all the nuances and caveats that would be found in a journal article" in a news story and "use as much space and time as it takes to get the information out there properly." But he notes that this isn't a realistic expectation in journalism (24).

Reporters must also compete with their colleagues within their own media organization for prime space or position for their stories, which can sometimes lead to sensationalism and hype. And copy editors, who write the headlines, can exacerbate the situation by highlighting the most controversial or sensational aspect of the story.

Complexity is another constraint journalists face. Reporters seek to provide balance by using a number of experts on both or all sides of an argument (8,13). But instead of clarifying complex issues, providing multiple contrasting viewpoints in stories can muddle things further. Reporters sometimes do not evaluate the quality of, or weight of evidence behind, competing claims, or are incapable of doing so (25). In these instances, stories may give the impression that all of the experts are equal and leave it up to the audience to decide which to believe:

> *The new media model routinely accords equal time and weight to two opposing points of view without regard to whether one might be factually demonstrable and the other off the deep end (26).*

Of course, the audience is no better equipped to evaluate the validity of competing claims than the reporter.

A Quest for Definitive Answers

Reporters share a desire with their audience for things to be black or white, not shades of gray. "Grayness" is difficult to handle in news stories, and reporters often pursue a quest for definitive answers even when none can exist. As a result, reporters would like epidemiologists and public health officials to communicate in ways they have been trained *not* to communicate: no careful qualifiers, no litany of exceptions, no hedging. Reporters strive to categorize things as safe or unsafe, people as heroes or villains, and issues as either a "Cause for Big Concern" or "Not to Worry." A reporter's dilemma is: will the information in my story lull the public into a false sense of security or needlessly alarm them?

Old Risks, New Risks

Reporters also face ideological constraints. Old, familiar risks are not as newsworthy as new, exotic ones (25). An example is the seasonal flu, which kills an estimated 36,000 Americans a year *(27)* but garners hardly any news coverage, while the H1N1 flu has received extensive coverage though the death toll to date has been substantially lower *(28)*. Every year before the beginning of flu season, Glen Nowak of the CDC says he faces the challenge of getting the news media to report on the need for people to get flu shots. While he gets some stories every year, Nowak said coverage "won't continue unless there's some new development and some new angle, some new idea, some new research, something new. At the end of the day, the first three letters of news are n-e-w" (24).

Controversy almost always makes better news than consensus. Questions about who is making the decisions, whether the decision makers can be trusted, and whether the public has a say can also add an element of uncertainty and suspicion to stories. In addition, old stereotypes are often perpetuated in the news media: government officials lack credibility, nongovernment organizations are always altruistic and have no agendas of their own, and corporations are interested only in profit. For all these reasons, the public may find it challenging to sort out important public health risks from inconsequential ones based on the amount and tone of media coverage.

What Reporters Want

What do reporters want from you? What they *say* they want is what you are well qualified to provide information, explanation, putting risks or a situation in context, future implications, and opinion. The following examples show how public health professionals and epidemiologists have been used in recent news stories:

Epidemiologists and Public Health Professionals in the News

To Educate:

> *"The message to parents and pediatricians is: vaccinating your child against the chickenpox is also a good way to reduce their chances of getting herpes zoster."*
>
> *Dr. HungFu Tseng, an epidemiologist at Kaiser Permanente in Pasadena, CA, in an article by Reuters (29).*

To Explain:

> *"This epidemic is different from the typical flu season, and we're having to respond in a different way. It's spreading like wildfire in the community and we need to protect the patients who are most vulnerable."*
>
> *Dr. Rekha K. Murthy, director of hospital epidemiology at Cedars-Sinai Medical Center, in a* Los Angeles Times *story on hospitals limiting visitors because of H1N1 (30).*

To Evaluate:

> *"This is going to be a huge help to the infection-control crowd," said Marcia Patrick, a nurse and board member of the Association of Professionals in Infection Control and Epidemiology… "How can we not do this? It would truly be penny-wise and pound-foolish. And it's the right thing to do for patients."*
>
> *Story in* The New York Times *about two new studies suggesting that hospitals could stop infections by tackling bacteria patients bring in (31).*

To Warn the Public about Health Risks:

> *"Many persons who may end up consuming these products may not be aware of those health risks. Are we prepared to let the philosophy of 'Buyer Beware' prevail when it comes to our food?"*
>
> *Dr. Tracy Murphy, Wyoming state epidemiologist, in a story in the* Wyoming Eagle-Tribune *about the illegality of selling raw milk in Wyoming (32).*

To Reassure the Public:

> *"There are no safety concerns with these lots of H1N1 vaccine. The concern is that the recalled vaccine may not be strong enough to provide full immunity. However, children in this age group should have adequate protection because we already recommend that they receive two doses of the vaccine."*

Dr. Megan Davies, an epidemiologist with the North Carolina Department of Health and Human Services, in a story in the Winston-Salem Journal *about the recall of some H1N1 vaccine (33).*

To Put Health Risks in Context:

"The bottom line here is that we still have high rates of influenza due to H1N1 in many parts of this province, in many parts of the country, in many parts of the United States and the European Union. And we cannot afford to let down our guard against this illness. We would rather saturate the population with vaccine rather than virus."

Dr. Arlene King, Ontario's chief medical officer of health, in a story in The Globe and Mail *about not becoming complacent about the H1N1 virus (34).*

To Offer Comment or Opinion:

Dr. Joseph F. Perz, a healthcare epidemiologist with the federal Centers for Disease Control and Prevention, said sometimes hospitals "assume health care workers know better" when it comes to basic infection control practices. "But I think we would like to see more attention paid to reviewing the basics when it comes to delivering IV medications or injections," he said.

Story in the South Florida Sun-Sentinel *about 1,800 hospital patients given tests by a nurse alleged to have knowingly violated infection control protocols (35).*

To Discuss Implications:

Dr. Paul Holtom, hospital epidemiologist at Los Angeles County-USC Medical Center, noted that the 1918 Spanish flu outbreak, which killed 50 million people, first struck in the spring, lost steam, then came back strong in the fall. "We really don't know what's going to happen," said Holtom. "These influenza outbreaks tend to ebb and flow."

Story in the San Bernardino County Sun *about the decline in H1N1 cases in California (36).*

Reporters want more from experts, however. First and foremost, reporters look for accessibility and rapid response; the most interesting information in the world is of no use if it arrives after a reporter's deadline. That means a reporter needs to be able to track you down quickly via phone or email. If possible, you should also suggest other sources the reporter may contact.

Second, the information or comment should be pithy, colorful, quotable, and memorable, which will help reporters in "selling" the story to their editor and, ultimately, to their audience. An example is the expressive metaphor used in the following story about mandatory reporting of hospital infection rates:

Staph infections "tend to ride in on instruments of medical progress," said Dr. Steve Schmitt, an infectious-disease expert from the Cleveland Clinic (37).

Language should be clear and simple, as this quote about predicting future deaths from the H1N1 virus demonstrates:

Michael T. Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, agreed that trying to guess how many would die by spring was "calling the score at halftime" (28).

Numbers should be used sparingly and selectively. An example is this quote in a magazine story about autism and vaccines:

"Out of the 100-odd million vaccines a year, we have just a handful of children" who develop a serious injury, says Dr. William Schaffner, a Vanderbilt University vaccine expert (38).

Other effective techniques include offering familiar comparisons to aid public understanding, providing information that can be presented visually, and telling a story. For example, comments from Mary J. Gilchrist, director of the Bureau of Laboratory Sciences in the Massachusetts Department of Public Health, and Dr. Richard T. Ellison III, hospital epidemiologist for UMass Memorial Medical Center, helped shape a news story about public health and hospital officials working to track down the source of a listeria outbreak into a compelling narrative that resembled an episode of the television drama *CSI*:

The recent listeria outbreak linked to three deaths and one miscarriage could have gone on indefinitely without the "detectives" at the state's public health laboratory, who tracked down, fingerprinted, identified and photographed the dangerous strain of bacteria, and then posted the prints in a national computer database to safeguard others (39).

Finally, since controversy is a valued ingredient in news stories, reporters encourage experts to weigh in on points of disagreement. An example is this story about whether New Jersey should have spent millions of dollars on antivirals that have so far gone unused:

"If you had a novel strain causing a pandemic that was responsive to antivirals and your state had no stockpile, I could predict that the public would be pretty upset," said Dr. Eddy Bresnitz, the state epidemiologist in New Jersey, which has bought 850,000 of the 900,000 courses available under the federal cost-sharing program. He acknowledged, however, that if the antivirals expire, "that's a lot of dollars flushed down the drain" (40).

RECENT CHANGES IN THE NEWS MEDIA LANDSCAPE

There have been enormous changes in the media environment over the last 25 years. Several trends have coalesced into a perfect storm buffeting the news industry and sending it "perilously close to a free fall" (41). The industry's business model has been upended by the recession, new

technology, the loss of readers and viewers, and the migration of advertising to the Internet. US newspaper ad revenues fell 23% between 2007 and 2009 and local television ad revenues fell by 7% in 2008, hastening a steady decline already in progress (41).

Other trends include the advent of the 24-hour news cycle. News is no longer just delivered at set times, such as a 6 PM nightly television newscast or when the daily newspaper is thrown on your front lawn. News is now available immediately—on demand, around the clock. Instead of depending on information pushed out to the public by media organizations, people increasingly pull information from the Internet on their own time and terms, hunting and gathering the exact information they want. This has made it considerably more challenging for journalists to cover the news. Information must be constantly updated and freshened, and pundits are increasingly being called on to offer opinion and commentary when new information is scarce. The public is left with a constantly changing smorgasbord of information lacking in context and interpretation:

> *… a problem that is worsening in this era of the 24/7 news cycle is the frequent failure to put new developments into any kind of reasonable context for readers or viewers. In this environment, reporters… conduct interviews that amount to a "hit and run" version of journalism (17).*

In addition, the public now uses media more for entertainment than for news. This helps explain why astrology columns and Sudoku, celebrity gossip, television reality shows, lifestyle features, and other "infotainment" offerings are on the rise, while the amount of "real" news—which costs far more to gather and produce—is on the wane.

Moreover, news is accessed in different ways, including online sites (such as Yahoo! News, MSNBC, Google News, and AOL News), cable television networks, cell phones, Twitter, and podcasts—all communication vehicles that didn't exist 25 years ago. More than 50 million people in the United States get their news online everyday, and the trend is accelerating. The number of Americans surveyed who said they got most of their national and international news online has increased 67% in the last 4 years (41). Meanwhile, newspaper readership and television news viewership continue to decline, and television ratings are flat or falling in the United States (41). And since people can select which information they are exposed to through news aggregators and RSS feeds that deliver a made-to-order news digest to their email inbox, they can avoid topics in which they lack interest.

As a result, newspapers and magazines have become a lot slimmer and newsroom resources and travel budgets have shriveled. The average number of stories produced per reporter has climbed 30%, which may impact quality (13). Journalists are also increasingly required to produce the same story for multiple news platforms, leaving less time to develop the original version. For example, a newspaper reporter may also have to produce a podcast or write a blog post on the same topic for the newspaper's website; a television reporter may also have to write a story for the station's website.

Some newspapers and magazines are in bankruptcy and others have ceased publication. Although nearly 150 US newspapers had a dedicated science section or page two decades ago, that number has dwindled to fewer than 20 today *(42)*. Meanwhile, health and science stories must compete with other stories to be included in the shrinking main section of newspapers. There is also less coverage of pure science and medicine and more consumer health "news you can use" and lifestyle coverage *(42,43)*.

Fewer Journalists, Less Coverage

By the end of 2009, the newsrooms of US daily newspapers employed 20% to 25% fewer people than in 2001 (41). Many experienced health and science reporters have been among the journalists being laid off or taking buyouts (13,*43,44*).

> *There is a greater need than ever before for journalists who are skilled in reporting both the underlying complexity of the science as well as the legal, ethical, and political ramifications of its uses. Unfortunately, jobs for full-time science writers at major print and electronic outlets are declining, while the number of important science and science policy developments is increasing (43).*

Natalie Angier, a science reporter for *The New York Times*, contends that science reporting in newspapers is "basically going out of existence" *(45)* while coverage on television has been greatly reduced. CNN eliminated its entire science and technology team in 2008. In 2009, *The Boston Globe* closed its science section, an action the *San Francisco Chronicle* had taken several years earlier *(42)*. According to Cristine Russell, a former *Washington Post* reporter who is president of the Council for the Advancement of Science Writing:

> *It's ironic that we have fewer writers in our major media focusing on science, while we have ever more issues that have a science base—from climate change to the health care debate, stem cells, evolution and swine flu—many of which are very controversial (42).*

It's a similar situation in Canada. Peter Calamai, a former science reporter for *The Toronto Star*, says most science news is no longer covered by a knowledgeable or discerning science journalist but by a general-assignment reporter who is probably expected to churn out several stories that day (46). He noted that when the Canadian Science Writers' Association was founded in 1971, there were at least 30 full-time staff reporters covering science and medicine for major Canadian newspapers and television and radio networks. That number has since dwindled to about six (46).

In Britain, science reporters are not immune to the pressures facing their peers in other countries, but the state of science journalism is healthier, according to a study by an expert group convened by the British government. The group's report noted that "… reports of a major crisis in science news reporting in the UK are exaggerated." The study noted that there has been a "dramatic increase in the number of science reporters," "an ever-expanding appetite for science stories within news rooms," and "a marked increase in the status of science specialist reporters in the news room" (47). For example, the BBC has gone from two science specialists to 30 in the last two decades (47).

Media Fragmentation

Fragmentation is another trend affecting the media landscape. The public has more choices for information than ever before, including online sites, niche magazines, and cable television networks that cater to specific political and cultural viewpoints. As a result, any single news media organization is less dominant.

Furthermore, journalists are no longer the only gatekeepers of information. Members of the public are increasingly assuming that role by creating their own content, commenting on information, and passing it along via cell phone photos, "tweets," blog posts, and YouTube videos. More than 57 million Americans read blogs regularly (41). There are 70 million blogs and about 900,000 new blog posts are created every day. As a result, the blogosphere continues to double in size about every 5.5 months. While many bloggers comment on and pass along news rather than report and write it, they nonetheless have a growing impact on public communication. But questions remain as to whether bloggers are journalists and whether they should follow the same professional code of ethics.

Credibility of the News Media

Meanwhile, public trust in the news media continues to erode. Public perceptions of media accuracy are at a two-decade low in the United States *(48)*. According to the Pew Research Center for the People & the Press, "The public continues to express skepticism about what they see, hear and read in the media. No major news outlet—whether broadcast or cable, print or online—stands out as particularly credible" *(49)*. Just 29% of Americans surveyed said news organizations get the facts straight while 63% said news stories were often inaccurate *(48)*. Nonetheless, the public continues to view media stories (or "earned media") as more credible than "paid media" (advertising). And most Americans surveyed said they believed it would be an important loss if major news sources shut down *(48)*.

What's Next?

It is impossible to predict whether newspapers will survive in printed form or whether television will increasingly proliferate into niche networks in which "news" will be defined in narrower and more partisan terms. There will always be new mass communication vehicles, but they are unlikely to supplant their predecessors—television did not replace radio and the Internet has not replaced television. Rather, new mass communication vehicles are likely to compete with, influence, complement, and change older ones. New communication techniques that allow people to bypass the news media and communicate directly with one another are also growing. But whether podcasts, wikis, Twitter, and text messaging will continue to flourish, or fade away like Friendster and instant messaging, the basics of effective communication will remain the same: know the objectives, the audiences you are trying to reach, and the messages you want to deliver before doing any communicating. We'll address those topics in the pages ahead.

WHEN A REPORTER CALLS

When you get a call from a reporter, it may seem as though it is coming out of the blue. While that may sometimes be the case, public health professionals, healthcare epidemiologists, and infection preventionists can often anticipate why a reporter is calling by knowing what is in the news. Media monitoring can provide a head's up on emerging issues beginning to capture the news media's interest, hot-button issues that are the subject of significant coverage, and once-hot issues beginning to recede from media and public attention. Keeping on top of the news can provide additional time to prepare when a reporter calls.

There are several ways to monitor relevant media coverage. First, there is no substitute for being an active news consumer. Second, the public relations team at your institution, organization, or agency probably already monitors relevant media coverage; you can request to have the stories or links sent to you. In addition, if the public relations team produces and distributes a daily or weekly email roundup of news stories, you can ask to be included on the distribution list. Third, you can use a news aggregator such as iCurrent or Google Alerts to create your own media monitoring function. News aggregators "crawl" the Internet looking for all stories and blog posts containing the keywords you specify and deliver them your email inbox daily.

Playing Reporter

When a reporter calls, you should politely turn tables and play reporter first. It is your only real opportunity to screen the request and to gather the information you need to help decide whether or not to do the interview, so it is worth the few extra minutes it takes (13). You shouldn't assume that the reporter is interested in a certain topic, even though it may dominate the news. You should always begin by asking the reporter what topic they are interested in, drilling down to specifics about the "angle" of the story. You should also ask about the type of story (a news story or a feature story?) and its expected length. The type of story will provide insight about its tone (serious and analytical or human interest?), while the expected length may suggest the extent of your role. In addition, you should ask whether the reporter proposes to do the interview by phone or in person, and whether an in-person interview would be done at your workplace, in a television studio, or another location.

Moreover, you should ask when the story will air or will be printed and the reporter's deadline. And finally, asking the reporter who else they have interviewed or plan to interview will give you an indication of where the story is headed. For example, if the reporter says they have interviewed several vaccination opponents, you may anticipate being called on to defend the safety of vaccines.

In addition, if you do not already know the reporter, you should always ask them to spell their first and last names and to tell you a little about their background and what they cover. The same goes for the media organization for which they work. The purpose is not to interrogate the reporter but to have a better understanding of who they are and where they are coming from, as well as the wider

audience you would be addressing (8). Quite simply, you need to know what you would be walking into if you decide to do the interview.

You should also ask for the reporter's phone number at work. The unspoken reason is that you will call the reporter back at their office to verify their identity. There have been cases of people in other professions masquerading as reporters to gain access to information. While verification is more difficult in these days of cell phones and freelance journalists who may work from home, try to get the reporter's office number.

After you finish the call, it can be helpful to gather more background information on the reporter and their media organization. One way is to Google the reporter and look at the website of the media organization if you are unfamiliar with it. You should also ask the public relations team at your institution, organization, or agency what they know about the reporter and media organization. In addition, you can do a quick search of the online archives of media organization's website or use a database such as Factiva or LexisNexis to read other stories by the reporter.

Never Doing an Interview Cold

How will you be able to do all this when the reporter is pressing you for "just one quote" and they emphasize how much of a hurry they are in? The worst thing is to succumb to the reporter's pleas or pressure and agree to do an interview "cold"—on the spot. You need to politely buy yourself time to gather and verify information and to prepare for the interview without making it appear as though you are stonewalling or being unhelpful. So after screening the reporter and their request during the initial call, tell the reporter graciously but firmly that you're in the middle of something and will call them back *before* their deadline.

If the reporter says their deadline is tomorrow or next week, you will have plenty of time to prepare, but even a reporter on the tightest of deadlines can spare 5 or 10 minutes in which you can verify their identify, decide whether to do the interview, get your head around the topic, and think about how best to respond to likely questions. Telling the reporter you're in the middle of something is not a lie because you *were* in the middle of something when they called. It's arrogant to assume you can flawlessly switch gears from meeting with colleagues or working on a technical report to answering a reporter's questions. Failing to take the time to compose yourself and get your head around the interview topic can have calamitous results. As Dr. William R. Jarvis, who did many media interviews during his 23 years at the CDC, notes: "You can't just 'wing it,' because if you do you're going to get burned."

After finishing the call with the reporter, it's a good idea to touch base with the public relations team at your institution, organization, or agency. Have they worked with the reporter and media organization before? Do they think you should talk with them? Why or why not? The public relations team may also be able to help you answer the three questions you should always ask yourself before accepting any media opportunity:

1. *Why are you giving an interview?* What are your objectives and those of your institution, organization, or agency? It's not enough to say that you are being helpful or nice. Is your objective to inform or educate? Explain or reassure? Dispel myths or put risks in context?
2. *Who are you trying to reach?* Who are the media organization's audiences? And do the two match up? While the "general public" may be an overly broad target, employees, neighbors, parents, community and civic leaders, and government officials—to name a few groups—may be among the audience for the story.
3. *What do you want to say?* What do you want people to take away from reading or hearing what you said?

Only if you can answer all three questions should you proceed with the media opportunity. If it's a "go," what background can the public relations team at your institution or organization's public relations team provide? What are the watch-outs, if any? Can they help you prepare for the interview? Can they provide communication materials, such as a fact sheet on the topic, to give the reporter?

When Can You Say "No"?

While it's a good idea to be as cooperative as possible with the news media, you shouldn't feel compelled to say "yes" to every interview request (8). Some requests will be easy to turn down; for example, if you lack expertise on the topic or there's someone better to recommend. Dr. Michael T. Osterholm, Director of the Center for Infectious Disease Research and Policy at the University of Minnesota, says he turns down about two-thirds of interview requests for that reason. "It's all about my expertise," he says. "If I don't believe I'm the best source or there's someone with more experience to provide greater credibility, I'll suggest another source."

There may also be media requests that raise your antennae or those of the public relations team where you work. Perhaps the request is from a reporter or blogger known to have a bias or agenda. Perhaps the media organization is not viewed as legitimate. Or perhaps you suspect, based on what the reporter told you about who else they have interviewed, that you will be positioned awkwardly in the story, such as the lone expert criticizing (or defending) a controversial issue, practice, or policy or while a bevy of experts take the other side.

In addition, some media opportunities simply may not measure up as worthwhile. For example, does it make sense for you to carve a half hour out of your schedule to explain flu-prevention tips to a reporter when that information is readily available online or in a brochure your institution, organization, or agency could provide? Or is the media organization so small, such as a local public-access cable television channel, that the audience is likely to be tiny or nonexistent?

Another reason to consider turning down a media request is when there isn't enough time to adequately prepare and practice. You may simply be too busy with pressing duties, such as dealing with an emergency (one that isn't the topic of the reporter's call). Sometimes, it can seem easy to say "yes" until you consider the time requirements involved: it can take a 20-minute interview to produce 15 seconds of quotes for a radio story (8).

WHAT TO EXPECT IN AN INTERVIEW

Reporters' individual style does not matter; the story they produce does. Reporters may come across as friendly and professional, demanding or standoffish. But they are likely to be genuinely interested in the information you provide.

Types of Interviews

There are some similarities between print, television, radio, and online interviews. All reporters, regardless of the type of media organization for which they work, look for accurate, clear, and interesting information and comment that is provided quickly, succinctly, and dependably. But there are numerous differences between print, television, radio, and online interviews. In-person, phone, and email interviews differ as well.

In-Person, Phone, and E-Mail Interviews

The primary advantage of an in-person interview is being able to "read" the reporter's body language (Is there a point on which they seem confused? Do they stop taking notes? Why are they frowning?). On the other hand, the primary advantage of a phone interview is that you can have your notes in front of you, which may make the experience less stressful. Notes are not meant to be a crutch, however, and reading them verbatim will sound stilted and unnatural. For phone interviews, pick a quiet location where you will not be interrupted. Close the door, put a sign on the door asking not to be interrupted, and stop incoming calls (8).

While reporters typically type notes on their computers during phone interviews, most take notes during in-person interviews. For most reporters, writing takes longer than typing, so speak slowly and clearly. Take a moment to collect your thoughts before beginning your answer. If needed, you can pause from time to time and let the reporter catch up with their note taking. Many reporters use tape recorders to supplement written notes. Tape recorders have pros and cons from the standpoint of the person being interviewed. Reporters can go back and check the precise words you said, which may increase accuracy. A tape recording can also help set the record straight if there is a disagreement over whether you were misquoted. Then again, knowing every word is being recorded makes some people more nervous. The best advice is to try to forget the tape recorder and focus on the reporter.

Today, more reporters conduct interviews by email, text messages, and even Twitter, especially when someone they want to interview is not available in person or by phone or when reporters face an imminent deadline. But the informality of a particular communication technology should not influence what you say or how you say it. The same care and precision that should guide you in any media interview should apply here as well. That means writing in full sentences with proper spelling and no slang or use of emoticons.

Print and Radio Interviews

Newspaper and magazine reporters typically do the longest interviews. They may seek considerable background information as well as quotes. The reporter may ask to sit down with you to do the interview, conduct it by phone, or send questions via email.

Radio reporters do interviews by phone or in person. In a radio interview, your voice and inflection can have as much impact as your words, so practicing in front of a mirror can be helpful. Speak slowly (but not too slowly) and clearly and enunciate well. And make a conscious effort to avoid words like "uh," "um," and "like."

Television Interviews

Stand-up television interviews are the type of interview people dread most. There's something about the lights and a microphone in your face that can turn the strongest knees to jelly. But the tips in this chapter can help you overcome these feelings.

Television reporters almost always request in-person interviews so their station or network will have visuals to accompany the story. An exception may occur when it is so close to deadline that a television reporter asks for information or a comment over the phone. Along with a recording of your voice, your quote will likely appear in words on the screen behind the head of the reporter or news anchor as they present the story. Most often, television reporters will want to come to your workplace (or home, if it is an evening or weekend) or suggest another interview location. For example, if the story is about an alleged cancer cluster in a certain community, doing the interview in that neighborhood might make sense (but see the caveats below about interview settings).

Television interviews are almost always taped, not live. The only exception is during a major crisis in which there isn't time or the ability to edit recorded video footage. Taped interviews are more forgiving than live ones, so don't feel compelled to spring to your answer like a racehorse out of the starting gate. Take the time to collect your thoughts after each question. And if you make a mistake, you can stop and ask to do it again. Television stations loathe so-called dead air because air time is a precious commodity. Footage of you pausing, thinking, or doing over an answer will be edited out unless the reporter is deliberately trying to make you look bad. In contrast, there are no "do-overs" in live television interviews.

Setting a Time Limit

Whatever the type of interview, setting a time limit is always recommended. You can tell the reporter something like, "*I have 20 minutes for us to talk before an 11:30 meeting*." Twenty minutes should be sufficient for any reporter to ask you almost anything. Most people are sharpest at the beginning of an interview, a topic we'll discuss in more detail later. Most people being interviewed get run down and tend to become more sloppy as the interview goes on, increasing the likelihood that the information the reporter has to choose from will include some you are displeased with.

Having a preestablished time limit gives you an out, which you can reinforce by arranging for a colleague or assistant to stop by. If reporter still keeps asking questions, you can stand up, thank them, say you're expected elsewhere, and escort them out. However, if you feel the interview is going well and want to extend it for some reason, you have that option as well.

Choosing an Interview Setting

You should not automatically agree to an interview setting the reporter steers you to. Rather, you should take the lead in suggesting—and if necessary, insisting—on a professional, neutral setting. If the interview takes place in your office, make sure all confidential papers are put away and that there is nothing on the walls that would raise a red flag if shown on television. If the interview takes place inside a facility, avoid being near signs that say *warning, danger, hazard, contamination,* or *quarantine*. If the interview takes place outdoors, avoid having the sun in your eyes, making you squint. And check what is behind you. Ask yourself: how would viewers react to what's in the background? Would it detract from what I'm saying or contradict what I'm saying?

PREPARING TO TALK WITH THE NEWS MEDIA

People are not born with good communication skills, they acquire them. Communication skills improve with practice, and, like other skills, get rusty when not used for a long time.

Journalists are often skilled at drawing out the people they interview. Whether it's chatting about the local professional sports team, the weather, upcoming holidays, or other small talk, the goal of reporters is to build rapport with people and help them feel at ease during the interview that will follow. Reporters know that taking a few minutes upfront to do so will help produce a better interview. It's designed to relax you (which is good, up to a point) and to persuade you to let your guard down (which is not). It may lead you to erroneously believe that the interview will be just like the opening chitchat: a friendly conversation.

Reporters have many different interviewing styles. They can be smiling and friendly, asking easy questions at first and nodding their head to show tacit support, then transitioning to tough questions before you realize what is happening. Or a reporter can have the personality of a pit bull, peppering you with difficult questions from the start. What matters, however, is not the reporter's interviewing style, but whether their story is accurate and fair.

Not a Conversation

The biggest peril for anyone talking with the news media is to be drawn into the "just a conversation" mentality. You would never speak at a professional conference with the mindset that it's "just a conversation": you'd be prepared, polished, and buttoned down. Nor would you ask your boss for a raise without knowing exactly what points you want to make to support your case. If you were to ramble, the chances of persuading your boss to increase your salary might be near zero. A media interview needs to be just as polished and put together; it should always be considered a *presentation,* not a *conversation*. After all, the reporter is just the conduit to their audience. And since you have established objectives for the interview, you need to focus on achieving them.

Why Key Messages are Needed

The way to achieve your objectives in an interview is clear and concise key messages: developing them, practicing them, using them, and repeating them. Messages cannot be developed "on the fly" once you are already talking with a reporter; they must be prepared in advance (13). And messages are not "spin"; rather, they are merely a way to break down the information you want to get across and help the audience focus on, understand, and remember what you say (13). After all, the world is inundated with information. There are more messages bombarding us—from billboards to text messages to cable TV and the Internet—than ever before, all competing for our increasingly fragmented attention. People forget approximately two-thirds of what they hear in 1 day and 98% in 30 days.

This "message clutter" has been exacerbated by the fact that while the number of media messages has proliferated, the amount of space or time available for individual messages has dwindled. This has led to an increased reliance on *sound bites*, snippets of information or comment that have become the building blocks of interviews, especially television interviews: "Journalists want the whole story in a few sound bites—their readers or viewers are not experts and need the information in a handful of pithy sentences" (8).

Sound bites have continued to shrink over time. In 1968, when television producers coined the term, a US presidential candidate spoke for about 43 uninterrupted seconds on television newscasts. But with each campaign sound bites got shorter, and by 1988 the average was only 9 seconds *(50)*. The most famous sound bite of that campaign was six words from former US President George H. W. Bush: "Read my lips: no new taxes." Since then, there has been some political pushback against sound bites. When Barack Obama ran for US president in 2008, he used YouTube and other websites to present lengthy policy speeches directly to viewers. But while presidential candidates can try to circumvent the news media and take their case directly to the public, others may lack that opportunity. As a result, the ability to condense what you have to say remains paramount.

Developing Effective Key Messages

Key messages are the three or four most important points you want to make during the interview. Yet scientists, physicians, and public health professionals sometimes think that the more points they can get across, the better, especially when the topic is complex. They may reason that the very next point will be the one that will help the reporter or their audience finally understand the situation or issue. Yet communicating too many messages is counterproductive. If you emphasized six or eight points rather than three or four, the reporter—not you—would determine your main message, and the story may not read or sound like you want it to. Focusing on only three or four key messages helps ensure that the reporter knows what's truly important (13).

Key messages should be concise and straightforward. Using short words and short sentences will help keep what you say simple, but you shouldn't dumb down the information to such an extent that the essence is lost (13). For example, substituting simpler terms for *comparative data,*

uniform baseline, and *environmental niche* in the following quotes could have aided public understanding without losing meaning:

> *"In terms of comparative data, I think we are probably several years off from having a uniform baseline," said Jerry Zuckerman, Head of Infection Prevention and Control at Albert Einstein Medical Center (51).*

> *"Only one bacterium out of a population has to survive in order to replenish that environmental niche with a complete new population of resistant organisms," Levy said (52).*

Key messages should use positive words whenever possible ("tests have shown that residents can drink the water" rather than "there is no documented evidence of health risks that would prevent people from drinking the water") and memorable phrases likely to capture the audience's attention:

> *Dr. Michael Osterholm, head of the University of Minnesota's Center for Infectious Disease Research and Policy, has called for a "Manhattan Project" to find a flu vaccine that does not need to be reformulated every year (53).*

Effective key messages can also help paint a mental picture for the audience, as shown by the following quote from Dr. Danuta Skowronski, an epidemiologist with the British Columbia Centre for Disease Control, in a story about the H1N1 virus:

> *"It is the nature of influenza outbreaks that they have that explosive upswing and then it's going to have to come down. But we're still at levels above the expected range, which means there is still sustained community transmission out there" (34).*

Key messages are not facts; they are value statements. They aim to *aspire* rather than to merely report or *describe*. "Our hospital reported 24 cases of infection during the past three months compared to 46 cases during the same period last year" is not a key message. It is a fact that could be used to help support a key message about the hospital's renewed commitment to reducing infection rates and to demonstrate that it is credible. Because key messages are value statements, one or two supporting points (or *proof points*) are needed to reinforce each key message. Proof points can be facts, statistics (used sparingly), analogies, and personal examples or anecdotes.

Using Key Messages

Why are key messages needed if the purpose of talking with a reporter is answering their questions? If you merely answer the reporter's questions, you will be helping them achieve their objectives for the interview but probably not your own. Instead, think about using the questions you are asked as a springboard to the messages you want to deliver. Key messages provide structure for the interview and help you maintain confidence and control. If you have good key messages and know them well, you can avoid becoming "lost" during the interview and saying things you wish you had not. Key messages can be a road map to guide you "home," back to the terra firma of what you want to say.

Limiting the Reporter's Choices

It's not only okay for you to repeat your key messages during an interview, it's desirable to reinforce them. Of course, you cannot keep repeating a message verbatim or you will sound like an automaton, but you can stick to the main point and change a few words here and there. Your goal is to limit the information choices a reporter has available for their story. You'd prefer they use one of your key messages rather than something that might be off the wall. That's why it's important to reiterate and reinforce your key messages. Think of it as a laying out an information smorgasbord for the reporter. Instead of offering a variety of main courses made of chicken, pork, fish, beef, and lamb, invite the reporter to the Chicken Buffet: offer only baked chicken, fried chicken, chicken fricassee, chicken kabobs, tandoori chicken, and chicken salad, to name a few dishes. All of them have the same main ingredient—your key messages—yet each has its own flavor and flair.

Using Visuals

Before talking with the media, it is important to decide whether you will use visuals to help illustrate what you plan to say. Using photos, charts, diagrams, and timelines during an interview may have both potential benefits and drawbacks. The best reason for using visuals is to provide information that is easier to understand or more compelling visually than verbally. If a visual doesn't add anything to what you have to say, complicates or contradicts your information, is outdated, difficult to read, or has poor-quality photos, you are better off not using it. Sometimes, people being interviewed use visuals as a crutch; they spend too much time going over the visuals and not enough time delivering their key messages. One suggestion is to ask a nontechnical colleague to look at the visual and decide whether it helps or hinders what you have to say.

Journalists at all types of media organizations may also request to post a copy of the visual on their websites. If this is possible, be prepared to tell reporters the source of the visual (or have it printed on the copy) so it can be attributed properly.

Getting Ready

Once you have developed key messages and decided whether to use visuals, the last major task before a media interview is to practice. Part of this task is rehearsing to deliver your key messages and proof points smoothly and professionally. The other part is to anticipate likely questions and practice answering them. Most people rightly worry about answering the tough questions. But sometimes it is simple questions that trip up someone being interviewed. For example, would you be able to give a simple, clear, and succinct answer if a reporter asked, "*Why do so many infections occur in hospitals*?" or even "*What do you do in the Department of Public Health?*"

You can ask a colleague, a member of the public relations team at your institution or organization, or a family member to role play as a reporter and ask you

some possible questions. Formal media training can also be very useful (resources provided at the end of the chapter). While anticipating questions and practicing answers will increase your self-confidence, you should not lose sleep worrying about every possible question. The single best piece of advice for preparing for an interview is to be well rested.

TALKING WITH THE NEWS MEDIA

When you have gathered background on the reporter and media organization, tapped the resources of the public relations team at your institution or organization, developed key messages, anticipated likely questions, and practiced answering them, it's time to talk with the news media. Using key messages reduces the chance of the reporter having to decipher what you said, guessing what your point is, or inaccurately describing your position (13). However, since you are not giving a speech but responding to questions, creating the opportunity to deliver your key messages can be challenging.

Staying on Course

You and the reporter have different game plans for the interview: the reporter has specific—sometimes very specific—information, comment, or opinion in mind that they would like you to say. You have key messages you want to deliver. It may sound as though a battle of wills may be brewing. But two key communication techniques, blocking and bridging and headlining, can help you stay on track during the interview without appearing to be nonresponsive.

Blocking and Bridging

Blocking and bridging is the technique used to take the questions you are asked and use them as a springboard to the messages you want to deliver. Blocking and bridging will seem unnatural and complicated at first and requires practice to do well. But done artfully, it is effective—and can look seamless. National political officials are often masters of blocking and bridging. Reporters may want to ask them about the economy, but if the officials prefer to talk that day about new education initiatives, they will use reporters' questions about economic issues to hammer home the importance of education to strengthening the economy.

Blocking and bridging is not about manipulating the news media or avoiding reporters' questions. But it is about taking full advantage of the interview to deliver the messages you have decided are important to your institution, organization, or agency—and to the public. To be successful, blocking and bridging requires both parts: the block and the bridge. The block is politely stopping the reporter's question in its tracks. The bridge is reframing the question so you take can the answer in a direction that aligns with one of your key messages. A block without a bridge looks as though you are being unresponsive. A bridge without a block may leave the reporter puzzled as to why you are talking about one subject when you were asked about another.

You must first acknowledge the reporter's question; never ignore it. But that doesn't mean you have to answer the question exactly the way it was posed. You can address the topic or the category of the question instead. For example, if you were asked: "*Isn't it true that thousands of otherwise healthy people go into hospitals every year for surgeries and become seriously ill or die from infections they acquire in the hospital?*" Answering that question precisely the way it was asked—"*Yes, but…*"—will immediately put you on the defensive and may lead to a series of equally negative follow-up questions. You recognize that what the reporter is asking about is patient safety. So using blocking and bridging, you can respond this way: "*I think what you're really asking me is what Northfield Medical Center does to protect the health of its patients. We have an excellent track record of ….*" and then continue with a clear, succinct explanation of one or two programs that have been implemented to help control infection.

You can also broaden or narrow the topic of the question. If you are asked about a problem, you can talk about a solution. And if you are asked about something you cannot talk about (such as a lawsuit involving your institution or organization), explain why.

A reporter may ask you to comment on behalf of another individual, institution, organization, or agency. For example, if you are an epidemiologist at County Hospital, you may be asked to comment on a recent outbreak at another hospital: "*What do you think caused the outbreak last week at Johnson Hospital? Does it signal a serious problem there*?" Since you cannot speak for anyone other than your own organization, institution, or agency, the "block" becomes a simple matter of saying, "*I can't speak for Johnson Hospital*." Your bridge might be: "*But as far as County Hospital is concerned ….*" and then talk about something County Hospital is doing or has planned to do to prevent outbreaks. In this way, you're taking a negative question about another institution and turning it around to say something positive about your own.

Reporters will sometimes ask hypothetical or speculative questions, such as: "*What will happen if the H1N1 flu virus mutates and becomes much more deadly to humans?"* While people being interviewed typically fear hypothetical questions, they are one of the easiest types of questions to block and bridge. Since you don't have a crystal ball, you can't answer hypothetical questions. Your answer might be: "*I can't speculate on what may or may not happen to the H1N1 virus in the months ahead. But what I can tell you is…*" and then talk about what your institution, organization, or agency is doing in terms of H1N1 preparedness.

Examples of Blocking and Bridging

"That's an interesting question. However, the real issue here is…"

"What you're asking me is…"

"I can't speak for ____. But as far as (my organization or institution) is concerned…"

"I can't speculate on what may or may not happen. But what I <u>can</u> tell you is…"

Headlining

Headlining is a communication technique to help you communicate successfully in today's sound bite-driven media environment. It means stating your conclusion first, just like a headline sums up the most important point in a story. This may seem alien to the way in which public health professionals and epidemiologists are trained to communicate: laying out the evidence piece by piece, summing up, and then presenting the conclusion. But if you use that approach during an interview, your conclusion may never see the light of day. The way in which you communicate with the news media needs to be the exact opposite: conclusion first, following by supporting material.

For example, if you are asked: "*If hospitals are so focused on cleanliness, why do so many patients get infections every year?*" you should resist the temptation to begin your response with a litany of infection-control measures the hospital has taken or plans to take and to conclude by saying that these measures have made patients and employees considerably safer. Instead, begin with the conclusion: "*The most important thing to know about Dandridge Medical Center is that it has become an increasingly safer place for patients and employees alike*." Then say: "*Here are just a few of the steps we've taken to reduce infection…*" and continue with a few clear, concise, understandable examples of specific actions and the results they have achieved. Adding these proof points will support your key message and help demonstrate that it is true.

Headlining also encourages the use of short, simple, bold words to make your messages meaningful and memorable. This helps audiences remember what you have to say.

Examples of Headlining

"The most important takeaway from this situation is…"

"Let me make one thing perfectly clear…."

"The real issue is…."

"It boils down to these three things…."

Avoiding Jargon

It's essential to avoid jargon when talking with reporters. Every field or profession has jargon—technical words, stock phrases, and acronyms you use every day as "verbal shorthand" with your peers. Often, people being interviewed cling to jargon as they would a life preserver, but it provides a false sense of security. The drawback is that neither the reporter nor the audience will understand. At best, using jargon will minimize the likelihood that your messages will be received clearly; at worst, it will make you come across as patronizing or condescending. This may prompt the audience to tune you out.

To strip jargon from your media vocabulary, you first need to be aware of what jargon you use and how often you use it. This includes acronyms such as *MRSA* and *C diff*., words like *pathogen* and *bacteremia*, and technical terms such as *nosocomial infections* and *symptomatic case-fatality ratio*. Jargon also includes terms laypeople have heard but may have difficulty deciphering: what is the difference between an *epidemic* and a *pandemic*, *contagious* and *communicable*, and *morbidity* and *mortality*? The audience may also think that *colonization* is a term from history books and that a *prion* is part of an atom. To be sure, run a "jargon check" on a friend outside your field, a family member, or neighbor.

As Dr. Michael T. Osterholm of the University of Minnesota notes, "Scientists feel the need to speak to the world in the same way they speak to try to impress their colleagues." But boiling down terms into everyday English and substituting simpler words for technical ones can boost clarity. Aiming for words that can be understood by a high school student— or, as Osterholm suggests, by your mother—is not a slight to the intelligence of the audience; rather, it reflects the fact that while you are an expert on the topic, your audience is not. And you cannot rely on reporters to signal when your words are too complex and ask you to translate. Sometimes, reporters will stop and ask what something means, but other times they may be too intimidated or embarrassed to acknowledge they don't understand and will let you continue, hoping—often futilely—that they can figure it out afterward.

Not Falling for Trap Questions

Most reporters don't deliberately set out to ask trap questions. Rather, it reflects the fact that their story is almost written by the time of your interview and the angle is most likely already decided. Reporters would like your information or opinion to fit neatly within those preconceived boundaries.

Of the four common types of trap questions, two have already been discussed in connection with blocking and bridging. The first is the hypothetical or speculative question. The second is the absent-party trap, in which the reporter asks you to put on the hat of another individual or organization and comment or explain on their behalf.

Another type of trap question is A or B dilemma, in which you are presented with two choices, both unappealing: "*Do employees at this hospital spread infection because they are careless about hygiene or because they aren't given adequate training?*" Pick either of the choices—perhaps the one you think is a lesser evil—and the reporter will likely ask a series of follow-up questions, while you have the potential to dig yourself deeper and deeper into a hole. But you don't have to pick either answer. Using blocking and bridging, you can steer the interview back to firmer ground: "*On the contrary, one of the top priorities at Mercy General is protecting the health of our patients, employees, and visitors. We do this by…*" and then cite two simple, concise examples of concrete actions to improve infection control.

The final type of trap question is the leading or loaded question, which is based on an erroneous assumption or faulty premise: "*Isn't it true that infection rates at Wellington Hospital have skyrocketed recently?*" or "*Since the government has been undercounting cases of H1N1, has it become more difficult to…?"* Since your answer will be built off that assumption or premise, you first need to politely but firmly correct the error: "*Before answering your question, I need to correct what you said about… In fact, …*"

Avoiding the Negative

Reporters often ask questions framed in a negative way. To buy themselves time to think of an answer, many people being interviewed tend to repeat reporters' negative

words and then negate them. It's the quickest and easiest response: "*No, this isn't a public health emergency*," or "*I wouldn't characterize this incident as a case of a rogue healthcare worker deliberately infecting patients*." But the audience tends to pick up on the negative words (*emergency*, *rogue, deliberately*, *infecting*) while mentally skipping over the "no," "not," or "wouldn't."

For example, when Joy Wells, director for health assessment at Cobb and Douglas Public Health in Georgia, told the *Atlanta Journal-Constitution*, "It doesn't mean that Cobb County is a hotbed of MRSA," she was likely repeating part of a reporter's negative question about reporting serious cases of community-associated MRSA *(54)*. But what is apt to stick in readers' minds is a single word: *hotbed*. And when Dr. Tim Brewer, an epidemiologist at McGill University, was quoted as saying, "This is not to engender fear or panic," in an *Ottawa Citizen* story about the government's response to a tripling in H1N1 cases, he was probably playing back the reporter's negative words *(55)*. While spreading fear and panic was the opposite of Dr. Brewer's aim, *fear* and *panic* may be the words readers most remember.

People being interviewed may also use negative words on their own, without prompting from a reporter, with equally damaging results:

> *"There are people who are thinking we're sweeping it (HIV) under the rug," said Jennifer Sizemore, a public affairs official with the health district. "But that's not the case at all" (56).*

Negative words to avoid include such seemingly innocuous words as "no," "not," "can't," "don't, "won't," and "never." They also include emotionally charged words, some obvious (*flesh-eating bacteria*) and others less so (*risk*, *danger*, *emergency*, *crisis*, *catastrophe*, and *problem*). There is a neutral word that can replace almost all these words, such as *incident* instead of *crisis* and *issue* or *challenge* rather than *problem*.

You can avoid repeating a reporter's negative words by beginning your response with a firm block that turns the direction of your response 180 degrees, such as: "*On the contrary…*" And you can circumvent using negative words of your own by pausing after the question to give yourself time to carefully craft your response.

When You Don't Understand the Question

If you do not understand a question, ask the reporter to repeat it. If you still don't understand, ask them to rephrase it. You can even play the question back to the reporter to make sure you are both on the same page: "*So is your question whether…?"* or "*If I understand you correctly, what you'd like to know is…*" The goal is not to make the reporter look foolish, but to prevent misunderstanding (8). Lack of understanding may also occur when a reporter asks a long, convoluted question with multiple clauses. There may even be multiple questions embedded within the question. Take the questions one at a time, and choose the question you want to respond to first.

Why You Should Avoid "No Comment"

It may seem that the easiest answer to a question you can't—or don't want to—answer is a simple "no comment." But you should strongly resist doing so. According to Dr. Vincent T. Covello, a risk communication expert, saying "no comment" makes it appear as though you are stonewalling or hiding something (57). And it is exactly the opposite of how you want to look in the news media, which is truthful, honest, frank, and open. If you can't answer the exact question, say why. For example: "*It is our hospital's policy not to comment on…*" or "*Government privacy regulations prevent me from talking about…*" But then try to follow up with something related that you are able to say: "*But I can tell you that…"*

When You Don't Know the Answer

Always be correct. If you don't know the answer to a question, don't guess or speculate. If it is possible to get the answer, offer to get the information for the reporter and call them back before their deadline—and then be sure to do so. If it is impossible to come up with an answer at this time, focus on what you do know and tell the reporter what actions you will take to get an answer.

Why You Should Not Go "Off the Record"

Reporters may ask you to go "off the record" and provide some information or comment you would be unwilling or unable to provide "on the record." Avoid going "off the record" because the term means different things to different reporters. Does "off the record" mean the information is for "background only" and cannot be print or broadcast at all? Or that the information can be used without attributing it to you? Either way, it's possible for a reporter to take what you say, shop it around to another source for confirmation or denial, and include the information in the story anyway.

Reporters seeking information "off the record" may appear to get chummy and make promises about how the information will and will not be used. Former CBS television reporter Connie Chung did that in 1995 when she interviewed the parents of Newt Gingrich, the new speaker of the U.S. House of Representatives. When Chung asked Kathleen Gingrich what her son thought of Hillary Clinton, wife of incoming US President Bill Clinton, Gingrich said she couldn't say. Chung leaned forward and said softly: "Just whisper it to me—just between you and me." Gingrich responded, "She's a bitch." The comment aired on national television and the video still circulates in cyberspace 15 years later. Rather than agree to a reporter's request to go "off the record," offer information you feel comfortable providing on the record.

Using Body Language to Your Advantage

Studies have shown that 80% of what viewers absorb from television newscasts is not the words of the person being interviewed but their body language. Even in an in-person newspaper or magazine interview, the reporter may pick up on your body language and reflect it in the story. Body language can hurt you (if it makes you look dishonest or stubborn) or help you (if you come across as credible, trustworthy, and authoritative). Since your goal is to come across as knowledgeable and sincere, following these few basic tips can help:

Body Language Tips for Television Interviews

- Watch your hands to avoid overgesturing with them. Letting your hands rest lightly in your lap (if sitting) or by your sides (if standing) is best.

- Don't jingle keys or coins in your pockets because it makes you look nervous.
- Don't cross your arms because it makes you look defensive.
- Don't put your hand over face because it makes you look as though you are hiding something.
- Don't look up at ceiling because it makes you look evasive or nervous.
- Keep your eyes on the reporter and don't look into the television camera; the camera person will frame your face.
- Don't smile inappropriately (for example, if you are talking about injuries).
- Don't rock back and forth when standing; plant one foot slightly in front of the other.
- If sitting, don't swivel in your chair.

What to Wear and What Not to Wear on Television

Dressing for a television interview is all about looking appropriate and professional, so your appearance will imbue credibility. Since you want people to pay attention to your words, anything about your appearance that distracts from what you have to say is a drawback. Small, busy patterns, such as checks and loudly patterned ties, do not come across well on television. The same goes for oversized, dangling, or noisy jewelry. If you are being interviewed outdoors, do not wear sunglasses. If it is a sit-down interview in a television studio and you are offered makeup by a professional makeup person, accept it. The combination of nervousness and the bright lights can make anyone perspire.

Ending the Interview

Near the end of the interview, you may feel that the reporter has neglected an important question or there is something you'd really like to say—or believe the audience should know. It's perfectly fine to point this out, and chances are the reporter will be only too happy to let you say it (8).

Talking with a reporter, whether it's a 5-minute stand-up interview with a television reporter or half an hour sitting across the table from a newspaper reporter, can be a tiring experience. You will be freshest and most likely to stay "on message" at the beginning of the interview; by the end, you may be getting tired. This is when mistakes are most likely to occur. As noted earlier, to prevent a situation in which a reporter can wear you down, set a time limit in advance for the interview and arrange to have a colleague or assistant stop in at that time to reinforce that you have other commitments.

Very few media interviews should require more than about 20 minutes. Dr. William R. Jarvis, the former CDC official, says he talked with a hospital official about her experience being interviewed about an outbreak for the CBS television news program "60 Minutes": "I asked her how long she talked with the reporter and she said, "45 minutes. It was great." I thought to myself that she was probably rambling forever and ever" and would ultimately be disappointed with the way she came across on television. Jarvis adds that he if he had been interviewed, would have set a strict time limit and ground rules, which he would have gone over in advance with the reporter.

You may notice that the reporter asks you the same question, perhaps worded slightly differently, multiple times. This reflects the fact that the reporter has a specific quote or comment in mind for the story. Being asked the same question over and over indicates you have done a good job sticking to your key messages and not a poor job answering the question. There was nothing wrong with your answer; it just didn't align with the reporter's preconceived notions. Don't let it make you stray from your key message. "If you don't keep drilling your sound bite—despite what the reporter wants to hear, which is not your sound bite—you could end up with a story that is very inflammatory," Jarvis says.

By the third time a reporter asks the same or similar question, it's perfectly okay to respond politely, "*I believe I've answered that question already to the best of my ability. Do you have another question?*"

It's Not Over Until…

It can seem a relief when the reporter finally closes their notebook or you see the light on the television camera being turned off. It's a great feeling to be done with the interview—except you're not. It's important to note that you are "on the record" with a reporter the entire time you are in their physical presence, whether it's riding in an elevator, having coffee, or walking them to their car. Even without a notebook, a reporter can make mental notes; even without camera lights, your voice may still be recorded by a microphone. Some reporters attempt to take advantage of the relief people feel when they think the interview is over and then ask the toughest question of all.

COMMUNICATING ABOUT RISK

Virtually every topic that public health professionals, healthcare epidemiologists, and infection preventionists deal with involves risk. Communicating with the public through the news media involves acknowledging and addressing those risks. But the situation may be fluid, the cause unknown, the outcome uncertain, misinformation rampant, and trust in short supply. What is the best way to talk with the news media in those types of situations?

What Kinds of Risks Do the Media Cover?

Mass communication researchers note that "there is an inherent conflict between the business of news and what social scientists and others call risk communication" (25). The news media communicate risk information "by the prominence and space accorded the account of a hazard, but these indirect signals need not correspond to the actual probability of its occurrence or the likelihood of its causing harm." Journalists have been criticized as "risk junkies" who seek out "ever more fantastic and doom-laden scenarios with which to titillate and terrify their audience" *(58)*. But studies show that the news media is just as likely to downplay the potential dangers of particular crises as it is to play them up *(58)*.

What the news media define as a hazard changes over time: nuclear energy and second-hand smoke are

but two examples of hazards whose perceived risks have fluctuated in media coverage. Moreover, there is no relationship between the amount of news coverage a hazard receives and the number of deaths it causes. There is an emphasis on catastrophic accidents rather than the "cumulatively greater but less spectacular risks" reflected in annual mortality figures (25). And patterns of media coverage do not necessarily parallel the actual trajectory of a particular threat (58). For example, coverage of *Salmonella* poisoning dramatically decreased in the British news media at the same time cases actually increased *(59)*.

The news media also emphasizes novel risks rather than chronic ones. This helps explain why avian flu and SARS make headlines, but seasonal flu does not. Risks are also perceived as more serious when there is someone to blame (for example, *E. coli* poisoning from a restaurant meal rather than exposure to radon gas from naturally occurring radioactive rock). And since "most existing information about risks is partial and contingent," risks can be simplified and distorted in news stories (25).

Different Interpretations of Risk

Research has found that members of the public look at risk very differently than do scientists, physicians, and public health professionals. Dr. Peter Sandman, a pioneer of risk communication, developed the classic equation:

Risk = Hazard + Outrage

While scientists and other technical people equate the level of risk with the technical degree of hazard, the public does not. For the public, outrage is the "wild card" in the equation: when feelings of outrage go up, perceptions of risk increase; when outrage is reduced, perceptions of risk diminish (60).

According to Sandman, factors involved in determining the level of public outrage include whether the risk is voluntary or involuntary, whether the risk is exotic or familiar, whether the risk is focused or diffused, whether there is a perception of trust or secrecy, and whether the risk is perceived as fair or unfair (for example, residents may be willing to put up with pollution from a nearby factory because they benefit from the jobs and taxes the facility provides, but once the factory's closing is announced the environmental risks may spark substantial community concern).

Communicating in a Crisis

The fundamentals of effective communication become even more important during a crisis. Simplicity, honesty, clarity, and brevity are the hallmarks of good crisis communication. According to Sandman, "Audiences are less tolerant of complexity when they're upset. Apathetic people just stop listening when they can't understand what's being said; interested people ask for clarification. But frightened or angry people decide you're trying to con them, and therefore become more frightened and more angry" *(61)*.

Dick Thompson, who manages outbreak communications for the World Health Organization, notes that every time you communicate during a crisis, you are either building trust or eroding it. "There are a lot of special things about outbreaks, but most important is that they're unfolding events," he says. "Nobody really knows where they're going and, especially in the beginning, there's high outrage and high concern in the absence of knowing what the hazard is" (24).

Ineffective communication—or the failure to communicate—can help a crisis grow and fester. Four excellent crisis communication tips from billionaire US investor and philanthropist Warren Buffett are as follows:

- Get it right
- Get it quick
- Get it out
- Get it over with

Speed is the essence of crisis communication. Try to get your key messages out first, because it will maximize the likelihood of balanced news stories. Otherwise, someone with less knowledge or no knowledge will attempt to fill the communication void. Your instinct may be to want to postpone talking to the news media because of lack of information, but it is okay to acknowledge that you don't have all the facts. It's important to communicate only what you know for sure and not to place blame. According to Covello, when in doubt, however, lean toward sharing more information, not less, so people do not think that something significant is being covered up or withheld (57).

Although it may seem like having to walk a verbal tightrope, do not minimize or exaggerate the level of risk, dismiss people's concerns, or overreassure (57). Keep your vocabulary simple and nontechnical and your messages short and clear. Sandman asserts there are a number of "risk words you can't use" during a crisis because of the possibility of misunderstanding, including *conservative*, *significant/insignificant, positive/negative, safe, prepared, confident*, and even the word *risk* itself *(62)*.

At the same time, use numbers carefully and sparingly. Do they make sense to laypeople? Are the numbers so big (billions of colonies of bacteria) or so small (parts per trillion of a toxin) that they are difficult to conceptualize? Making risk comparisons can also be tricky. Comparing the relative risks of something that is involuntary (such as a hospital-acquired infection) to things that are voluntary (such as smoking) can be perceived as callous, nonsensical, patronizing, or an attempt to belittle the risk at hand.

Caring and concern should be communicated during a crisis by expressing empathy. Empathy is putting yourself in other people's shoes and acknowledging the validity of their emotions and positions (57). An example is this quote in a story about a doubling in child deaths in Iowa from respiratory illnesses:

> *"What we're trying to do is see if there is a particular respiratory virus in some of these deaths," said Dr. Patricia Quinlisk, the state epidemiologist. "Any child's death is a tragedy and most of these children were otherwise healthy" (63).*

AFTER THE INTERVIEW

After talking with a reporter, it's a good idea to invite them to call if they have questions and provide contact information where you can be reached while the story is being written or produced. You can also offer to review the

technical points in the story before it airs, is published, or appears online. Some reporters will accept your invitation; others won't. A reporter may not have enough time before their deadline or believe they understand the information you provided. On the other hand, a reporter may appreciate the opportunity to run complicated parts of the story by you.

However, you should not insist on previewing the entire story before it is broadcast, published, or posted online. While prepublication review may be part of health and science, it is not part of journalism. Many reporters and their editors would consider it precensorship and bristle at the suggestion. In addition, numerous media organizations have policies forbidding sharing stories with sources prior to publication or broadcast. And if the reporter doesn't call you back, you shouldn't contact them again because it appears as though you are checking up on them (8). The exceptions are if you are following up with the answer to a question or believe you left out a crucial piece of information.

Evaluating Errors

After the story comes out, you may wonder why you spent so much time with the reporter just to have a sentence in a lengthy magazine article or a single sound bite in a television story. You may also have concerns about the content or tone of the story. Despite good intentions and hard work, reporters sometimes make mistakes. Reporters want people they have interviewed to let them know about factual mistakes in their stories but not to overreact. If you believe there are problems, evaluate them before you pick up the phone or click on the mouse to complain. You may also want to ask the opinion of the public relations team at your institution, organization, or agency.

Is there an egregious factual error? If so, be courteous and professional in requesting a correction. Sometimes, however, your concern is that the story was not written like you would have. Of course, if it was written as an academic piece, no one but your peers would read it. Perhaps you believe that the reporter "got it wrong" because of information that was excluded. But brevity is a constant characteristic of journalism; stories don't have room for all details, qualifications, and nuances scientists and public health professionals would like. Or perhaps you object because opposing views were included that challenge or undercut the information or comments you provided. But journalists are supposed to write balanced stories, which can mean providing equal time or space to opposing views.

Ultimately, you may have to balance what you believe to be weaknesses in the story versus the benefits of getting the coverage—and getting the information out to the readers, viewers, or listeners. Remember that the final audience is not the journalist or even other public health professionals, but the public.

OTHER MEDIA COMMUNICATION TOOLS

Interviews are only one way in which public health professionals can communicate with the public through the news media. Several other tools are described below.

News Releases

News releases are frequently used to communicate information to the news media. While the public relations team at your organization or institution will draft the release and decide how and where to distribute it, you may be asked to contribute information or be quoted. News releases can be distributed to specific types of reporters (such as health reporters) or to the editors who decide which stories will be covered by their media organizations (city editors at newspapers and assignment editors or news editors at television stations). They can also be customized for media organizations in specific geographic locations (for example, your state or province) or for certain kinds of media organizations (such as hospital industry publications).

The information in most news releases is available to be used as soon as the media organization receives it. Some news releases are embargoed, however. That means that the information cannot be used until a specific date and time. The goal is to allow equal access to information, but sometimes embargoes are broken by media organizations that want to get a jump on their competitions. Video news releases are like print news releases except they are accompanied by video and photos that can be used on air by television stations.

News Conferences

A news conference is another vehicle to get information to the public through the news media. During a news conference, one or more speakers provide information using a script or key messages. Afterward, reporters are allowed to ask questions.

An advantage of a news conference is that all reporters can be accommodated together, using the speakers' time efficiently. In addition, all media organizations get the same information, resulting in a level playing field. There are several potential drawbacks to news conferences, however. Competing "breaking" local news may limit attendance. Speakers need to be extremely well prepared; a gaffe made during an interview with a single reporter will be magnified when said to a roomful of journalists. A skeptical or critical reporter may turn the questioning hostile and other reporters may chime in. And reporters may still want individual interviews afterward to try to get unique information.

The Internet can extend the geographic reach and longevity of a news conference in two ways. In some instances, reporters who cannot attend a news conference can watch streaming video of the event online. They can then use a toll-free phone number to ask questions just like reporters there in person. A second type of news conference is conducted entirely online: reporters call a toll-free phone number while also calling up a PowerPoint presentation. The speaker or speakers walk through the presentation over the phone and the reporters then ask questions by phone. The presentation materials remain online for viewing and downloading, along with an audio file of the news conference.

If you are participating in a news conference, you need to develop key messages just like you would for an interview. Other tips include checking out the location beforehand and rehearsing your remarks until you can deliver

them smoothly and confidently. If there will be other speakers, it's a good idea to rehearse together to avoid duplication and inconsistencies. Give yourself plenty of time to practice answering likely questions. Before the news conference begins, remember to turn off your cell phone. And when others are speaking, it's important to remain engaged and not look bored.

Op-Eds, Guest Columns, and Letters to the Editor

Another way to provide information to the public through the news media—but unfiltered by a reporter—is to write it yourself. Letters to the editor are brief and may reflect a personal viewpoint on an issue or topic covered in the newspaper or magazine. Op-eds, so called because they appear on the page opposite of the editorial page in newspapers, provide a longer format. Guest columns in magazines or online news sites provide similar opportunities. Both enable you to demonstrate expertise by explaining a situation or issue, helping to put an issue or development into context, presenting or expounding on findings, or providing perspective and opinion. Both are edited by the publication for length. Once you publish an op-ed or guest column, you can extend its reach by turning it into a blog post or newsletter item.

Desk-Side Briefings

Desk-side briefings are a great way to get to know reporters who cover health issues in your community. You can offer to meet with them at their office to provide background on an issue, explain what you do, put a human face on your institution or organization, and provide your contact information (alternatively, you can invite the reporter to your facility). This can be especially helpful for a reporter new to the beat. Like other situations in which you talk with the news media, however, you should establish ground rules upfront: will everything you say be on the record? A desk-side briefing typically does not result in immediate news coverage, but it helps establish you as a "go-to" resource for future stories.

KEYS TO A SUCCESSFUL WORKING RELATIONSHIP

Some public health professionals, healthcare epidemiologists, and infection preventionists not only survive the experience of talking with the news media, they realize that continuing to do so can provide ongoing benefits to the public, to their institution or organization, and/or to their own reputation. They may make the transition from once-reluctant interview subject to trusted news source.

Being a news source is a reciprocal relationship. The reporter contacts you for opinion or information; at the same time, you proactively contact the reporter with story ideas and information or views you believe should be communicated to the media organization's audience.

What Reporters Look for in Sources

In addition to expertise, reporters typically look for three other characteristics in potential sources. The first is accessibility and responsiveness. Willingness to talk to a reporter and having the most fascinating information to share won't suffice if it takes days to return their call or to gather promised information. Recognizing that reporters face frequent deadlines and, often, fierce competition, this may mean taking or returning calls on nights, weekends, or holidays. In this era of a 24-hour news cycle, responding promptly to a reporter can make the difference between their story being "the first" or an "also ran."

Another valued attribute in an expert source is truthfulness. Beyond not lying or stretching the truth, it means being upfront when you don't know an answer. And your expertise only goes so far: if someone else would be a better expert for a story, let the reporter know.

While reliability and truthfulness may be easy to acquire, pithiness—the third prized attribute—may seem more like an art form. It's the ability to get to the heart of an issue, to say something worthwhile and interesting in a simple, concise, and sometimes unexpected way, using colorful but down-to-earth metaphors and analogies rather than abstract concepts. An example is the following story about a measles outbreak linked to an increase in the number of parents rejecting childhood vaccinations:

> *"The very success of immunizations has turned out to be an Achilles' heel," said Dr. Mark Sawyer, a pediatrician and infectious disease specialist at Rady Children's Hospital in San Diego. "Most of these parents have never seen measles, and don't realize it could be a bad disease so they turn their concerns to unfounded risks. They do not perceive risk of the disease but perceive risk of the vaccine" (64).*

Over time, mutual trust will hopefully develop between the reporter and source. Dr. Michael T. Osterholm of the University of Minnesota says he has been a source for some reporters for 15 to 20 years. "They trust me and I trust them," he says. Sources and reporters also need to negotiate boundaries: Is it okay to call on weekends? Are you willing to do stand-up television interviews on a half-hour notice? Are there topics that are off limits? Don't be surprised that once you become a source to one reporter, you are contacted by other reporters who see you quoted in stories and think you may make a good source for them as well.

A Friendly Relationship, but Not Friends

Reporters may act in a friendly way, but they are not your friend. While you share the broad goal of serving the public, there may be an inherent conflict in your respective missions. As a representative of an institution, organization, or agency, you want a story that will support your position, issue, colleagues, or organization—that will hopefully promote it, defend it, justify it, and put it in the best possible light. On the other hand, reporters want a story, period, and the more controversial or sensational, the better. As long as the two of you understand and accept each other's motives and missions, you can have a positive professional relationship. But becoming friends blurs the lines between the professional and the personal and raises potential pitfalls, including troublesome questions about when and where you are "on" and "off" the record.

RESOURCES

Many resources are available to help you become more skilled at communicating with the public through the news media. Following are some suggestions:

Books

- *A Scientist's Guide to Talking with the Media* (2006)—This book is detailed and thorough yet accessible and easy to read. Richard Hayes, media director for the Union of Concerned Scientists, and Daniel Grossman, a science journalist, team up to share practical advice based on their considerable professional experience.
- *Am I Making Myself Clear? A Scientist's Guide to Talking to the Public* (2009)—Cornelia Dean, a science reporter and former science editor at *The New York Times*, wrote this book to encourage scientists to take a more active role in communicating with the public. In addition to explaining how journalists cover science, she provides tips on how to tell science stories on radio, TV, and online.
- *Don't be Such a Scientist: Talking Substance in an Age of Style* (2009)—Randy Olson, a former marine biologist turned filmmaker ("Flock of Dodos"), authored this book to spread the message that scientists have to loosen up, be likable, and learn how to tell stories if they want to have a greater impact on society.
- *Handbook of Science Communication* (1998)—This book, compiled by Anthony Wilson, is broader than *A Scientist's Guide to Talking with the Media* and includes how to give presentations and write up research. Chapter 4, "Working with the Media," is especially relevant.

Online Resources

- The Science Media Centre in the UK has three concise guides available for downloading to help scientists talk with the news media. "Top Tips for Media Work," is a useful overview for scientists who are new to talking with reporters; it is available at: http://www.sciencemediacentre.org/uploadDir/admintop_tips.pdf. "Communicating Risk in a Sound Bite" and "Communicating Uncertainty in a Sound Bite" can help scientists prepare for broadcast interviews. They are available at: http://www.sciencemediacentre.org/uploadDir/admincommunicating_risk.pdf and http://www.sciencemediacentre.org/uploadDir/adminuncertainty_in_a_sound bite.pdf
- "Why Scientists Should Talk to the News Media"—A video of a panel discussion at the Yale University School of Medicine about the importance of communicating with the public. Practical advice is offered by Denise Grady, health reporter for *The New York Times;* Ron Winslow, a reporter for *The Wall Street Journal;* and Mariette DiChristina, editor in chief of *Scientific American*. You can watch the video on the website of the Council for the Advancement of Science Writing: http://casw.org/videos-october-2009-brown-bag-event-yale

Training

There is no substitute for hands-on media training. A half-day or daylong media training session can help you feel confident and prepared when you talk with reporters. Media training involves hands-on practice, in which you are videotaped doing mock media interviews on realistic topics. Afterward, the interviews are played back and critiqued.

If you are interested in media training, ask the public relations team at your institution, organization, or agency if they have media training experience and capability. If not, they may be able to arrange a session conducted by an outside public relations professional who specializes in media training or a member of the public relations faculty at a local university. Other media training resources include:

- APIC has offered a media training workshop at annual conferences. While the 1-hour workshop does not provide hands-on training and critique, it covers basic points in how to prepare for and conduct interviews. To find out if a similar workshop will be offered at an upcoming annual conference, go to www.apic.org and click on the conference link on the home page.
- Research! America offers communication training for scientists. Contact Karen Goralewski at: kgoraleski@researchamerica.org.
- Media training opportunities for scientists in the United Kingdom are described on a government-sponsored website, Science So What? So Everything: http://sciencesowhat.direct.gov.uk/get-involved-in-science/get-involved/media-training-for-scientists
- The Aldo Leopold Leadership Program at the Woods Institute for the Environment at Stanford University provides media training for environmental researchers. Pam Matson, the leadership institute's scientific director, gave an overview of the training program on National Public Radio's "On the Media" program. It can be accessed at: http://www.onthemedia.org/transcripts/2009/02/13/05

Other

- Both the American Association for the Advancement of Science and the British Science Association offer fellowships for scientists to work for short periods at media organizations to experience what it is like to communicate with the public. More information is available at: http://www.aaas.org/programs/education/MassMedia/ and at http://www.britishscienceassociation.org/web/ScienceinSociety/MediaFellowships/index.htm

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SECTION III
Informatics in Healthcare Epidemiology

CHAPTER 15

Using the Personal Computer for Healthcare Epidemiology

John A. Sellick, Jr., Keith F. Woeltje, and Rebecca Wurtz

We live in the information age. The effective and comprehensive use of digital information in healthcare epidemiology and infection control is both desirable and necessary. This chapter discusses computer systems, networks, and the Internet from a high-level perspective. Because of space limitations, it is not possible to discuss each computer system, software package, network configuration, or troubleshooting program or to refer to specific products. Rather, this chapter provides a conceptual framework for discussing information services (ISs) in a healthcare setting.

THE ROLE OF THE HEALTHCARE EPIDEMIOLOGIST IN HEALTH INFORMATION MANAGEMENT

For the purposes of this chapter, health information management will be defined as the storage, exchange, and analysis of data generated by healthcare. The term "health information system" encompasses the digital hardware and software applications, architecture and network structure, interoperability standards, and policies governing the generation and use of health data.

The healthcare epidemiologist (HE) and quality officer obviously have a fundamental need for the data generated in electronic health systems. Almost no one else in the hospital and ambulatory setting routinely and systematically analyzes aggregated clinical data and data patterns. A common complaint following the implementation of enterprise-wide health information systems is that "data goes in, but I can't get anything out." It is essential for the HE to be knowledgeable about and involved in discussions about data elements, extraction, analysis, and visualization during the implementation and updating of information systems. Ideally, the HE develops the skills and permissions necessary for querying databases and extracting data without requiring a middleman. Healthcare organization IT departments are often overburdened and may not respond in a timely way to requests for query construction and data.

COMPUTER SYSTEMS AND NETWORKS

Historical Perspective

The Era of the Mainframe Historically, electronic data processing in large organizations, including hospitals, was done on mainframe computer systems. These monolithic systems were developed to support the fiscal and demographic data needs of healthcare organizations and became known as management information systems (MISs). Healthcare MISs have matured to include clinical components such as laboratory, pharmacy, and radiology information systems and clinician order entry, making important patient data more readily available to care providers. Data management systems for a myriad of other discrete purposes, such as surgical, obstetrical, and emergency department resource and inventory management, are available. Data input generally is from a keyboard terminal or directly from laboratory equipment. Printing may be done at central, high-speed printers or distributed network printers.

Mainframe computer software operating systems (OSs) and applications software typically were cryptic and complicated, requiring extensive expertise and time for setup and maintenance. Access for end users usually was through a hard-wired (directly connected) dumb terminal, essentially a monitor with an attached keyboard. User interaction was restricted to a set of defined keyboard commands and functions, often in the setting of predesigned menus or screens.

Attempts were made to develop customized mainframe infection control software to capture relevant demographic and clinical data, and then merge them with surveillance data collected and entered for individual healthcare-associated events (1,2). Standard reporting templates allowed the production of a wide variety of summary reports at set intervals, and provisions were made for the retrieval of data via *ad hoc* queries when the standard reports were insufficient (3). These custom-developed mainframe infection control data management systems typically were developed through cooperative efforts between infection control and the IS departments of a few larger hospitals. They were usually computer OS specific and thus difficult to adapt to other institutions with different computing configurations. Their high development (1) and maintenance costs and their lack of adaptability to other computing environments made them impractical.

The Rise of Personal Computers In the 1970s and 1980s, desktop microcomputers, often called personal computers (PCs), were developed by Apple, Inc. (Cupertino, CA) and International Business Machines Corp. (Armonk, NY). They have become so ubiquitous that most people associate the term computer with desktop microcomputers. The terms personal computer, desktop computer, and microcomputer all describe the same machine and are used interchangeably. These user-friendly machines sport a graphical user interface (GUI) and a control device such as a mouse or trackpad along with the ability to connect to a network and local printer. External input devices such as scanners and bar-code readers are inexpensive and easily attached, as are removable media (hard drive, disk, cartridge, or tape) storage and backup devices. (The standards for such connections are set by the Information Technology Working Group of the Institute of Electrical and Electronics Engineers [IEEE] and often are referred to by number.)

Stand-alone desktop computer hardware and software tools allow for a large measure of autonomy in developing and maintaining data management systems independent of the hospital's information system. As a result, they have significantly altered the practice of surveillance, data management, and data analysis in healthcare epidemiology. Both infection control-specific software programs and generic database management programs are available to develop customized infection control databases. Word processing, statistical analysis, charting, communications, and presentation programs fulfill the remaining needs for most healthcare epidemiology and infection control providers.

Unfortunately, the learning curve for computers and software may be steep, and even software designed specifically for infection control may be difficult to use (4,5). Data often must be manually entered, which is time-consuming and leads to errors. Moreover, the distributed nature of personal computing has resulted in both duplicative and fragmented data sets throughout organizations. Similarly, the keepers of individual databases may be unwilling to share data with others and may not take the necessary steps to ensure the integrity and safety of their data.

The Advent of Client/Server Computing The desire for both the flexibility of a microcomputer and access to the data archives and computing power of a mainframe computer system led to the development of client/server computing. In this system, the desktop computer is a "client" that can connect to a "server" of data and software applications via a network. A network is a series of hardware devices and wiring that connect any number of client or server computers, printers, storage devices, etc. The network also requires its own software or protocol in order for the various devices to communicate and function with one another. Ethernet is the commonest network hardware specification and communications protocol for local area networks (LANs) in use today. There are a variety of network operating system (NOS) software products available to control the services, for example, access to files and printers, provided by the LAN.

A server may simply store files, deliver messages, and queue print jobs, or, in the true sense of client/server computing, it may provide for interaction and shared computing capability between the client and the server. The potential benefits for healthcare epidemiology and infection control services of having a computer attached to an information-laden server on a LAN are readily apparent. With proper client software, the organization's demographic, clinical, laboratory, and financial databases can be searched, data analyzed, and items of interest moved to the client computer for further use or analysis. Other tasks such as providing backup copies of files or sharing documents and mail with other clients on the network are easily accomplished.

The appeal and potential benefits for client/server networks is considerable, but so are the potential problems of implementation. The databases on large servers generally are built using proprietary systems that require additional software and training for appropriate use. Intermediary programs, collectively called middleware, may be needed to create an interface between the client and the database to extract the information desired by the healthcare epidemiology service. However, if this can be accomplished, the rewards can be great once the desired data are identified, collected, and analyzed.

Recommendations for Personal Computer Systems

It is not possible to recommend a "one-size-fits-all" approach to computerizing a healthcare epidemiology or infection control service. As with purchasing a car, the users must evaluate their requirements and budget. Most organizations have moved to a client/server model of computing, making it feasible for healthcare epidemiology team members to have PCs that may fill several roles and satisfy multiple needs. The selection of hardware and software should take into consideration the requirements of connecting to a LAN and accessing a mainframe or other server(s). Consultation with the appropriate university, hospital, or other organization's IS department can provide guidance in these areas.

Hardware If choosing a PC, the first decision to be made is whether to purchase a desktop/minitower or a laptop. The former traditionally have offered the potential of greater power and expandability; however, current laptop models have more than adequate power for almost all healthcare epidemiology functions, plus the advantage and potential problems of portability. Likewise, the availability of universal serial bus, IEEE 1394 ("Firewire"), and ExpressCard or CardBus ports make laptops widely expandable as well. Laptops typically come with active matrix (thin film transistor) liquid crystal diode displays, but a display is a separate item for desktop units. The ultimate decision regarding the choice of desktop vs. laptop often will be a financial one, but the issues of ergonomics and security of the equipment also must be considered.

Regardless of whether a desktop or laptop unit is chosen, it is important that it have adequate random access memory (RAM) for anticipated tasks, an adequate size hard disk drive, and an optical drive. The latter may be a CD-ROM reader or a drive that both reads and writes CD-ROM media (CD-RW). Drives that combine CD-RW with the ability to read and write DVD-ROM (digital versatile disk) media also are widely available as either internal drives or external drives. These will accommodate the use of the many software titles, educational programs, and databases available on optical media. Appropriate networking connections such as Ethernet cable ports or adapters or wireless networking receivers (see below) also are necessary. If not connected to a network, a telephone modem will be needed to connect to the Internet.

Information "output" is a critical part of healthcare epidemiology and infection control and a variety of options are available. Often, a printer will be used and the two types in widespread use are the laser and inkjet varieties. The laser printer fuses microscopic plastic toner particles to a page (paper or transparency) the same way a photocopier does, while inkjet printers deposit droplets of ink on the pages. Laser printers usually are monochrome/grayscale, while almost all inkjet printers produce a full spectrum of colors, including the ability to produce photographic quality prints. Laser printers generally cost more to purchase, but inkjet printers usually have a higher cost of "consumables," namely, ink cartridges and specially coated photographic paper and transparencies. It is important to compare per page costs and also individual needs, that is, frequent presentations might argue for an inkjet printer that can produce color transparencies while predominantly paper reports might favor a laser. It is worthwhile to investigate if a workgroup printer, available to several individuals or departments, is available since it may allow costs to be shared or even avoided.

Presentations may be sent directly to electronic multimedia projectors, but these devices generally are too expensive for individual or even departmental purchase. Most hospitals and universities have them installed in conference/lecture rooms or available for use and/or loan. Information also can be "published" on an intranet or the Internet (see below) using one of the many simple software programs available.

A method to provide backup or duplicate copies of important data must be provided, whether through a local device (such as an external hard drive) or a network file server, so that important or unique information may be retrieved in the event of equipment failure or theft. Many organizations provide each user with "space" on a network file server for copying important files, though this may not be large enough to copy an entire hard disk drive. A DVD-RW with appropriate software is a convenient and inexpensive way to make duplicate copies of important files or even an entire hard disk drive. External hard disk drives now are very inexpensive and much faster than optical drives. They may be disconnected and stored in a safe place.

Operating Systems An OS is the core software that enables computers to function, communicate with the hard disk drive and other devices. Several such systems are in widespread use. Microsoft Windows (Microsoft Corporation, Redmond, WA) is most widely used. However, Apple MacOS and a number of UNIX variants such as the freeware Linux also are popular. OS software often is hardware specific in either type or speed, sometimes both. Other than applications written in Sun's Java programming language, software written for one OS does not run on computers that use a different OS. Also, application software may be specific for different versions of the same OS. For example, documents created using Windows 7 may not open on prior Windows versions. It is important to thoroughly understand the processor, memory, and hard disk space requirements of any OS or application software prior to purchasing it.

Basic Software Aside from the OS software, application software programs (often called applications, software or programs for short) are needed to make a PC more than an expensive Tetris machine. Basic software tools include a word processor for making reports and writing correspondence; a spreadsheet for making calculations and graphing data; a database for storing information, such as surveillance data; and a presentation program for making electronic slideshows and other visual reports. These basic tools often come as part of an "office" suite of software, which may be proprietary (e.g., Microsoft Office) or open source (e.g., OpenOffice.) Price, required RAM, hard drive storage space and the expertise required for efficient use are variable. Before purchasing software, attempt to evaluate it with a demonstration version (often available from publisher Web sites) or on a colleague's PC. Software user reviews are widely available online. Universities, hospitals, and other large organizations often have site license agreements with software publishers that will provide basic software at little or no cost to employees or affiliated professionals.

Basic software also may include statistical analysis software, which no longer requires a mainframe computer to use. Many commercial packages as well as the freeware Epi Info from the Centers for Disease Control and Prevention (http://www.cdc.gov/epiinfo) are available for PCs.

Modern software, running on a GUI-based computer, has the ability to change typefaces (fonts), manipulate typeface styles, organize materials, and add tables, charts, or images to a document. A report of epidemiologic activity, therefore, could include text with bold headings, a table of key data, and several salient charts that result in a clear, concise, and compelling document. However, the very features that allow for this flexibility also can make the report

garishly unattractive if used in excess. In general, multiple typefaces should not be used in a single document, and script or other specialty typefaces should be avoided since they are difficult to read. Likewise, underlining and ALL CAPITALS are distracting and difficult to read in a body of text; emphasis may be added with boldface or italics. Some of the most egregious violations of publishing taste occur with newsletters and information sheets which, along with excessive typeface manipulation, often contain excessive amounts of clip art and other nontext items. Many publications are available to provide guidance for creating attractive documents and compelling visual displays of quantitative information (6,7).

Personal Digital Assistants and Smartphones

The last decade has witnessed the explosive growth of shirt-pocket–size devices known as personal digital assistants (PDAs). Originally developed to be date books and a place to store names and contact information, these small computers have increased in speed and memory and now can provide data retrieval, basic word processing, statistical and database functions. Newer models include wireless access to the Internet or to local networks using the IEEE 802.11 standard. As with PCs, there are competing product platforms available: the original PDAs were produced to run the Palm computing platform (Palm, Inc., Sunnyvale, CA) or a "mobile" version of Microsoft Windows.

Many popular cellular telephone network devices, such as the BlackBerry devices of Research In Motion (RIM, Waterloo, ON, Canada), have emerged in the past few years. Dubbed "smartphones," they offer PDA functions along with Internet/electronic mail access as well as voice telephony. Palm also has transitioned completely away from standalone PDAs to smartphones.

In early 2007, Apple, Inc., introduced the first iPhone and has released several updated versions. Along with PDA, audio playback and telephone functions, this device runs small applications, now commonly called "apps," which gives it computer-like functionality. A nearly identical device, the iPod Touch, and the recently released iPad tablet have the same functions without cellular telephone capability. These devices offer 802.11 wireless Internet communications as well.

Apps for the iPhone, iPod Touch, and iPad have been developed for many purposes including medical applications and can be purchased and/or downloaded from the iTunes store. These include drug databases, medical calculators, and a hand hygiene assistant called iScrub that was developed at the University of Iowa *(8)*. Through the use of third-party software, it also is possible to read Microsoft Office and Adobe portable document format (pdf; Adobe Systems, San Jose, CA) documents. Audio programs called "podcasts" also may be downloaded, and there are many medical lectures, news summaries, journal commentaries, etc., available. In response, some smartphone device manufacturers such as RIM have updated their OSs to offer similar apps and services.

In a recurring theme, the software made for one platform will not run on another and not all titles are available for all platforms. The potential user must evaluate these devices based on intended use, availability of apps and cellular network. Note that the iPhone and smartphone cellular contracts mandate an additional network data service charge beyond cellular voice service charges. Since PDAs and smartphones do not have built-in hard disk drives, it may be necessary to "synchronize" them with a PC to ensure data retention, availability, and security.

This group of devices holds promise in the healthcare setting though there are few data describing specific uses in healthcare epidemiology and infection control (*8*,9). Most uses appear to be for schedules, calculators *(10)*, and pharmaceutical databases, so cost, personal preference, etc., will determine purchasing decisions. One theoretical "downside" of these devices is the potential to be fomites (11,12).

CONVERTING DATA TO INFORMATION

Data

Data for infection prevention can come from a wide variety of sources. Manually collected data (e.g., device days) can be entered by hand. Many data can be obtained electronically from hospital systems. Chapter 16 discusses the use of the electronic medical record for infection prevention and enterprise-level surveillance support. But even those who use their desktop PCs for supporting infection prevention activities can benefit greatly by receiving reports electronically in formats that can be imported into the analytic software they use. Many hospital departments may be able to generate reports (e.g., lists of surgical patients, patient days by ward) in standardized formats (see below) that many PC programs can import. This is certainly faster than reentering the data, but more importantly, avoids the possibility of transcription errors.

When trying to use data from multiple sources, it is important to ensure that the same terminology is used consistently. A wide variety of standardized terminologies exist for medical purposes (e.g., ICD-9, SNOMED). While each terminology is usually used for specific purposes—such as ICD-9 for billing—these often overlap, and even within a single institution different departments or computer systems may use different terms for the same fundamental concept. In such cases, there will be a need to settle on a standard terminology for infection prevention, and translate or "normalize" other codes or terms when necessary.

Once systems are in place to obtain data, provisions should be made for ensuring data integrity and completeness: that all relevant data are transmitted intact, that missing data are detected and replaced, and that new systems and terms are handled appropriately.

Spreadsheets

Even more so than word processing software, spreadsheet software ushered in the PC era. Spreadsheet software remains one of the most versatile tools at the disposal of the HE. Spreadsheet software is any application that allows data to be stored in the familiar row and column layout; Excel (Microsoft, Redmond, WA) is one example. All infection control personnel should know how to use an electronic spreadsheet.

Flat-file Database The column and row design of computer spreadsheets lends itself well to use as a "flat-file"

database. This is a database where all of the information can be contained on a single page (see the discussion of databases below for other types of databases). Typically, the first row is used to enter headings for the information to be collected (i.e., the database "field"; e.g., Name, Age, etc.). Each subsequent row is then used to store information for one subject (i.e., a database "record").

Although database programs can also be used for such flat-file databases, using a spreadsheet for this purpose has a number of advantages. For many users, a spreadsheet is almost always included with their office suite of software, whereas a database program will probably have to be purchased separately. Some users familiar with the use of a spreadsheet for calculations can extend that familiarity more easily than learning an entirely new program. Some statistical software may be able to import data from a spreadsheet table, making the spreadsheet file format a "common denominator" for sharing data between programs.

One of the handiest features of spreadsheets is the "filtering" function. This allows the user to see only records that meet a certain criterion. Although the same information may be obtained from a true database program, it typically involves more work. For example, an ICU may want to keep track of the intravenous devices used on various patients. In a spreadsheet, there may be a column for patient name, and others for medical record number, date of admission to the ICU, etc. A column could then be made for "IV device used." Then, "peripheral catheter" or peripherally inserted central catheter (PICC) or "triple-lumen catheter" could be entered into this column. By using the filter function, one could readily see all of the patients that had a PICC line. But typically, an ICU patient will have multiple types of IV catheters. One could have a column "IV catheter 1" and another column "IV catheter 2," and so on. But consider what would be necessary to find all of the patients who had a triple lumen catheter. First one would have to filter for "triple-lumen catheter" in the "IV catheter 1" column, then in the "IV catheter 2" column, etc. One way to get around this is to have only one column for device and then enter a new row for each type of catheter the patient had. However, this would mean duplicating the patient demographic data for each row and would make a simple count of the patients or calculations like the mean patient age difficult. A more effective option would be to have a column for "triple-lumen catheter" with either "Yes" or "No" listed for each patient. A search for patients with such a catheter would only require that "Yes" be filtered for in that column. Obviously, such a system would become unwieldy if there were a large number of options, but for limited numbers of choices, looking up data can be very efficient. Many spreadsheets will filter on multiple columns, so that, for example, patients with both a PICC line and a triple-lumen would require only filtering for "Yes" in both of these columns.

Simple Calculations Although spreadsheets can be used for simple database functions, they were designed primarily to do mathematical calculations. Spreadsheet software can easily handle nonstatistical data needs of an HE. Users can enter very complex formulas, although for most purposes only relatively simple formulas are necessary. Rates, the fundamental calculation of the epidemiologist, are trivial calculations for these programs. Tables can be created to show rates over time such as monthly. As we'll see, such time series also lend themselves to graphing the data.

A great deal of the power of spreadsheets comes from the ability to program formulas that refer to other cells, even cells that are on sheets other than the one with the formulas. This can be used to great advantage. A user can, for example, use one sheet for entering National Healthcare Safety Network (NHSN) rates into designated cells. That way all other pages are automatically updated for the latest rates without having to enter them into each page or formula separately.

Another powerful capability of spreadsheets is the ability to copy formulas from one cell to another. Thus, once a formula is written, say for a rate calculation, it need not be reentered from scratch over and over again, but can simply be copied. One must be careful to ensure that formulas are copied correctly. Each cell in a spreadsheet has a unique "address," typically formed by the column letter and row number of that particular cell. Thus, the cell in column "C" on row "22" is designated "C22." Sometimes, when copying formulas, the user wants the column or row number to change. Consider a column D with January surgical site infection data. Row 8 has the number of infections and row 9 the number of procedures. Row 10 is designed to have the rates. The user can enter a formula like (D8/D9)*100 to calculate the SSI rate per 100 surgeries in cell D10 (the exact method to designate that there is a formula within in a cell, as opposed to just text, will vary depending on the spreadsheet software used). Column E then will represent February data. Rather than retyping the formula in cell E10, the user can copy the formula from row D10. But the formula must read (E8/E9)*100—the February, not the January data must be used. In other cases, for example, when calculating standardized infection ratios, the user will likely want to use the NHSN rate in multiple calculations. If the spreadsheet is set up as previously mentioned, with NHSN rates entered into designated cells, then the user must be sure that that cell reference stays the same even when formulas are copied. Spreadsheet software has different ways to designate whether the cell references can be changed when a formula is copied.

Although users can enter formulas to calculate summary data (e.g., adding up monthly numbers of VAP cases to get annual numbers of VAP cases), most spreadsheet software allows for more automated ways of doing this. These summary tables go by different names depending on the software; Microsoft Excel (Microsoft Corp., Redmond, WA) calls them "Pivot Tables," whereas OpenOffice Calc (OpenOffice.Org, www.openoffice.org) uses the term "DataPilot." They can be used to quickly aggregate data into a variety of formats (e.g., number of positive blood cultures by patient care unit by month) that would be tedious to program by hand.

ADVANCED STATISTICS

Spreadsheet software programs can readily handle the calculations needed for most statistics, providing simple built-in statistical formulas in which to enter data. The user must select the appropriate statistical test, but the

software does the calculation. Devising and entering very complicated formulas, however, is often tedious and error prone. In addition, these programs typically allow for "add-ins." These add-ins are additional pieces of software that extend the functionality of the base program. Statistical add-ins may come with the spreadsheet software itself (but not installed with the basic program) or are available from commercial software houses. As an example, Microsoft Excel comes with additional tools in what is called the "Analysis ToolPak." This allows more advanced statistics, such as analysis of variance (ANOVA), to be run. These add-ins can certainly extend the capabilities of spreadsheets to do fairly advanced statistics; however, even with these functions, there is still a need for a significant amount of formula entry by the user (frequently along with some programming using the macro language available in the software).

Besides add-ins, spreadsheet templates may be available. These are typically spreadsheets with column or row labels that indicate where data should go. Formulas are already entered in, so that all the user needs to do is fill in the blanks. These are typically much easier to use than add-ins, but one must be sure that the context for which the template was designed actually fits the user's situation.

For users who are very familiar with their spreadsheet software and who are comfortable modifying formulas in templates that may have been written by others, or writing complicated formulas themselves, add-ins and templates may provide a good solution for their needs. For most HEs, however, a specific statistical software program may be easier to use.

Database Software

Although spreadsheets are often used for data storage, they have distinct drawbacks. Databases made in spreadsheets are often termed "flat-file" databases—with their column and row layout they are like a flat sheet of paper. Although many times data collected for epidemiology can easily be fitted to this flat-file model, all too often data are forced to fit this model in an awkward manner. This was somewhat apparent in the previous discussion on using a spreadsheet to capture ICU patient catheter data. One can imagine that if there are multiple variables to be captured, such as microorganisms cultured or which healthcare workers saw a given patient, then any of the options for using a flat-file database would be unmanageable. In such circumstances, a true database program is called for.

True database programs were designed specifically for the task of organizing complicated data. There are a variety of types of databases. Some inexpensive "database" software provides essentially the functionality of electronic index cards. While such software may be adequate for keeping addresses or recipes, for research purposes these are functionally flat-file databases, and thus have all of the disadvantages of storing data in spreadsheets. A number of other database types exist, which vary in how they model or represent the data conceptually. The most popular type currently is the relational database model. Relational databases are popular because of their flexibility in storing data and their conceptual simplicity. They use multiple tables to store data, with a mechanism for relating the tables to one another. Thus, in the ICU line study example considered previously, one might have one table containing patient demographics, a second table containing information on IV catheters, and a third table with blood culture results. Each item would have associated with it some piece of unique information (such as a medical record number) that could be used to determine which data on one table were related to data on the other table. This relational database model is incredibly powerful, and most large hospital systems are built around relational database systems, such as Oracle (Oracle Corp., Redwood City, CA) or PostgreSQL (www.postgresql.org) that run on mainframe computers or high-end database servers. However, very functional relational database software is available for desktop PCs. This would include programs such as FileMaker Pro (FileMaker, Inc., Santa Clara, CA), OpenOffice.org Base (www.openoffice.org), and Microsoft Access (Microsoft Corp., Redmond, WA). Such database software may not be included in typical software "office" suites and must be purchased separately.

Using relational databases properly is somewhat more complicated than using spreadsheets. This is to be expected, given the more complicated structure of the information. Most PC-based database software packages have tools that dramatically simplify the use of the program. These tools also make it possible to generate attractive reports from the databases. Because their purpose is different, database programs do not have the broad range of calculating functions present in spreadsheets. Nevertheless, most of these programs can provide some simple information like tallies or means. To design databases optimally, it is useful to have an understanding of the relational database model. There are large numbers of online tutorials and books available, some of which are general (13) and some of which are specific to a particular database program. Although tools and "wizards" are typically used to elicit results from the programs, advance users can frequently get results not available otherwise by querying the database directly. Structured query language (SQL) is a relatively simple language designed specifically to extract information from relational databases (14). Although used more frequently on large-scale databases, PC-based programs typically provide an option for querying the database directly for advance users. As with spreadsheets, PC-based databases typically allow advanced users to write programs to extend the functionality of the database.

Epi Info

Epi Info is a program available for free from the US Centers for Disease Control and Prevention (CDC). Originally designed for Epidemiology Intelligence Service officers to perform outbreak investigations, it has grown into an extensive data management and analysis tool. Initially written to run on early DOS-based PCs, the software was extensively rewritten in 2000 to run on MS Windows.

Epi Info consists of several major components. These components were designed to facilitate epidemiological analysis from start to finish. MakeView allows the epidemiologist to design data entry screens for collecting pertinent data and automatically creates a database to hold the data. Data entry screens can be made more attractive and functional by allowing related data items to be gathered into a group, which may have a distinct back-

ground to aid the person entering the data. Since Epi Info is built on a true relational database, MakeView allows for the collection of data and of related data in separate tables. Unlike most database programs, Epi Info automatically maintains the proper relationship between the tables. To generate data collection forms, it is possible to print the data entry forms from MakeView. However, using a word processing program to design the forms will yield more control over the printed version and allow for a more aesthetic data collection tool.

The Enter program allows users to enter data into the questionnaire previously designed in MakeView. Enter will also allow for searching of entered data.

The Analysis program provides multiple options for statistical analysis of data. Besides reading data entered using MakeView and Enter, Analysis can import data from other database and spreadsheet formats, and from older versions of Epi Info. Analysis provides a full range of data manipulation and analysis tools. Basic statistics include simple frequency tabulations, contingency tables (which can be stratified), and analysis of variance (ANOVA, both parametric and nonparametric). Advanced statistical functions include linear and logistic regression, Kaplan–Meier survival, Cox proportional hazards, and complex sample statistics (contingency tables and ANOVA). Users can also create new variables within Analysis and can use fairly complicated rules to assign values to these new variables based on the values of existing data. Short programs for automating analyses that are done repeatedly can be written and stored in Analysis.

Epi Report facilitates gathering output from Analysis, Enter, as well as data from Microsoft Access or Microsoft SQL Server databases and formatting them into professional looking reports. These reports can also be saved as hypertext markup language (HTML) files for easy Web publication.

Overall, Epi Info provides the HE with essentially all of the statistical analysis tools he or she will need. Like any complicated program, learning to use the entire package well takes studying and practice. However, the program is simple enough that users who are familiar with the fundamentals of statistics used in healthcare epidemiology (see Chapters 2 and 3), and who have data in a compatible format will be able to run fairly complicated analyses shortly after installing the program. The program comes with extensive online help. The same content can be downloaded as manuals in both Microsoft Word and Adobe Acrobat (.pdf) formats. A tutorial and exercises are included to get users up to speed with the various components of the software. A quick Internet search will turn up other tutorials and educational materials to assist new users.

Specialized Infection Control Software

In addition to general-purpose statistical software, software developed specifically for infection control purposes is available. AICE (ICPA, Austin, TX) and EpiQuest (EpiQuest LLC, Key Largo, FL) are two such packages. Specialized programs guide users in selecting and analyzing data. This is especially useful for those just starting out in infection control or in using computers (or both). The trade-off is that, by nature, these programs are less flexible than general-purpose tools, and thus, may be difficult to tailor to any particular circumstances or *ad hoc* studies. However, over the years, many of these programs have become quite sophisticated. Some allow for automated entry of electronically available data. Such programs may also be used to efficiently generate reports that are mandatory in some states. Some can even send these reports electronically. Another example of reports that some systems can generate is health department reports for certain conditions (e.g., a positive RPR) drawing on the laboratory system as well as the admission system for demographic information.

Some specialized software can be relatively expensive. However, rather than just considering the purchase cost alone, the cost in time and effort to set up general-purpose tools to do the same thing that the specific programs can do must be accounted for. Unless someone locally is facile at setting up spreadsheets and databases, or specific research needs are not met, then specialized infection control software may be a very cost-effective purchase.

Spatially Enabled Data (GIS)

Geographic information and geographic information systems (GISs) are terms that invoke community-wide maps of disease incidence. The use of location data to aid in understanding the geographic correlates of health and disease is not new to the electronic era, as John Snow's well-known map of London's 1854 cholera outbreak attests. However, GIS, more accurately described as spatially enabled data, has many applications for the HE, including illustrating healthcare-associated transmission within a hospital unit, interpreting air movement patterns in operating rooms, and understanding community contributions to drug-resistance patterns in the in-patient setting. Visualization of data using location can aid in understanding many problems in healthcare epidemiology as well as communicate the nature of the problem to other healthcare stakeholders.

There are a number of relatively inexpensive desktop GIS software applications with the features needed by an HE. The most widely used commercial GIS software is produced by ESRI (Redlands, CA). In addition, there are several free applications. EpiMap, an Epi Info component, allows the user to link data contained in Epi Info files to maps. EpiMap uses maps in the popular ESRI SHAPE file format. GIS software applications are somewhat complex, and often the user needs assistance to use the program effectively. Free tutorials are widely available on the Internet, and most academic institutions offer educational sessions for faculty and staff. In addition, courses and certificate programs in GIS are becoming more available.

Free geographic information data for many locations, such as all US states and counties and many countries, are freely available on the Internet. Tools are available to create custom maps. The data to create more localized maps, such as of a hospital unit or building, are more difficult to generate but can be obtained by working with facility engineers and architects.

Visualization of Quantitative Data

The visual display of quantitative information is a critical part of communicating infection control information. Besides performing extensive calculations, most spreadsheet applications provide simple graphing tools. For the epidemiologist, bar and line graphs will be most

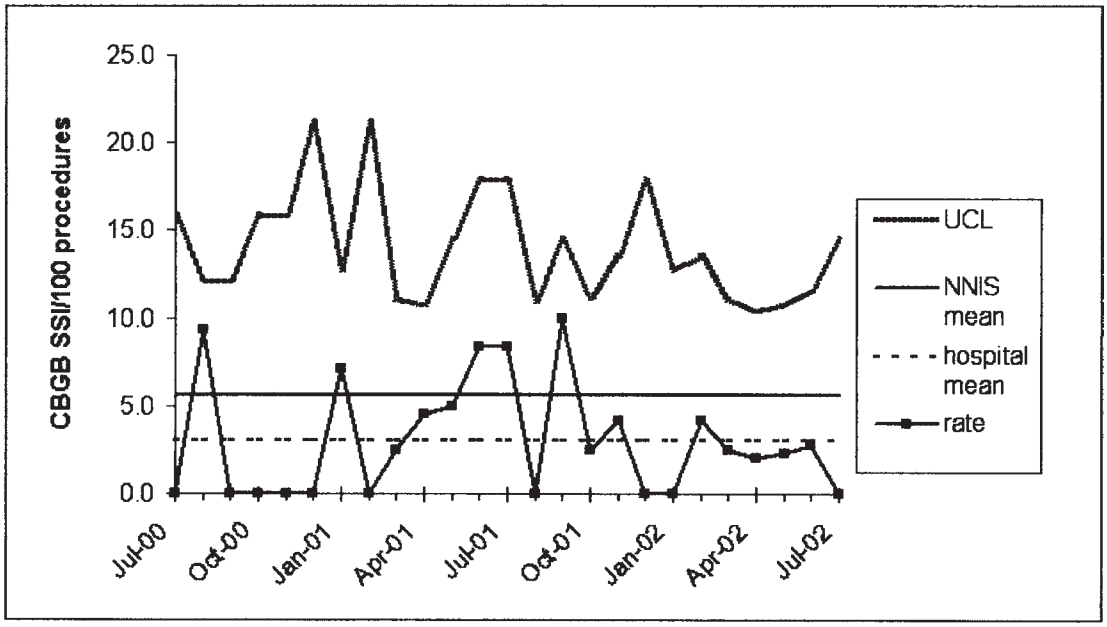

FIGURE 15-1 Control chart for coronary artery bypass surgery (risk category 2) produced on a PC with spreadsheet software. UCL, upper control limit.

frequently used. Bar graphs can be used to show epidemic curves. Line graphs are especially useful for showing trends, such as surgical site infection rates, over time. Other relevant data can be shown on the graph, such as the NHSN mean rate and the mean of the local rates, as well as upper control limits for process control charting (Fig. 15-1). It is important for infection control personnel to learn to use the graphing tools that accompany spreadsheet programs.

Beyond spreadsheets, many advanced statistical programs, including Epi Info Analysis, can produce graphics that are helpful in visualizing epidemiological data.

THE INTERNET

The Internet has become synonymous with the information superhighway, and many of the tools and techniques of accessing and navigating the Internet have been adapted for use on intranets and LANs. Therefore, a discussion of the Internet is an appropriate prelude to a discussion of information management.

Internet Structure and Function

The Internet arose from a network of government and university computer systems that was used to exchange files and information starting in the 1970s (*15*,16,17). With the wider availability of network connections and user-friendly software tools, the number of computers attached to and accessing the Internet has grown astronomically. Much of this growth has been in commercial areas, and commercial carriers now provide most of the pipelines that connect to and constitute the Internet. However, education and healthcare resources continue to thrive as well. A high-speed next-generation Internet or Internet2 has been developed for education and research institutions to rapidly exchange information (http://www.internet2.edu).

Analogous to the telecommunications system that preceded it, the Internet is composed of many computers that are attached to LANs. The LANs are in turn attached to larger networks that eventually become attached to the backbone of the Internet. Most of the computers that access the Internet are on the client side, that is, seeking information, while the minority are servers that provide the information. Like telephones and facsimile machines, each computer on the Internet must have a unique designation in order to send and receive data. These are called Internet protocol addresses (IP addresses for short) and have both numeric and name equivalents. IP addresses are organized by domain, and particular computers or servers within the domain; for example, wings.buffalo.edu designates the central campus Web server in the University at Buffalo second-level domain, within the education top-level domain. The numerical equivalent address for this server is 128.205.4.174. Other common top-level domains are .com for commercial sites, .gov for government sponsored sites, and .org for noncommercial sites. Country or state designations occasionally may supersede the traditional top-level domains at the far right of the IP address, for example, www.health.state.ny.us is the New York State Health Department home page.

While there is no central control agency for the Internet, IP addresses are assigned under the direction of an agency called the Internet Corporation for Assigned Names and Numbers (ICANN; www.internic.net). This maintains order and assures that all computers on the Internet are reliably able to be located.

Also analogous to the telephone system, computers on the Internet must use a common set of instructions in order for communications to move appropriately from source to destination. Most of the servers on the Internet use one of the variants of the UNIX OS, but most of the PC clients are MacOS or Windows based; smartphone devices also are able to access the Internet. To allow these diverse OSs to

communicate with one another, the Internet uses a set of platform-independent protocols that are determined by an international body of experts. The most important of these standards is the networking scheme called transmission control protocol/internet protocol (TCP/IP), which determines how the computers on the Internet connect and communicate with one another. Any computer running any OS can access the Internet if it has an appropriate network connection and is TCP/IP compliant. LANs that utilize proprietary networking protocols still can connect to the Internet through an appropriate router or bridge. TCP/IP also can coexist with Ethernet and the NOS on a LAN, which is important in allowing connectivity and compatibility.

Unlike the telephone system, Internet transmission utilizes packets of digital information rather than a continuous stream of analog data. Each file or message is converted into properly addressed packets before being sent. The address in the packet header instructs the servers on the Internet to relay the packet in a process called packet switching. This allows for many client/server connections to use the same Internet lines simultaneously, rather than keeping a line tied up as happens with telephone circuit switching. The downside of packet switching is that lost or misdirected packets, which increase with heavy Internet usage, can slow the user experience to maddening levels.

Connecting to the Internet

The best connection to the Internet is from a network where a PC is actually a node or a connection point on the Internet with its own IP address. Due to the nature of wiring and routing systems, network broadband connections are capable of very fast and high-capacity transmission compliant with Internet standards. Some networks do not permanently assign a separate IP address to each computer but rather reserve a range of addresses that are assigned electronically to computers as needed, using the dynamic host configuration protocol. Most universities, large hospitals, and other large organizations are able to provide direct LAN access for staff computers. Cable television and telephone companies in many areas provide individual users with broadband connections via fiberoptic cable modems that may approach the speed of traditional Internet network connections.

The development of wireless LAN and Internet connections referred to as Wi-Fi (wireless fidelity) allows a desktop or laptop computer, smartphone, or PDA-type device, with appropriate networking hardware based on the IEEE 802.11 standard to "connect" with network signals provided by an antenna connected to the Internet or a LAN. The antenna may be in the "open" or within a building or even a home. In a hospital, this would allow for real-time entry or retrieval of patient-related information at the bedside. Many issues, such as signal strength (which determines effective range for service), service interruptions and security of confidential information, need to be addressed for successful implementation.

If not directly connected to a network, as might be the case in a small facility or private office, using a telephone modem to dial into a host computer using the point-to-point protocol (PPP) is the next best option. The PPP server of an Internet service provider (ISP) temporarily makes a desktop computer a node on the Internet with its own dynamically assigned IP address. The bandwidth of this service is dependent on the speed of the client and server computers' modems. The development of integrated services digital network and asymmetric digital subscriber line telephone line protocols offers much higher bandwidth than even the fastest current telephone modem connection speeds. These, like fiber optic cable connections, require special modems that are more expensive than standard modems, and the monthly service charge also will be significant. Bandwidth is expensive!

Some organizations, including hospitals, may provide employees with remote access to the corporate network using a virtual private network (VPN). VPN client and server software uses a tunneling protocol to securely transmit information over the Internet using cable or telephone modems. This could allow professionals at remote sites to access electronic mail, databases, and other network-based resources.

Internet Tools

As noted above, the Internet originally was developed to allow scientists to exchange messages and files electronically. This was done with text-based software tools or clients that resided on the large Internet servers and required knowledge of the locations of files as well as the commands to retrieve them. While the use of newer software tools has supplanted the older tools, descendants of the original file transfer and terminal connection tools still are valuable and will be discussed further. The reader is directed to other sources for information about the other tools such as Gopher, Veronica, and Archie (16,17,*18*).

Files can be moved from one computer to another using the Internet file transfer protocol (FTP), and the software program that does this is referred to as an FTP client. (Client may refer to the software application or to the computer on which it resides.) If one knows the IP address of the server that contains a file of interest, this can be entered into the FTP client and a list of the folders (directories) on the server will be returned. This is useful for uploading large files or the pages of an Internet Web site.

Many files on Internet servers are compressed by special software to make the file size smaller for transfer and encoded into American Standard Code for Information Interchange (ASCII) text format to ensure safe passage over the network. This requires that the client computer have appropriate software for decoding and decompression. Compression formats vary among computer platforms. Disk image (.dmg) for Macintosh, Zip (.zip) for Macintosh and Windows, and tape archive (.tar) for UNIX are common. There are freeware, shareware, and commercial products available to decode and expand these files.

Telnet is the other important descendant tool though it too has shown its age. A Telnet software client application allows a client computer to connect to a server or mainframe computer. This in essence re-creates the dumb terminal situation described above, giving the client access to the software programs and files on the host computer. This will be in a text-only mode, generally with keyboard-only commands as defined by the host computer, and printing may be restricted to printers attached to the

mainframe. Since Telnet gives access to the functioning parts of the host (server), password access is generally required, as it would be when logging on from a hardwired terminal. Telnet may be the only means of gaining access to mainframe computers or other servers, so having a Telnet client is essential for anyone who wishes to obtain information from these machines.

Perhaps the most significant nonhardware milestones related to the Internet have been the development of the hypertext transfer protocol (HTTP), HTML, and browsers *(19)*. Together, they have transformed the client/server interface on the Internet from a cryptic, command line, text-based system to a "point and click," visually rich environment known as the World Wide Web (WWW or Web). Hypertext and HTML make it possible to include stylized text, tables, and images as well as hyperlinks (links for short), which, when clicked, move the user from the current location on the Web to another. Browsers are software client applications that understand HTTP as well as FTP and other Internet protocols and make it possible to view (browse), save, or print HTML pages, and to download files from HTTP or FTP sites. The user combines the desired protocol and IP address into the uniform resource locator, which then instructs the browser client to attach to the desired Web server. The Web server must run appropriate software to complete the interaction and deliver the appropriate file or page.

Graphic images such as pictures, scanned images, copies of graphs and other nontext artwork commonly appear in one of several formats on the Web: graphics interchange format (GIF; .gif), which is good for nonphotographic images since it displays only 256 colors but keeps sharp edges, portable network graphics (PNG; .png), a nonproprietary image format that was created as an alternative to GIF, and joint photographic experts group (JPEG; .jpg), which can display millions of colors and is better for photographs and other complex images. Charts, scanned images of electrophoresis gels, and other items of interest to HEs can be saved in one of these formats and placed on a Web page. Browsers can display these image types, as can most word processor, graphic, and page layout software programs.

Java, JavaScript, and Plug-Ins Web pages can be enhanced further with Java, JavaScript, and plug-ins *(20)*. Java is a platform-independent computer programming language developed by Sun Microsystems (now a subsidiary of Oracle Corporation, Redwood Shores, CA). It is used to operate thin client computers and program middleware for database systems, but small Java applications known as applets provide a variety of enhancements to Web sites, such as animation, forms, and messages. Recent versions of popular browsers can run Java applets though the appearance may not be consistent on different products. Java applications also can operate on any computer, smartphone, or other device platform that has a Java Virtual Machine.

JavaScript is a scripting language, unrelated to Java, originally developed by Netscape Communications Corp. (now part of AOL, New York, NY) to provide enhancements such as pull-down menus and scrolling messages for Web pages. It is less complex and less capable than Java, but exists totally within the HTML code of a Web page rather than as a separate applet.

Plug-ins are small pieces of software that can add functions to larger software programs. They are popular for use with Web browsers as a way to add capabilities that are not part of the intrinsic browser repertoire. Plug-ins have proliferated and now are necessary to view the full content of many Web pages. Examples are the Adobe Reader plug-in, which allows the user to view a PDF file (see below) within the browser, and the Adobe Flash plug-in that plays static or streaming (continuous) audio or video. The latter can be used for Web-based transmission of lectures or conferences.

Desktop Widgets Desktop widgets are "one trick ponies" that allow for a specific type of data or function to be seen on a computer desktop, such as weather, CDC alerts, and a calculator. Most are designed to continuously update information when the computer is connected to the Internet. Common widget engines are Macintosh Dashboard, Microsoft Gadgets, Yahoo (Yahoo! Inc., Sunnyvale, CA) widgets, and Google (Google Inc., Mountainview, CA) desktop portlets.

Internet Electronic Mail Electronic mail, or e-mail, is a way to rapidly send messages across the Internet or other networks *(21,22)*. The sending and delivery end points of e-mail transmission are mail servers, so messages are delivered continuously and near instantaneously, rather than slowly and episodically as with postal or "snail" mail. Internet e-mail is governed by standards like all other Internet transmissions. An e-mail software client on a PC or other computer is linked to a mail server that utilizes simple mail transport protocol for sending mail. There are two different client/server relationships for receiving Internet e-mail: post office protocol (POP) and Internet message access protocol (IMAP). POP creates a simple relationship when the client logs into the server, whereby received messages are transferred to the client's computer e-mail program. The e-mail messages then can be sorted into folders and address books can be maintained. IMAP maintains the e-mail and address book on the server, and the client software manipulates the mailboxes and address books. The advantage of IMAP is that stored mail messages and address books can be accessed from any computer that has IMAP-compliant mail client software. Many e-mail systems also can be set up to allow Internet access through the use of a Web browser (Web mail) that allows one to remain "in contact" when traveling.

Along with sending messages via e-mail, appropriately encoded documents or files can be attached to the messages. E-mail clients that are multipurpose Internet mail extension (MIME) compliant can manage messages with files and graphics embedded in them, thereby eliminating the need for encoding. When sending documents or files as attachments, remember that along with incompatibilities among computer OSs, there are incompatibilities among the file formats used by application software programs or even different versions of the same program. There are several approaches to this problem: (a) Have everyone with whom you share a document use the same software, preferably in the same version. This may be possible

within an organization, but is highly problematic when exchanging data in an educational institution or across the Internet. (b) Use one of the file interchange formats that can be accessed through the open, import, save as, or export commands in most software programs. Common formats are rich text format (.rtf) for word processors and dbase (.dbf), and data interchange format (.dif) or symbolic link (.slk) for spreadsheets and databases. Special formatting often is lost in these formats. (c) Transmit the document as an ASCII text document, which will be devoid of formatting but will contain all of the data. (d) Convert the document to platform and software independent Adobe portable document format (PDF; .pdf) using Adobe Acrobat or other software (MacOS has this function built into the print driver). The PDF file, when viewed or printed, provides a document that appears identical to the original. A free Adobe Reader application is available (http://www.adobe. com) for most computer platforms and as a browser plug-in.

Many LANs in hospitals and other organizations use proprietary e-mail software systems. These often have the advantages of having a central post office for both sending and receiving mail and a master address book for everyone who has access to the LAN. Most are IP compliant and communicate well with POP/IMAP servers though there may be some incompatibilities.

Network News Network News can be thought of as a large bulletin board on the Internet where messages and responses can be posted to newsgroups, each of which is devoted to a particular topic *(15)*. The newsgroups may be part of the established Usenet (users network) or may be restricted to a part of the Internet, such as a university. Postings to newsgroups are transmitted over the Internet by the network news transport protocol (NNTP) and posted on NNTP servers, which then make the postings available to clients who subscribe. The postings are read with a newsreader software client, which may be a standalone product or part of a browser or e-mail package. Like the cork bulletin board at the student center, newsgroups generally are not moderated. Caveat lector!

RSS Really simple syndication (RSS) is a Web feed format used to publish frequently updated information such as news headlines in a standardized format. Many news sources such as Reuters Health, CDC, and many professional societies have RSS feeds. An RSS reader, which may be a separate RSS client software program or part of a current browser, is used to continuously retrieve and view selected feeds.

Cloud Computing

The only "constant" in the Internet is constant change. As the complexity and cost of computer infrastructure and software have risen, the concept of providing those services over the Web arose (23). The cloud metaphor draws from the common depiction of the Internet as a cloud in network drawings. A variety of services may be available—enterprise collaboration, software, storage, hardware leasing—in a variety of fee formats. The simplicity lies in the fact that only a Web browser or another "front-end" software solution is needed to access these services.

Personal use of cloud computing ranges from online banking to "office" software suites to epidemiologic statistics. They require only a Web browser (see below) rather than specific banking, office, or statistical software and are provided at no cost to the user. A simple and appropriate example of this is OpenEpi (http://www.openepi.com), which is a subset of EpiInfo statistical software. It does not require any particular OS or software other than a JavaScript-enabled browser.

Despite the attractiveness and potential cost savings, it remains to be seen to what extent healthcare organizations will adopt this model, largely because of concerns over security and confidentiality of patient information (24). However, organizations already use Web interfaces for a variety of functions when patient and other confidential data are protected by a firewall (25). The latter is hardware and/or software that prevent external access to unapproved users.

Information from the Internet

The Internet contains a wealth of information and data that may be important or useful to the HE or infection preventionist. Most of it is contained on the Web or may be obtained by e-mail, so these areas will be highlighted. As noted above, along with commercial growth on the Web, there is a vibrant education presence as well. This is due to the general availability of Web server space at universities and other organizations and the ease with which Web pages can be constructed.

Medical Web sites may be found in several general categories: government, bibliographic databases, professional societies and organizations, educational institutions, publications, and commercial interests. Among the government Web sites, the CDC (http://www.cdc.gov/) has extensive information available including the Morbidity and Mortality Weekly Report (MMWR), Emerging Infectious Diseases, guidelines, course/program announcements, and surveillance reports. Many of these are available as Adobe PDFs, which provide printed copy identical to the offset printed version available by snail-mail subscription. Included in this group are the reports of the NHSN; the tabular data can be printed or cut and pasted to a spreadsheet for use in internal benchmarking. The CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) site (http://wonder.cdc.gov) contains a search engine that can locate documents and data from CDC databases. Other government sites with information or data of potential use to HEs include the CDC Emergency Preparedness and Response page (http://www.bt.cdc.gov/), the Occupational Safety and Health Administration (OSHA; http://www.osha.gov/), and the Food and Drug Administration (FDA; http://www.fda.gov/). Many state health departments similarly post policies, notices, and statistics.

The key medical database of the National Library of Medicine (NLM), Medical Literature Analysis and Retrieval System (MEDLARS), has been available in electronic format for many years through MEDLINE (MEDlars on-LINE). This often has been through telephone modem access or in CD-ROM format, both of which have entailed subscription charges. NLM now provides free Web access to MEDLINE with a number of enhancements, including access to other NLM resources, through PubMed (http://www.pubmed.gov).

Links are provided to full-text journal articles, some of which are free, often after a set period of time from print publication. There also are commercial MEDLINE-based products that may include additional databases and search capabilities available for university or other organization servers. Some may include access to a select number of full-text journals. The latter products usually are licensed on a number-of-seats basis, so access is restricted to the members of the university or organization that has purchased the product or service. Nonetheless, access to the literature of medicine, healthcare epidemiology, and infection control never before has been easier or less expensive.

The Web has provided a tremendous opportunity for many professional societies and similar organizations to interact with a global audience. These organizations can provide news, membership applications, meeting and course brochures, and links to other sources of information. Professional society Web sites of interest to HEs and infection control team members include the Society for Healthcare Epidemiology of America (SHEA; http://www.shea-online.org/), the Association of Professionals in Infection Control and Epidemiology (APIC; http://www.apic.org/), the Healthcare Infection Society (HIS; http://www.his.org.uk/), and the Joint Commission (JCAHO; http://www.jointcommission.org/). The SHEA Web pages include an extensive set of links to other healthcare epidemiology and quality improvement resources, and the APIC site includes a searchable index of topics discussed in their Internet e-mail discussion list.

The healthcare epidemiology and infection control services of several academic institutions have Web sites that contain results of outbreak investigations or ongoing surveillance activities. Information databases, such as the Health Information Research Unit (http://hiru.mcmaster.ca/) of McMaster University and the National Guideline Clearinghouse (http://www.guideline.gov/), add to the diverse sources of critical evaluation of data. In a similar context are the sites of peer-reviewed publications that often are associated with professional societies. These sites may offer the table of contents of journal issues, article abstracts, or full text of articles. The latter usually require society membership or a subscription, and access is password controlled. Finally, it should be noted that most providers of medical products and services have Web sites for self-promotion. Some of these may include data that may be helpful in purchasing or usage decisions. Many of these can be found by using an Internet search engine such as Google (http://www.google.com/) or Ask (http://www.ask.com).

Along with exchanging messages and files with individual colleagues, Internet e-mail can be an important source of information for the HE via mail lists. Automated e-mail list servers send a message to everyone subscribed to the list in a manner analogous to broadcast facsimile, though much more rapidly and inexpensively. Lists can be used to send notices to members of an association, announce availability of products or publications, provide breaking news, or allow list members to ask questions and read/post responses. Individuals interested in the service(s) or topic(s) covered by a mail list subscribe to it by sending an e-mail message to the list administrator or to an automatic subscription program on the list server. Subscribers then receive an e-mail message whenever that message is sent to the posting address for the list. Lists may be one way, where a designated person is the only one who can post a message to the list, or two way, where any message that is posted is sent automatically to all list subscribers. One-way lists may be used as a means of notification; the CDC has e-mail lists by which subscribers are notified of the availability of each edition of the MMWR (http://www.cdc.gov/mmwr/mmwrsubscribe.html) and the occurrence of important healthcare events and publications (http://www2.cdc.gov/ncidod/hip/rns/hip_rns_ subscribe.html). Moderated discussion lists usually are one way as well; all postings must be reviewed and approved by the list moderator prior to being posted. Though this is not peer review, it does control the content and tone of the list. Two-way lists, along with network news groups, do not require any approval for posting messages and tend to become cluttered with redundant, unnecessary, or inappropriate postings. As a result, the volume of e-mail subscribers receive becomes large and the quality of the mail tends to suffer. Again, caveat lector!

Security

The widespread use of the Internet has raised many questions about the security, safety, and confidentiality of the information that is transmitted over it (17). While the topic is too complex for detailed discussion here, some general recommendations can be made. User identification and passwords must not be shared or divulged and proper logoff procedures should be followed; this will protect users and their system by not allowing unauthorized use. E-mail is the least secure form of transmission, and sensitive data such as confidential correspondence or credit card numbers should not be sent this way unless encrypted. Web browsing, online purchasing, or completing surveys may be done with higher levels of security that probably make it safe to undertake these transactions at reputable sites. However, be aware that the server to which you attach may acquire information about you and your computer through bits of information, called cookies, exchanged with your browser. Other information you provide may place you on a mailing list or be shared or sold to other parties.

Downloaded software programs or some e-mail messages may be infected with small programs called viruses, macroviruses, worms, or Trojan horses. Many of these are malicious or destructive to other files on the client computer, and some may send personal information from the infected computer to another source. Others send multiple copies of themselves to all of the addresses in an e-mail account, clogging mail servers. Software programs sent by e-mail or obtained from uncertain sources never should be opened, and unsolicited messages such as these should be deleted. Many organizations require the use of an antiviral utility program by all users who download or exchange files, and incoming mail often will be scanned for malicious programs.

Analogous to junk mail, junk faxes, and recorded telemarketing calls, unsolicited e-mail has burgeoned in the past several years. Often referred to as “spam,” much to the chagrin of the manufacturer of the processed meat product, such mail has ranged from nuisance to disruptive. “Spammers” utilize net robots to seek e-mail addresses from newsgroups, outgoing mail servers, and other sources to

develop a database of target addresses. Some organizations will sell e-mail addresses obtained at the time of a Web interaction (such as opening a free mail account) to others, eventually resulting in addition to a spam list. Responding to spam messages to attempt removal of an e-mail address from a list may actually verify that an account is real and result in even more unsolicited e-mail. Some browsers have antispam filters, and there are a number of third-party software packages that promise to remove spam messages. None of these are perfect, but they often decrease the volume of unwanted mail. Unfortunately, the spammers often are a step ahead of the attempts to foil them. A number of Web sites, including http://www.junkbusters.org/, have more information on avoiding and fighting spam.

Internet chain letters and hoaxes, often threatening the user or user's computer with dire consequences, also have proliferated, and these are best ignored and deleted. More information on security issues and hoaxes is available at the United States Department of Homeland Security Computer Emergency Readiness Team Web site: http://www.us-cert.gov.

Recommendations for Internet Connectivity and Software

It is necessary for healthcare epidemiology and infection control program staff to have access to the Internet using one of the methods described above, preferably from a desktop microcomputer directly connected to a network. An Internet e-mail account likewise is desirable, but a LAN e-mail account that is bridged to the Internet is acceptable. The basic software tools for Internet use include a browser, an e-mail client, and software for decoding/expanding files. No recommendations are made for specific products, and many open source (http://sourceforge.net/) or low-cost shareware products are sufficiently capable to preclude the purchase of more expensive commercial products. The freeware Adobe Reader software also is recommended. If software is available from a university or organization IS department, this should be considered for use since it is likely to be compliant with Internet or LAN standards. Training and support are likely to be available as well.

Currently, three browsers account for the majority of WWW clients: Firefox (Mozilla.org, the open source descendant of the original Netscape browser), Safari (Apple Inc.), and Internet Explorer (Microsoft Corp.). All are freely available: Firefox for Macintosh/Windows/Linux, Safari for Macintosh/Windows, and Internet Explorer for Windows. All have many features—some would say too many features—beyond basic HTTP and FTP functions. All have a closely associated Internet e-mail client: Thunderbird for Firefox, Mail for Safari (Macintosh only), and Outlook for Internet Explorer (part of Microsoft Office for Windows). There are several other browsers and e-mail clients available, each with particular features and proponents; the choice is like the choice of any computer software—very dependent on individual needs and preferences. Note that some content may not display properly in a particular browser or e-mail client, but may be rendered appropriately in another. This is due to ever-evolving standards and the willingness (or unwillingness) of a software company to follow the standards.

As noted in the beginning of this section, the same tools used for accessing data from the Internet also can be used to obtain information on many university or hospital intranets/LANs *(20)*.

DATA SECURITY

One obvious and real danger of using local or mobile computing devices to store and manipulate healthcare epidemiology data is the potential privacy breaches for named or individually identifiable health data. Considerable attention has been directed by healthcare organizations to ensure the safety of identifiable personal health information (PHI), following the well-publicized loss of laptop computers and external hard disk drives containing large volumes of PHI.

Even when housed in a monitored or locked infection control office, files on a table-top computer should be password protected. The general policy for access to infection control data should be a need-to-know basis, which may mean different levels of access (e.g., password-protected files, with the password known only to those with a need to know).

Anyone who uses mobile information storage devices, including laptops, PDAs, and smart phones, must be mindful of the potentially severe consequences of lost or stolen data. If PHI does reside on a portable device, steps must be taken to keep it physically secure when in use and during transit. Regardless of this, all computers, handhelds, smart phones, flash drives, external hard drives, or readable media containing PHI (including e-mail messages) should be at least password-protected and preferably encrypted (26). Most healthcare organizations have policies about security requirements for portable computing devices. Once obsolete or no longer used, any storage devices such as hard drives must be physically rendered unreadable by crushing or degaussing. Other media such as CDs/DVDs/tapes should be shredded or otherwise destroyed, as should any printed versions of the data.

Ideally, all identifiable PHI should be stored on a secure server rather than on the local or portable device. System security technology and practices will help ensure the confidentiality of data stored in this manner, but ultimately, data security and integrity depend on the system users.

Data transmission by electronic mail or other electronic means likewise must be encrypted if it includes PHI. Most hospitals and other healthcare organizations have the necessary software and tools to accomplish this, and some do it automatically. The user's information technology service should be consulted for details. A good reference framework for data security is available at the CDC's National Program of Cancer Registries *(27)*.

"Publishing" Infection Control Policies

It is easy to "publish" infection control policies and procedures to the hospital's intranet. Web enabling the infection control manual makes it more accessible, and perhaps more used, by hospital personnel. The simplest approach to this is to make an index page, similar to a

printed index page, of the manual using a word processor, text editor, or dedicated Web-authoring software (e.g., the freeware NVU, http://www.nvu.com/). Each of the chapters or policies in the index then link to the appropriate document that can be either in Adobe PDF format or that of the word processor used to create it. The more industrious user could use Web-authoring software to develop a truly interactive manual with links between chapters, to other references, etc.

RESOURCES

Many users enter the world of computing and the Internet with trepidation, and this is understandable. However, the potential benefits to HEs and infection preventionists should serve as impetus to overcome fear and ignorance to take advantage of the resources that are and will become available. Introductory courses are offered at educational institutions, libraries, and in healthcare organizations, and are a good starting point for the newcomer. Advanced and specific topic courses also are available.

Books about general and specific computing topics have proliferated and provide additional resources for beginners and more experienced users. Particularly useful for general audiences are the "For Dummies" (Wiley Publishing, Inc., Hoboken, NJ; http://www.dummies.com) and the O'Reilly (O'Reilly Media, Inc., Sebastopol, CA; http://www.oreilly.com) book series. These are readable, are inexpensive, cover a variety of basic and advanced topics, and are widely available. There are magazines for essentially every computer topic, platform, and use area, and many also have some or all of their content posted on the Web. Finally, local computer user groups and educational Web sites provide additional or more detailed information for more advanced users or on specific topics. A useful encyclopedia resource for computer technology is at: http://www.whatis.com/.

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CHAPTER 16

The Electronic Health Record: An Essential Technology for Healthcare Epidemiology

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Healthcare is an information-intensive industry. Information management is integral to clinical practice, and little occurs in the complex matrix of healthcare that does not involve information management (1,*2–9*,10,11,*12*,13, *14–19*,20,21,*22–32*,33,*34–49*). Clinicians, among their other unique duties, are information managers. In the day-to-day practice of medicine, they must acquire, process, store, retrieve, and apply information. This ability is paramount to the delivery of efficient and optimal healthcare and is becoming increasingly important with the fractionation of healthcare delivery. During the last 50 years, information management has risen to a pivotal role in modern healthcare (1,*2,25–28,34*,*42*). There has been an explosion of information in healthcare. In 2009, Medline indexed over 850,000 new articles from those published in the biomedical literature with over 20 million articles in the database compared with just over 485,000 in 1999. Reports on genetic, genomic, and proteomic data are on the rise, and most providers have little background in such areas. These are areas where information technology (IT) is increasingly important for finding relevant knowledge.

In addition to more knowledge, there has been a corollary growth in patient-specific information. The volume and complexity of patient information has increased dramatically. This increase is due to multiple factors that have occurred in healthcare, such as the greater number of patient visits; higher patient acuity; a proliferation of new data elements arising from new diagnostic techniques; developments in the delivery system that result in many patients receiving care at multiple sites and in multiple systems; and the maturation of high-throughput genomic biotechnology, some of which is now marketed directly to consumers. This dramatic growth has resulted in a situation where effective clinical information management has exceeded the cognitive capabilities of the human mind. Some authors have referred to this phenomenon as "information pollution" *(44)*. In fact, in modern healthcare we are drowning in data while starving for information, and each year this gap widens.

Providing high-quality, cost-effective healthcare is an information-dependent process. Each provider and class of providers in healthcare has developed a unique set of information requirements that have become ever more task/specialty focused. However, in order to deliver truly comprehensive care, at some point in the healthcare delivery process, other providers need access to those information sets. The medical record is the repository of information concerning the patient's health. Virtually everyone involved in providing, receiving, and reimbursing for healthcare needs to interact with it.

It has been estimated that as many as 22 different people need access to a hospital patient's medical record at any given time *(17)*. An estimated 35% to 39% of total hospital operating costs has been associated with provider and patient information activities. Physicians spend an estimated 38% and nurses and estimated 50% of their time documenting in the patient's medical record. Furthermore, 70% of hospital patients' paper medical records are incomplete. This lack of detail is reflected in the fact that 40% of the time the paper medical record does not contain the patient's diagnosis and 27% of the time the patient's chief complaint is not documented *(50)*. This lack of completeness also results in 11% of laboratory tests that have to be reordered, because the results are not in the patient's paper medical record, which leads to significant manual effort to review the patient chart for source data.

Despite the many technologic advances in healthcare over the last 50 years and the plethora of associated problems with the typical patient record, the record has not changed much. Many institutions that have adopted a variety of health information technology (HIT) modalities still rely on paper-based physician documentation. The failure of the modern patient record to have evolved with the other technologic advances in healthcare is now creating additional stress within the already burdened US healthcare system. Because of this failure, the information needs of providers, patients, administrators, third-party payers, researchers, and policy makers, not to mention infection control specialists, are often unmet.

The electronic health record (EHR) seeks to overcome the failures of the traditional paper record (1,*14,15,17,34*). The EHR can make a major contribution to improving the information management problems of healthcare. A 1991 General Accounting Office (GAO) report on automated patient records, still valid today, identified three major ways in which improved patient records can benefit healthcare (1). First, an automated patient record can improve healthcare delivery through its direct impact on

the delivery of care. It can provide easy access to multiple parties simultaneously, faster data retrieval, and, potentially, higher-quality data. The EHR can also enhance decision support capabilities, present clinical reminders to assist patient care, and support quality improvement activities, although implementation successes may vary widely. Second, computerized medical records have the potential to enhance outcomes research by automatically capturing clinical information for evaluation. Third, automated patient records can increase hospital efficiency by reducing costs and improving staff productivity. The GAO reported that an automated patient record system reduced hospital costs by $600 per patient in a Department of Veterans Affairs hospital because of shorter lengths of stay *(51)*.

Ideally, the EHR provides patient-specific, integrated information that is collected during the provision of care and is available among all caregivers in an organized, comprehensive, accurate, timely, and accessible form. Uncontrolled and unorganized information (as available in the paper record) leads to "information pollution" and is a counterproductive force in an information-oriented industry *(44)*. Information collected, presented, and available in an electronic form becomes a valuable resource when properly structured.

OVERVIEW OF ELECTRONIC HEALTH RECORDS

With any endeavor in healthcare, there are definitions and acronyms that one has to be familiar with to effectively communicate. This is particularly true in the area of healthcare information management. The glossary at the end of this chapter lists many of these terms. With respect to information systems, Ledley and Lusted (52) in 1960 defined an information system as consisting of three essential components: a system for organizing or documenting the information in a file; a method or a routine for accessing the information in the file; and a method to ensure that the information was current. Lindberg *(53)* took the definition a step further and concluded that a medical information system (MIS) (or what we now would call an EHR) contained a set of formal arrangements by which health-related facts, those concerning the individual health of the patient as well as the care of that patient, were stored and processed in computers *(27–29)*. Based on this conception, an MIS is a complex hierarchical integration of multiple systems that include an inpatient hospital information system (HIS); an outpatient information system; and clinical support systems, such as pharmacy, radiology, and laboratory information systems. In most current configurations, this can include an inpatient EHR, an outpatient EHR (sometimes integrated with inpatient), as well as ancillary departmental systems for laboratory and pharmacy. A true EHR would contain a longitudinal patient record that contains the complete health status and healthcare delivery of an individual patient from birth to death. Only a few, mostly closed, healthcare systems have even approached such an integrated information system (e.g., Kaiser Permanente), even so, patients often venture outside of such systems for some of their care over the course of their lives.

Both ambulatory and inpatient information systems usually include administrative and financial (or practice management) components and clinical components, all of which are usually separate systems. Administrative information systems (AISs) include data elements such as patient demographic, eligibility, and payer data; patient identification, registration, and appointment schedules; hospital admission, discharge, and transfer (ADT) data; bed census or occupancy data; cost accounting; resource utilization; employee records; and inventory. Generally, AISs are the first computer applications implemented in a hospital or outpatient setting.

Clinical information systems (CISs) are designed to manage information concerning the direct care of the patient and are the foundation of the EHR. The CIS contains both objective and subjective clinical data. Because the practice of medicine and the delivery of healthcare is a dynamic process, the functional requirements of a CIS are continually changing as new treatments, procedures, and diagnostics evolve. However, any CIS has some essential core functions. Some of these functions include an electronic medical record (EMR) that can communicate and manage patient data from multiple sources (e.g., pharmacy, radiology, surgery, laboratory) within the healthcare delivery system; provide healthcare workers with decision support tools; provide a clinical database for epidemiologic research; support medical education; maintain patient confidentiality; and satisfy the requirement for the integrity, reliability, and security of patient data.

In the United States, the hospital has been recognized since the 1960s as the natural laboratory for automation and computerization in healthcare. This realization was partly due to the complexity and scope of the information available within the bounds of a single organization, and the fact that the hospital represented the largest segment of the healthcare industry, commanding over 50% of all healthcare spending *(54)*. Economies of scale dictate that a hospital would have access to much greater IT resources than, say, a small independent physician practice. Additionally, hospitals have regulatory requirements for collecting information and developing rates for defined outcomes such as mortality, length of stay, and costs for various diagnoses and surgical procedures *(55–57)*. Indeed, the hospital setting is probably the most sophisticated segment of the healthcare market with respect to information management. However, to date, less than 10% of US hospitals can truly call themselves "paperless" across all disciplines, departments, and functions, and 85% of the outpatient record remains paper based. The US government's 2009 HITECH stimulus program supporting "meaningful use" of EHRs (discussed below) hopes to rapidly stimulate much greater adoption.

The basic kinds of information that hospitals require and manage have changed little since the early 1960s. What has changed is the volume of that information and the recognition that numerous providers need simultaneous access to the information. Because of these factors and healthcare's insatiable demand for information, the EHR has become a key emerging technology in US hospitals. What differentiates an EHR from a compilation

of departmental information systems within a hospital is the integrated database *(18,58–60)*. Friedman and Dieterle *(18)* have called integration the "holy grail of hospital computing." To effectively use patient care data to improve outcomes and manage care, hospitals need access to fully integrated information. The primary function of an EHR is to communicate data *(58)*. To perform this function, an EHR must have software and hardware components that allow the computer to acquire, process, store, retrieve, and rearrange data, and then display that data throughout the institution. The premise that underlies this design strategy is that many providers, including the medical staff, nurses, pharmacists, radiology, laboratory, respiratory therapy, physical therapy, occupational therapy, dietary, and so on, create patient care data, and those providers need access at almost all times to a variety of patient care data. The key is that the provider-created data must be inclusive. Within an integrated EHR, the design should allow for patient data to be entered once and then be available for all users. Ideally, data should be entered at the point of care. For example, the temperature of a patient should be entered into the database at the bedside, once the healthcare provider has obtained the temperature. This allows for maximum use of patient data, since clinical data are now temporally related to the course of hospitalization. This temporal relationship allows providers to analyze the patient's clinical progress and to relate outcomes to specific events during hospitalization. Point-of-care data entry goes beyond the human provider and is equally applicable to automated devices and analyzers, for example, ventilators or blood chemistries. The technology to accomplish this automated point of care data capture is readily available *(61)*.

Regional/National Health Information Exchange

Electronic patient data, both clinical and administrative, is too often imprisoned in institutional silos due to technical incompatibilities, financial disincentives, and interinstitutional politics. There has been a recent groundswell of support for inter-institutional data exchange (of both identified and de-identified data) to support patient continuity of care and healthcare quality improvement activities. Such data exchange can occur on a peer-to-peer institutional level, on a regional level, and on a state or federal level. Regional Health Information Organizations (RHIOs) and Health Information Exchange (HIE) organizations are two types of collaborative organizations that have formed to enable such exchanges and have met with varying success (and failure). Many RHIOs formed since the late 1990s have struggled with financial, political, and technical barriers. Notable successes on a large scale include the Indiana Health Information Exchange, the New England Healthcare Exchange Network, and the New York Clinical Information Exchange. The recent HITECH funding (see below) has catalyzed the formation of numerous HIE efforts nationally, prompted by the rationale that healthcare data exchange is necessary for healthcare reform and improving health outcomes. However, there remain many challenges ahead for large-scale regional data sharing, including data selection, legal/ethical discussions, privacy standards, and technical/implementation hurdles.

EHRS AND HEALTHCARE OPERATIONS

The inefficiencies of the paper medical record absorb large amounts of a hospital's budget and are directly responsible for many of the failures in the quality of care delivered, including medication errors, misdiagnosis, and poor record keeping. Over the years, HISs and current EHRs have demonstrated many benefits, but perhaps the three that will have the greatest impact on healthcare delivery and cost are (a) improved logistics and organization of the medical record to speed care, prevent duplication of data and procedures, and improve the caregiver's efficiency; (b) automatic computer review of the medical record to aid decision support, limit errors, identify exceptions in care, and identify those in need of care; and (c) systematic analysis of present and past clinical experiences and outcomes to guide future practice and policies (1,*14,30*).

Improved Logistics and Organization of Patient Data

The EHR, with the patient as the central information unit, provides large clinical databases allowing for more comprehensive and accurate patient data collection, more complete data integration and interpretation, and greater facilitation of data analysis (1,*2,17,30,34*). Multiple providers can gain simultaneous access to computer-based data, and data duplications across multiple systems are eliminated. Once stored in the EHR, data can be displayed in numerous different ways, providing for cost-effective utilization of services. A past investigation has demonstrated that in an emergency department with computer-displayed data, physicians ordered 15% fewer tests than when computer display of data was not available *(62)*. Another investigation has shown that when the EHR displayed previous test results to physicians when they were ordering new tests, there was a reduction in test ordering *(63)*. An EHR provides a cohesive, integrated, accurate, and up-to-date record that encourages and enables providers to make informed cost-conscious decisions (*62–67,*68). Computers also serve the information needs of medical, pharmacy, and nursing students *(16,22,47,48,69,70)* as well as the patient *(71)*. The use of an HIS to present clinical guidelines for management of personnel with occupational exposure to body fluids was shown to improve documentation, compliance with guidelines, and percentage of charges spent on indicated activities, while decreasing overall charges *(72)*.

Clinical Decision Support

Humans are prone to a number of inherent cognitive biases and predictably make frequent errors, including overlooking rare and uncommon events *(73)*. An integrated EHR with an intelligent rules engine can monitor patient data for unusual patterns in care and alert healthcare providers; this is commonly referred to as clinical decision support (CDS). Computer-generated reminders have been shown to dramatically affect the outcomes of many different aspects of care (*62–67,73–75*,76,77). Recent investigations into the use of HISs and computerized CDS have demonstrated the potential of remarkable cost savings and improved patient outcomes (68,*78,*79,*80–87,*88,89,*90–95,*96,*97–99*), although there have also been some notable failures.

The EHR can promote a healthcare system that emphasizes prevention, early diagnosis and treatment, and effective management *(100)*. These aspects of healthcare delivery are further facilitated by the advent of computerized decision support (10,13,*101–122*). Six major use cases of decision support that now exist in hospitals with integrated information systems and attendant EHRs are alerting, interpretation, assisting, critiquing, diagnostic, and management.

Alerting decision support is defined as the automatic notification of appropriate providers of time critical decisions. Drug–drug interactions, drug–laboratory interactions, drug–disease interactions, adverse drug reactions, and drug allergy alerts are common clinical examples of this type of decision support *(83,85,86,90)*. These types of alerts are generated at the time of either a medication order or laboratory results reporting if alerting criteria are met. Furthermore, an EHR with this alerting function can monitor patient data continuously; if appropriate criteria are met anytime in the course of hospitalization, specific personnel (such as the ordering physician, the patient's nurse, the pharmacy, and so on) can be notified. Notification can be escalated based on the urgency of the alert. Alerts requiring immediate attention may be sent by a pager or text message. Less urgent alerts can be sent by email or placed in an inbox to be viewed when the user logs on to the EHR.

Interpreting decision support refers to the gathering, arranging, and analyzing of patient data, resulting in a conceptual understanding of that data, usually in relationship to a specific test. One of the earliest applications of interpretive decision support in hospitals was computer analysis and interpretation of electrocardiograms (*7*,11,*36*). Mammograms and Pap smear reading have also seen improved interpretation demonstrated through automated decision support.

Assisting decision support is used to maximize and simplify human interaction with an EHR. This model of decision support usually consists of predictive knowledge about a particular problem or task. Computer-assisted physician ordering is an example of this type of decision support *(66,67,111,117–120,123,124)*. Assisting decision support can be as simple as fixed standing order lists or as sophisticated as computer-assisted antibiotic ordering *(97,99)*.

Critiquing decision support is defined as computer-assisted analysis or review of human decisions for appropriateness. This type of decision support uses the EHR knowledge base to evaluate human decisions and to report to the user the result of the computer analysis. Critiquing decision support has been used by investigators to develop protocols for ventilator management in the intensive care unit (ICU) setting *(115)* and to determine the appropriateness of ordering various laboratory tests *(84,121)*.

Diagnostic decision support is defined as decision support that provides a computer-assisted diagnosis of patient medical problems such as the identification of patients with a healthcare-associated pneumonia. This type of decision support has been the most widely studied of all decision support techniques in medical informatics *(78,103,106,108,109,112,118)*. Today, these tools are generally found in standalone software products, such as VisualDX, Theradoc, or Isabel, used to generate differential diagnoses for patients with complex presentations.

Management decision support is the automatic generation of decisions that are oriented to the therapeutic care of the patient. Management decision support differs from critiquing decision support in that, in the former, the computer manages patient care and suggests treatments; whereas in the latter, the computer reacts to treatment plans or orders initiated by the physician. In clinical management decision support, the physician critiques the computer rather than the computer critiquing the physician. Computerized clinical practice guidelines or "best practice" alerts are examples of this model of decision support. Management decision support techniques are currently being investigated in the ICU setting to assist in the management of patients with adult respiratory distress syndrome *(116,125)*.

The utility of these various modes of decision support is highly dependent on the context in which they function. Without appropriately structured patient data, many of the rule functions underlying these decision support tools may fail to function properly. Furthermore, the presentations of the alerts to the end user can be quite varied, ranging from pop-up windows to cell phone text messages, from hard stops during order entry to reports generated on a weekly basis.

Systematic Analysis of Clinical Data

Another benefit of an automated patient record is access to large amounts of archived clinical data to provide information on past clinical experience. Computers have the capability to examine large amounts of data and statistically summarize various aspects of care to answer administrative and management or clinical research questions. The ability to systematically analyze large numbers of clinical events and correlate these to different outcomes is one of the functions of clinical business intelligence tools, such as a clinical data warehouse. Modern quality management techniques rely on these types of analysis. Many modern clinical practices, however, distribute these data over a disconnected series of systems. Investigators have realized since the late 1970s that there exists a wide variability in the patterns of clinical practice in the United States *(126,127)*. The net results of this variability in clinical practice are the inflating of the healthcare dollar and less than optimal patient care. The EHR provides the necessary tool to identify variation in various aspects of care, where it may exist (1,*4,43,81,98*). Once identified, corrective measures can be developed to reduce the variation or manage exceptions more appropriately.

The computerized medical record has become one of the "agenda items" of the federal government in its attempt to control healthcare costs and improve the quality of care (see below). This is evidenced by recent reports from the Institute of Medicine (IOM) (1) and the Centers for Medicare and Medicaid Services (CMS), as well as Congress's commitment of financial and political support for this initiative. Certainly, the EHR will not, in and of itself, be the sole answer to the US healthcare dilemma, but it has the potential to have major impact by providing superior information to the market.

ELECTRONIC HEALTH RECORDS AND THE INTERNET

Perhaps no technologic advance since the personal computer has had a more profound impact than the rise of the Internet and its most popular usage, the World Wide Web. The Internet has revolutionized communication and provided a unique forum for the exchange of information. This forum has changed the way commerce is conducted and has significantly altered the approach to building and using information systems in all industries. Healthcare has not been immune to this rising tide, but as always in the area of information systems, healthcare organizations have been slower to adapt this new technology *(128)*. Because the Internet and use in healthcare is still developing, it is hard to predict exactly how an Internet-based healthcare system will evolve.

We have already seen the integration of platform-independent graphical user interfaces to EHRs using the Internet *(129,130)*. These types of Web-enabled interfaces have allowed clinicians to access patient data from remote locations, thus expanding the caregiver's ability to provide continuity of care from outside of the hospital setting and helping expand data collected for healthcare epidemiology. Web-based interface tools can also expand the functionality of legacy clinical databases by providing a more user-friendly front end. An added advantage of these interfaces is that they provide a portal of access to the latest scientific information (e.g., treatment guidelines) available either on the local internal servers ("intranet") or supplied by Internet tools such as electronic journals, Micromedex, or UpToDate. An Internet application has already been developed that performs global surveillance on influenza and can be used by clinicians to guide the diagnosis of influenza in their community *(131)*.

The evolution of the Internet's potential to connect individual EHRs is evident in the Centers for Disease Control and Prevention's (CDC) drive to automate its data reporting process. The National Nosocomial Infections Surveillance (NNIS) system is a cooperative effort that began in 1970 between CDC and participating hospitals to create a national nosocomial infections database. In 2005, the CDC established the National Healthcare Safety Network (NHSN) to integrate and expand NNIS along with the Dialysis Surveillance Network and the National Surveillance System for Healthcare Workers. Data from participating healthcare providers are collected uniformly by trained infection control personnel and are reported routinely to the CDC where they are aggregated into a central database. In addition, many facilities use the same data to electronically comply with state reporting mandates. Over 2,600 facilities currently report data directly into NHSN.

The promise of healthcare interconnectivity is the seamless linkage of textual information, aggregated data, and video and audio images all on the same screen through the use of browser technology *(132–134)*. Because of the pervasiveness of the Internet, the improved access to information can bring the patient data directly into the healthcare organizations' computing systems. Additionally, patients will have greater access to their own healthcare information via personal health records. The Internet dramatically increases the boundaries of what constitute a CIS or an EHR by making this information much more broadly available.

Electronic Health Records and Application Service Providers

Application service providers (ASPs) can be thought of as computer applications that are provided on demand via the Internet. These are typically subscriber-based models where a user or institution is provided with accounts (e.g., via the Web) to a remote application. The application is operated and maintained in a remote data center, and users access it with a unique login and password. No local software need be installed. These ASP models are gaining popularity under a new term: "cloud computing," which refers to a very large super-aggregated version of ASP models. This phrase will likely replace the ASP term over the next several years.

One advantage of the ASP model is that there are greatly decreased installation and support costs. Users can leverage the work of others with the same problem(s). ASP disadvantages include an institution becoming wholly reliant on the ASP vendor and their Internet connectivity. Some vendors' applications lack customizability and flexibility. ASP applications can draw data from other HIS systems (e.g., where the ASP may be epidemiologic analytics tools), or they may serve as the EHR itself. Nonetheless, this type of approach is very popular with small physician offices that often lack the capability of making large capital expenditures for EHRs.

MOBILE COMPUTING

In recent years, the growth of mobile computing has mirrored the growth of the Internet and may be on pace to exceed it. The demand for mobile devices, from smart phones to personal digital assistants (PDAs), and now wireless tablets, continues to explode. Witness:

- The number of wireless Internet users in the United States will reach 136 million by the end of 2010, or 59% *(135)*.
- By the end of 2010, there will be 205 million browser-enabled smart phones *(136)*.
- The wireless LAN market was expected to reach $2.5 billion in 2010.
- Over 50 million iPhones sold within 3 years of release, and over 2 million iPads sold within 3 months of release.

An increasing number of healthcare mobile computing applications today access data via the Internet. *Mobile computing* or *wireless* refers to the underlying technology that supports the transport of data between the mobile handheld computing device and a networked main computer system without a wired connection between them. Mobile computing includes a range of solutions that enable end-user mobility by providing access to data anytime, from any location. Hospital-based mobile computing has three main components:

- Underlying hospital, clinic, or central CIS (EHR)
- Connecting technology that allows information to pass between the site's information system and the handheld device
- Handheld computing devices (aka mobile computing devices, mobile devices, handheld devices, handhelds, smart phones, tablets)

It is helpful to see how these work together in a clinical example. The end user enters or accesses data—such as vital signs, charge information, clinical notes, and medication orders—using a software application on the handheld computing device. Using one of several connecting technologies, the new data are transmitted from the handheld to the site's information system where system files are updated and the new data are accessible to other system users—the billing department, for example. Now both systems (the handheld and the site's computer) have the same information and are synchronized. The process works the same way starting from the other direction. For example, a physician may want to have access to all new laboratory results for today's clinic patients. This information is stored in the site's EHR and now needs to be transmitted to the handheld device. Again, the connecting technology delivers the data to the handheld device, and the physician can move from room to room, accessing the appropriate information from the handheld device. The process is similar to the way a desktop PC accesses the organization's applications, except that the end-user device is not physically connected to the organization's systems. The communication between the end-user device and the site's information system can use different methods for transferring and synchronizing data. Some common data transfer approaches include:

- Wireless local area network (WLAN)
- Wireless Internet or wireless Web over cellular networks
- Hot synching or data synching using docking cradles or docking stations that are connected directly to the organization's information system via the wired local area network (LAN)

Wireless LAN

WLAN is a flexible data and communications system used in addition to, or instead of, a wired LAN. Using radio frequency (RF) technology, WLANs transmit and receive data over the air, minimizing the need for wired connections and enabling user mobility. In a WLAN, the caregiver enters data into a handheld device such as a PDA or a laptop computer that has a special WLAN card. This card has an antenna that transmits the data in real time using RF technology to an access terminal, usually connected to a ceiling or wall. The access terminal is connected to the wired LAN and sends the data received—or requests for data—from the handheld device to the patient care information system. Conversely, data from the site's information system can be sent to the handheld device using the same technology. PDAs, popularly used by physicians, have a very small screen size that is best suited to only limited data viewing and data collection functions such as laboratory order entry, single results display, and very limited clinical notes entry. Laptops and tablets provide improved processing capabilities, more data storage, better keyboards, and larger displays, so end users can make more extensive use of entire patient records and view results in a number or graphical formats. Complex applications whether inpatient or outpatient work best in a wireless LAN environment that uses these larger devices.

The Wireless Web

Wireless Internet, also known as the wireless web, provides mobile computing access to data using the Internet and specially equipped handheld devices. For example, using a Web-enabled smart phone, the end user can display data accessible from the Internet. Technically speaking, the mobile device connected to the cellular system sends the request to a computer link server. This server acts as a gateway that translates signals from the handheld device into language the Web can understand, using an access and communication protocol. One of the leading protocols is called Wireless Access Protocol. The server also forwards the request over the Internet to a Web site, such as Yahoo or Google or the organization's own Web servers, connected to the CIS. The Web site responds to the request and sends the information back through the link server. The response is translated into a wireless markup language, so it is viewable on a small cell phone screen. This translated response is then sent to the cellular system and finally to the Web-enabled mobile computing device. Examples of the current uses of the wireless Internet include accessing short emails, quick lookup capabilities (stocks, weather, flights, directions, movies, and restaurants), retailing transactions (e.g., Amazon.com), and alert messaging in healthcare. Newer faster technologies are steadily moving these portable devices closer to full workstation functionality over a wireless connection.

Synchronization Synchronization or hot synching provides many of the benefits of mobile computing without the necessity of installing wireless LAN equipment or needing access to the Internet. Information is periodically downloaded from the EHR to the handheld device and then uploaded from the device to the EHR. The major drawback of data synchronization is that it does not provide real-time access to data. Data synching is not a wireless data transfer method since data are transferred from the mobile computing device to the site's information system through a docking (or synching) cradle wired to the LAN. However, since the end-user device is only physically attached to the LAN during the batch data transfers, it is still considered a mobile device.

Mobile Computing Devices

An ever-increasing number of mobile computing devices are available for use in the healthcare setting *(137)*:

- *Web phones*: cellular phones with Internet access and Internet browser that allow limited email, calendar, appointment scheduling, and directories. There are currently a growing number of healthcare content and vendor-specific healthcare applications on Web-enabled phones.
- *PDA/phone*: combination of a Web phone with PDA functionality with Internet browser functions including email, calendar, appointment scheduling, and directories (e.g., iPhone, Trio, Blackberry). Healthcare functions include charge entry, prescription writing, and Internet access.
- *PDA or pocket PC*: handheld computerized information organizers (e.g., Palm Pilot, Handspring Visor, Compaq iPaq) with email, calendar, appointment scheduling, and directories, including some desktop application functions (e.g., Word and Excel), pen-based system for data entry, and bar-coding functions. Healthcare applications include charge capture, prescription writing, lab results review, and multiple functions using browser technology with wireless LAN.

- *Handheld PC*: small hand size personal computer with a keyboard. Much more powerful than a PDA device with some desktop application functions (e.g., Word and Excel), keyboard for data entry, voice recognition, and recording options. Healthcare functions similar to those cited above.
- *Tablet/laptop*: tablets are flat paneled computing devices, including laptops, tablet computer, and iPads. Tablets use pen or touchscreen technology and allows for multiple integrated functions, for example, full EHR capabilities.

Mobile Computing Applications

Given the new and evolving application market and continually advancing technology components, today's most effective software applications are those focused on tasks that require data access at the point of care but do not require sophisticated infrastructures to transfer data between the device and the organization's computer system. These types of tools currently include the following.

Alert Messaging and Communication These applications go far beyond the pagers long used by on-call physicians, often allowing them to receive test results and send messages. The biggest challenge for these products is the ability to deliver secure, uninterrupted messages. As electronic interactions between ambulatory physicians and patients become more common, devices may be able to deliver messages and alerts to physicians in that setting as well *(138)*.

Clinical Documentation Rapidly increasing regulatory requirements and changing payment documentation needs are increasing the need for point-of-care clinical documentation systems. Tools with a wide range of functionality from basic notes templates on PDAs to images that can be displayed on a laptop help clinicians quickly document clinical activities, as well as organize and track patient information from one encounter to the next. Most mobile software applications supporting inpatient care are focused on nursing documentation; only a few vendors currently support applications for physicians in the ambulatory setting. As more physicians and other providers begin to participate in disease management, which requires increased data collection and monitoring, tools that enable providers to cope with the volume of data at the point of care will become increasingly valuable and will be accessible via mobile computing.

Charge Capture and Coding These popular tools for both inpatient and outpatient care enable caregivers to record information at the point of care instead of after the fact. The handheld computing application replaces the antiquated index card system for recording charges. It includes coding tools for translating increasingly complex payer rules, especially in the ambulatory setting. These applications can have a positive financial impact by capturing more accurate and complete information about diagnoses, procedures, and other care-related services. In the future, charge and coding functions will likely be integrated with other clinical computing tools, thus capturing financial information as part of the automated care documentation process.

Lab Order Entry and Results Reporting Most often found in the inpatient setting, these applications allow users to order laboratory tests and view results at the point of care. Most focus first on one aspect of the process and then move to the other. For example, one vendor decided to start with result viewing because of the limited handheld processing and customization required, and then moved toward a total ordering and result viewing application. Lab order entry streamlines the ordering process; results reporting allows access to often critical patient information anytime and anywhere. Because these functions require real-time interfaces with existing ordering and resulting systems, success so far has been limited to a few vendors who have either partnered with well-known traditional vendors or added integrating tools to their products. As the technology advances, allowing for better integration of applications, laboratory order entry and results reporting tools will likely become common.

Prescription Writing Using a smartphone, tablet, PDA, or pocket PC instead of a prescription pad, physicians can now generate prescriptions by clicking on the patient, medication, and dose. Many e-prescribing tools can also check prescriptions for drug interactions and potential allergic reactions and transmit completed prescriptions directly to the pharmacy. Products on the market today differ in almost every step of the process, from how patient data are obtained, to where processing occurs, to how scripts are sent to the pharmacy, making this a crowded and confusing vendor field. E-prescribing tools are likely to advance rapidly as problems of integration with patient data and data transmission are overcome *(139,140)*.

In many ways, these applications are mobile extensions of the traditional EHR. Some of the most popular inpatient applications are bedside charting, emergency room documentation, and remote access to data for physicians *(141)*. Mobile solutions for inpatient clinical computing are likely to be offered by traditional EHR vendors; these vendors will likely partner with wireless technology providers and mobile computing vendors.

Physician use is the primary focus of mobile computing, and that is in the outpatient setting *(142,143)*. Mobile computing devices are well suited to physician practice since physicians often spend their whole day moving between exam rooms and offices and need continuous access to clinical data. Mobile computing also avoids the cost of hardwiring many physician offices and exam rooms. In the physician office, mobile devices that use batch synchronization of data are most common. In addition to reference tools, handheld applications are focused largely on high-stake individual processes such as charge capture or prescription management *(144,145)*.

Mobile Computing Infectious Diseases Applications

PDAs, smartphones, pocket personal computers, and the like, provide immediate access to clinically relevant infectious diseases information at the point of care. Several infectious diseases applications are available that provide information on pathogens, diagnosis, medication, and treatment.

One well-studied example is ePocrates Rx, a comprehensive drug information guide that is downloadable free from the Internet and designed for multiple mobile computing platforms. A 7-day online survey of 3,000 randomly selected ePocrates Rx users was conducted observing the following parameters: user technology experience, product evaluation, usage patterns, and the effects of the drug reference database on information-seeking behavior, practice efficiency, decision making, and patient care. The survey response rate was 32%; 946 physicians who used the program reported that it saved time during information retrieval, is easily incorporated into their usual workflow, and improves drug-related decision making. They also felt that it reduced the rate of preventable adverse drug events (ADEs). The clinical and practical value of using these devices in clinical settings will clearly grow further as wireless communication becomes more ubiquitous and as more applications become available *(146)*.

In another study, several infectious diseases PDA applications were reviewed *(147)*; these included ePocrates ID (part of ePocrates Rx Pro), the Johns Hopkins Division of Infectious Diseases Antibiotic Guide, the 2002 Sanford Guide to Antimicrobial Therapy, and Infectious Diseases and Antimicrobials Notes. Drug information, including clinical pharmacology, dosing in patients with renal insufficiency, adverse reactions, and drug interactions, was evaluated for completeness and accuracy by comparison of each application with the package insert. Treatment recommendations for six diseases using these programs were compared with current practice guidelines. Each PDA infectious diseases application reviewed was found to have unique advantages and disadvantages. This critical review will help healthcare professionals select the infectious diseases PDA application best tailored to meet their individual information needs *(147)*.

AUTOMATED ELECTRONIC CLINICAL SURVEILLANCE SYSTEMS

Background

Surveillance has been defined as the collection, collation, analysis, and dissemination of data *(148,149)*. Several methods have been developed to perform this task in hospitals and other settings of care. The traditional method includes collection of data through extensive chart review, a time- and labor-intensive process. Computerized methods have been developed for hospital surveillance; several PC-based programs in infection control are available, which are reviewed in Chapter 15. These systems offer added efficiencies in the analysis of data but not in the collection of data. As surveillance in hospitals is expanded from infection control to other areas, more efficient means of data collection will be essential. The development and implementation of comprehensive enterprise HIT offer the potential for improving, enlarging, and more efficiently conducting hospital-wide surveillance. This section reviews hospital surveillance systems that make use of a previously installed EHR.

Data Sources

The creation and adoption of healthcare data standards has been a massive undertaking that has engaged the informatics community for several decades. A detailed discussion of the myriad issues involved in information harmonization is beyond the scope of this chapter. Those interested in a more detailed look at proposed Federal interoperability standards and implementation protocols are referred to the work of the Healthcare Information Technology Standards Panel, a cooperative partnership between the public and private sectors under contract to the U.S. Office of the National Coordinator for HIT (ONC).

Administrative HIT systems

A complete computerized medical record is not necessary before computerized surveillance can begin. Indeed, most institutions build a computerized medical record gradually over several years *(150–152)*. However, certain key areas are essential before beginning hospital-wide surveillance. Virtually all hospitals have established computerized systems for ADT information. These programs are implemented for administrative purposes, but they often collect important demographic information, including admission dates, diagnoses, lengths of stay, and discharge status, that informs the core of the inpatient medical record. Some organizations choose to implement an enterprise master patient index to facilitate administrative and clinical data from disparate systems that may not share patient identifiers. Generally, integrated clinical computer systems will have some kind of patient demographic system as a foundation to which other information is added.

Most American administrative healthcare computer systems index healthcare data using the International Classification of Diseases (ICD). ICD was originally developed by the World Health Organization for reporting morbidity and mortality statistics, but has been adapted for billing and administrative purposes. Healthcare facilities in the United States generally make use of a clinically modified version of the 9th edition (ICD-9-CM), although the CMS has announced it will begin using ICD-10 exclusively beginning October 2013.

Recent work (153) has highlighted the advantages and limitations of using administrative coding data for healthcare-associated infection surveillance. Notably, diagnosis code lists may be artificially abbreviated; codes may not correspond directly to clinical syndromes; and codes may be optimized for billing, rather than clinical, purposes.

Clinical Documentation in HIT Systems

As EHRs become more widespread, electronic clinical documentation has become increasingly available to infection preventionists (IPs). And, while free text documentation cannot readily be analyzed by automated surveillance systems, there are relevant clinical observations (such as temperature, presence of a urinary catheter, and so on) that are valuable for surveillance activities. Additionally, clinical problem lists may adhere to a standardized nomenclature. Traditionally, structured problem lists have utilized ICD-9-CM, but, as described above, the ICD classification system has been optimized as a billing and administrative tool.

The Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT) offers better promise for descriptive terminology that is relevant to both clinical practice and epidemiology. SNOMED, which was developed by the College of American Pathologists and is made freely available

by the National Library of Medicine, utilizes 11 axes (or components) that can be combined into useful clinical concepts. For instance, components enumerating anatomical structures, microorganisms, findings, and procedures might be combined to describe "a chest tube inserted to drain a left lower lobe pneumococcal pneumonia and associated empyema."

SNOMED's strength as a descriptive clinical terminology has also been its limitation, as its complexity has limited its adoption and implementation. However, it is widely understood that CMS will require providers to report clinical observations and problem lists in SNOMED CT format in order to receive HITECH incentive funding under future definitions of the "meaningful use" of EHRs.

Laboratory HIT Systems

Clinical laboratory systems, a rich source of clinical data, are ubiquitous within healthcare and are increasingly interfaced with a variety of external systems, including EHRs and clinical data repositories *(154–157)*. Legacy lab systems may not adhere to data standards, but more modern systems (and, increasingly, those belonging to large reference laboratories like Quest or LabCorp) will utilize several key standardized terminologies. The Logical Observation Identifiers Names and Codes (LOINC) nomenclature provides a set of universal names and ID codes for identifying laboratory and clinical test results facilitating the exchange and pooling of results for clinical care, outcomes management, and research. The EHR-Lab Interoperability and Connectivity Specification (ELINCS) can be used to define interfaces for results reporting from external laboratories.

Unfortunately, the least standardized aspect of laboratory systems is the microbiology laboratory. Microbiology data are often represented in free text form with frequent updates as culture data evolve, which frustrates automated analysis. Furthermore, heterogeneity in reporting susceptibility profiles complicates the usage of standardized tools. Ideally, microbiology reporting systems can utilize a combination of LOINC and SNOMED to reduce the reliance on free text, although this is rarely done in practice. Nevertheless, because of their great relevance to infection control surveillance, customized interfaces and extraction of microbiology reports are usually worthwhile endeavors for implementers of infection control systems.

Pharmacy HIT Systems

Many hospitals have computerized pharmacy systems, both for automation of pharmacy operations and for drug ordering (e-prescribing) or drug administration (usually in the form of bedside barcode medication administration). Pharmacy data may help the IP identify patients suspected as having a healthcare-associated infection (e.g., those receiving oral vancomycin may be suspected of having *Clostridium difficile*–associated diarrhea), or those who may have a communicable illness that requires special precautions (e.g., orders for permetherin suggesting treatment of an ectoparasitic infestation). Older CISs have not always adhered to pharmacy data standards, but the ONC regulations for EHRs specify a few key standard nomenclatures for medications that will be the norm for EHRs in the future.

The first is the National Council for Prescription Drug Programs (NCPDP) Script standard for sending prescription messages between pharmacies, prescribers, intermediaries, and payers. The standard supports messages regarding new prescriptions, prescription changes, refill requests, and medication history.

NCPDP Script defines the syntax and message structure between systems; RxNorm provides normalized drug names and links to many proprietary drug vocabularies, such as those provided by First Databank, Micromedex, and others. RxNorm is a product of the National Library of Medicine and is freely available.

Medication allergy terminology has proven particularly resistant to standardization, given the great variation in classifications of drug reactions and intolerances, drug components acting as allergens, and workflow in recording these critical data elements. ONC's current guidance is to use a combination of RxNorm, SNOMED CT, and the Unique Ingredient Identifier codes, which include inactive drug additives (e.g., dyes and fillers). Few existing CISs adhere to these allergy standards today.

Automated Infection Control Surveillance Using HIT Systems

A combined clinical data set, with discrete values as defined by standardized terminologies above, can be stored in a computer database (such as a clinical data warehouse) that is optimized for sophisticated analytical queries. In some cases, manual or *ad hoc* analyses may be sufficient. However, in order to automate surveillance, the IP will require a knowledge base or a rules engine. Rules can be simple ("Send an alert for all new MRSA isolates.") or quite sophisticated (a multistep algorithm to determine automated device-days calculations for device-associated infection). In general, rules should be tested carefully against standard methodologies, such as chart review, to determine their test characteristics (sensitivity and specificity) and limitations before being used routinely (158).

The *American Journal of Infection Control* recently highlighted the value of automated surveillance systems (77), including the ability to generate individual alerts for sentinel events or microorganisms; *ad hoc* data requests and line lists; automated cluster detection; and regular computerized infection reports. IPs have generally been pleased with these tools and their ability to automated rote and mundane data collection, reduce the risk of transcription error, and identify unusual trends in the data that may not have otherwise been identified.

Automated infection surveillance systems in the United States were first developed primarily in academic medical centers, including LDS Hospital in Salt Lake City *(159,160)*, Barnes-Jewish Hospital in Saint Louis (*161*,162), and New York Presbyterian Hospital *(163)*. Public hospitals in the United States and abroad have also had success with implementation of clinical data warehouses *(164)*, automated surveillance for surgical site infections *(165)*, and healthcare-associated ICU infections *(166)*.

Studies of these standalone systems have generally demonstrated substantial potential. The adoption of the LDS surveillance system resulted in the savings of two fulltime equivalent positions in the infection control department *(159,160)*, while identifying significantly more healthcare-associated infections than manual surveyors. The use of this program has also resulted in significantly

more patients being placed on appropriate isolation and better coordination of the infection control isolation program (*159,160*,167). Automated screening for surgical site infections by Saint Joseph Hospital in Paris identified nearly as many cases as manual review, but in 60% less time (*165*). New York Presbyterian Hospital screened radiology reports to identify healthcare-associated pneumonias in the neonatal ICU with a sensitivity of 71% and specificity of 99.8%.

Many infection control systems have become available as commercial software available for purchase and implementation. These products include TheraDoc Infection Control Assistant, Cardinal Health MedMined, Premier SafetySurveillor, rL Solutions Infection MonitorPro, and Sentri7. These systems have not yet been subjected to rigorous comparative evaluation in a peer-reviewed publication, but there have been a number of case reports suggesting their value *(51,168)*. Generally, these tools offer the ability to mine raw surveillance data for unexpected patterns and generate *ad hoc* or routine reports based on infection control queries (77). Some additional features include automated infection control reporting to public health departments and alerts upon detection of clusters of unusual syndromes or microorganisms.

APIC's 2009 position paper on the importance of surveillance technologies in the prevention of HAIs "supports the use of automated surveillance technologies as an essential part of infection prevention and control activities (169)." They highlight the benefits of these systems, including facilitating efficient review of surveillance data; expanding the scope of infection prevention activities; reducing infection prevention time spent on clerical tasks; and improving regulatory compliance and financial performance. APIC also provides an "Infection Prevention and Control Surveillance Technology Assessment Tool" on their Web site to aid IPs in selecting the right product (170).

IPs have generally welcomed the automation of surveillance activities, but the technology has catalyzed a shift in their job duties *(61)*. The time previously spent engaged in manual data collection and aggregation can now be spent on investigations, interventions, and education. Additionally, IPs now have the new responsibility of ensuring that their automated systems remain updated with the latest software, that reports and decision rules stay in sync with the data provided from other clinical systems, and that changes in clinical workflow don't create "blind spots" in automated surveillance reports and consequent falsely assuring negative findings.

Adverse Drug Event Surveillance Programs Using HIT systems An emerging area of healthcare epidemiology is drug-use surveillance. Pharmacy information systems can also be adapted to target and monitor specific drugs. Such a program at LDS Hospital was used to prospectively monitor the use and safety profile of imipenem/cilastatin, a drug associated with seizures *(98)*. Over 1,900 patients were studied and the observed seizure rate was 0.2%, which was markedly less than the 2% rate noted with the use of the drug at other centers. In addition, using creatinine clearances and other indicators of renal function that are automatically collected and stored on every patient, it was determined that all three patients experiencing seizures were receiving significant overdosage based on their renal function, thus associating the observed seizures with improper imipenem/cilastatin dosing. This system was also used for noninfectious adverse events associated with the use of midazolam, a benzodiazepine *(92)*. In this study, respiratory arrests were found to be related to drug overdosage. Both studies allowed for appropriate physician education and improved therapeutic use of both agents.

ADEs from antibiotics are only the tip of the safety iceberg for hospital patients; potentially surveillance can be broadened to include all ADEs in hospital patients. However, the routine method for detecting and reporting ADEs at hospitals involves voluntary reporting by physicians, who are required to complete and sign incident reports and submit documentation to the FDA, but rarely do in practice. Computer methods have been developed to automate the detection of hospital-associated ADEs *(91)*. These programs allow for both voluntary and nonvoluntary detection. Computer programs automatically conduct surveillance on all laboratory values of all patients, looking for certain arbitrary abnormalities such as eosinophilia, leukopenia, increased creatinine, and drug levels. Rule-based algorithms using medical decision logic are also used to detect ADEs.

For example, pharmacy orders are automatically screened for potential antidotes, sudden stop orders, and dose reduction orders. Each day, a report of all potential ADEs detected in the last 24 hours is printed out. A pharmacist reviews the records and interviews healthcare personnel relevant to all patients identified as having a potential ADE. The pharmacist then determines likely ADEs and enters his report into the patient's permanent record and the hospital ADE file. This report includes the time course of the event, pertinent subjective data, and the subsequent clinical course, all of which are stored in the ADE file. In addition, surveillance systems integrated with EHRs can automatically record the drug indication, administration time, duration of therapy, route of administration, and the National Drug Code. Each patient's ADE can be permanently stored in the record, and, if the offending drug is reordered, an alert may be generated to the appropriate clinical personnel.

THE FUTURE OF EHRS—MEANINGFUL USE OF HEALTH INFORMATION TECHNOLOGY

In the landmark report "To Err is Human," the IOM called for the adoption of EHRs as an essential infrastructure for improving the safety and quality of care in the United States (171). During the past decade, many hospitals and ambulatory care sites have begun implementing EHRs, but most care is still delivered without these systems. Furthermore, recent studies reveal that, despite considerable investment in these systems, many organizations have so far made only limited use of the most powerful capabilities of these systems to improve the quality and safety of care *(172)*.

The US government had previously invested relatively little in HIT compared to other nations, and lags far behind many other developed countries with respect to

HIT adoption. This level of investment, however, is about to change radically—the American Recovery and Reinvestment Act (ARRA) of 2009 provides up to $45 billion for the adoption and use of Health Information Technology (commonly called HITECH); prior federal spending on HIT in this area was approximately $50 million per year *(173)*. Most of this funding will go as financial incentives to physicians (individual non-hospital "eligible providers") and hospitals able to demonstrate that they are using "certified EHR technology in a meaningful manner" *(173)*. The ARRA underscores several specific areas of EHR use that fit the overall EHR-enabled improvements called for by the IOM. For both the hospital and the physician delivering ambulatory care, these requirements include "using the EHR to report on designated clinical quality measures, to exchange health information to support continuity of care, and to write orders electronically (Computerized Physician Order Entry [CPOE] or electronic prescribing [e-Rx], respectively) to gain the benefit of clinical decision support (CDS) to improve the safety and quality of patient care."

Tying financial incentives to the concept of meaningful use is essential because merely implementing an EHR does not necessarily mean that providers are using the software in the manner necessary to achieve the desired improvements in care. EHR vendor products are not all the same and cannot be used "out of the box"; local organizational EHR configuration and customization are always required regardless of the setting of care. In one survey, in the 14.8% of US nongovernment hospitals using CPOE, only 70% were using any decision support in CPOE, only 52% had CPOE in use for all inpatient beds, and only 39% had physicians entering at least 75% of orders *(174)*. In the outpatient setting, national data show that simply using an EHR was not associated with improved quality of care across a wide array of quality measures *(175)*.

To receive the financial incentives, eligible providers and hospitals must achieve "meaningful use" of an EHR. Meaningful use requirements are grouped into three stages, but the designations are no longer tied to specific dates as originally proposed (2011, 2013, and 2015). In Stage 1, the focus is on capturing data, in Stage 2 on reporting health information and tracking key clinical conditions, and in Stage 3 on improving performance and health outcomes (176,177). In the rules released in July 2010, hospitals and providers would be able to qualify for their first payment using Stage 1 criteria up until 2014. In the first payment year, only 3 months of meaningful use needs to be demonstrated to receive incentive payments, while in future years, meaningful use must be demonstrated for the entire year. To get the maximum Medicare payments, eligible providers need to qualify by CY 2012 and hospitals by FY 2013. Both physicians and hospitals also need to meet Stage 3 criteria by 2015 to avoid Medicare penalties. Physicians who provide more than 90% of their care in a hospital inpatient, hospital outpatient, or ED (point of service codes 21, 22, and 23) are not eligible for incentives. Eligible hospitals are defined by their unique CMS Certification Number (CCN or OSCAR codes).

The new rules break the criteria down to those to be achieved in 2011 (Stage 1), those to be achieved in 2013 (Stage 2), and those to be achieved in 2015 (Stage 3) (176). Only those criteria for 2011 (Stage 1) are included in the final rule. These criteria are quite specific for both the inpatient and outpatient settings of care and, although they include percentages for some measures such as computerized medication order entry, it is the quality measures themselves that will require the most significant effort on the part of all organizations to collect and report with their EHR. In addition, the infrastructure at the state and federal levels to receive these reports is not yet in place. Thus, quality measure reporting electronically will not be formally required until 2012, but the burden of collecting and reporting these measures through an EHR will still be substantial.

Healthcare organizations and physicians are understandably anxious about meeting these stringent meaningful use requirements in time to achieve the financial incentives by 2011. The Rules on Meaningful Use include both objectives and potential measures for meaningful use; many of these measures are currently reported and collected quality-of-care measures. However, some of these areas of performance are already measured in nearly all inpatient institutions whether they use an EHR or not; and hospitals, most without a comprehensive EHR, have initiated complex, labor-intensive processes to improve performance in these areas.

In terms of infection control, these criteria will require reporting of multiple types of data electronically to both state and federal agencies. The requirements include immunization data, reportable laboratory results of interest to public health, and electronic syndromic surveillance data.

In addition, there is a requirement for reporting nationally endorsed quality measures, many of which touch on infection control. The challenge here is that the requirements for this public reporting will start in 2012, and it will require collection of these data from the EHR and electronic submission to state and federal agencies as well as public health authorities. The meaningful use requirements mandate collection of these data through the EHR rather than through the ancillary systems where most hospitals manually enter their quality measurement data.

Hospitals should begin this journey by selecting an EHR product that includes the functions and features necessary to achieving meaningful use. ARRA is explicit that "the EHR technology used must be certified." At the time of this writing, the CMS is putting the finishing touches on an EHR certification program. At a minimum, these criteria are expected to include data capture and reporting for quality measurement. For both inpatient and ambulatory care settings, certified HIE capabilities will likely be expanded to include the Continuity of Care Document (CCD) (an existing HIT EHR standard vehicle for transmitting patient clinical summaries among providers) and capabilities for medication reconciliation across the continuum of care. EHR certification may also be expanded to address ease of use by providers and additional safeguards to protect patient privacy and information security (176,177).

For meaningful use, certification—though necessary—is alone not sufficient. How certified EHRs are actually implemented by hospitals is probably even more important. First, the manner in which the EHR software is implemented (what features are turned on and applied) must offer providers all of the capabilities needed to use it in a meaningful way. Second, physicians, nurses, and other healthcare workers must incorporate the use of the EHR into their routine workflow. These points require different approaches for the hospital and the physician practice, but can be based on the same principles.

CMS has stated that the threshold for "meaningful use" will be raised over time, incentivizing incremental implementation to meet increasing requirements from 2011 to 2015 or Stages 1, 2, and 3. Hospitals are further incentivized to help providers implement EHR and e-prescribing through exemptions to the Stark laws that allow hospitals and group practices to support providers with nonmonetary donations of hardware, software, and related training.

Because of the urgent call by the IOM and others for improved patient safety for the hospital setting, targeted EHR functionality will include CPOE with CDS, capability for HIE, and electronic clinical documentation for both nurses and physicians. The right implementation must include setup and configuration of CPOE to cover medication orders at a minimum and to leverage the CDS tools to address the common, serious ADEs that still occur in hospitals today. The best practice implementation must also accommodate the electronic clinical information exchanges that will be occurring with increasing frequency at patient admission and discharge as more physician practices and other providers are able to participate in electronic exchanges during patient transitions in care. This will include the ability to exchange structured problem list, labs, or radiology test results. Medication management including administration and dispensing is included, because these care processes, like order writing, can be made significantly safer through the use of such interventions as electronic medication administration record (eMAR) with bar coding *(178)*.

Successful infection control applications within EHR products will benefit from the above requirements being in place. Hospitals should immediately explore their chosen EHR vendor's path to achieving meaningful use of infection control data collection and reporting. Although many hospitals will likely report these data from standalone or ancillary systems initially, the long-term strategy should be to transition this function to the EHR as incentivized by meaningful use requirements.

Approach to Data Analysis: Use of Data Warehouses

HISs offer many advantages to the healthcare epidemiologists and IPs. They provide comprehensive detailed and integrated clinical information in a timely fashion to help with outbreak investigation and design of interventional programs for the prevention and control of healthcare-associated events. Additionally, the healthcare epidemiologist can automate analysis of infection control data on a regular basis to detect trends and changes suggestive of healthcare-associated outbreaks.

Most EHRs, however, are optimized to support individualized patient care, and are not designed to support analysis across cohorts and populations. In addition, complex statistical queries made against an EHR's active patient database may reduce the performance of the clinical system to the extent that it may actually interrupt the clinical workflow at the bedside.

For this reason, the most practical approach to data analysis is not to use the EHR for this task, but to analyze the data in a separate data warehouse. Data warehouses can be complex information systems implemented on an enterprise level, or, in more resource-constrained settings, they can be simple database programs loaded onto personal computers.

This approach allows flexibility, convenience, and computational efficiencies that are not often available on an EHR. In addition, there are many software tools widely available for data analysis such as statistical packages and spreadsheet programs for report generation.

For epidemiologists, this approach is hampered by (a) additional cost for an institution to develop and maintain a data warehouse, (b) the need to separately integrate additional relevant data that may not have been part of the clinical record, and (c) data fields often not structured properly for epidemiological queries (e.g., microbiological data). In practice, creating an epidemiologically complete data warehouse is nontrivial, and proper implementation eludes many sites.

Role of the Healthcare Epidemiologist in Selection and Implementation of EHRs

The healthcare epidemiologist has training and experience in infection control and healthcare epidemiology; these fields require considerable sophistication in data collection, data analysis, statistical interpretation, and experimental study design. The healthcare epidemiologist is also often involved in ongoing programs to improve antibiotic use, prevent healthcare-associated infections, and detect potential healthcare-associated outbreaks. As a physician, the healthcare epidemiologist is intimately involved with direct patient care and in many institutions is viewed by the medical staff as role model. The combination of medical staff credibility and a strong foundation in epidemiology offers the healthcare epidemiologist a natural leadership position in helping lead the selection and implementation of computerized patient information systems. Unfortunately, leadership in acquisition of clinical computing systems often has come from administrators who are more interested in realizing financial benefits without a clear understanding of clinical needs *(179)*, leading to clinicians' frustration with the clinical functionality of computer systems in their institutions.

System selection and implementation requires at least one (and often several) physician champion. The champion role does not require significant computer experience or a background in computer science; in fact, being perceived as the medical staff computer "nerd" can be damaging to one's credibility. A physician leader must be able to see the broad view of clinical computerization, the institutional needs, and the goals and not have this view poisoned by narrow interests in specific computer applications.

However, a physician leader should have experience in data collection and analysis for an understanding of the important role these issues play in EHRs. Clinical epidemiology experience is a great fit, because it encompasses issues related to data collection, structure, and analysis, combined with deep understanding of the workflow of nearly every unit in the medical setting.

A physician leader should have clinical credibility with medical staff in order to facilitate the implementation of an EHR. Because healthcare epidemiologists are often well-regarded opinion leaders, they have a significant leadership potential with the medical staff. They are a natural choice for involvement on a physician task force for selecting and implementing an EHR. Medical staff involvement at all stages of the process is critical; no other group can

effectively customize an EHR. Physician leaders must take a strong role in setting vision and educating medical staff members about the goals of implementation.

Each institution that is considering an EHR needs not only a vision, but also, on a more practical level, a concrete set of institutional goals for information management. These goals are pivotal in setting the requirements for an information system. These goals need to consider the history and tradition as well as the mission of the institution. From this list of goals, a group of needs can be generated, taking into account the existing resources at that institution. Obviously, all the needs cannot be met given limited resources; thus, some form of prioritization of needs is necessary. Based on this analysis, specific criteria for an information system can and must be developed. This is crucial for a rational choice among the multitude of systems available. Once these factors have been delineated, they must be presented and agreed upon by the medical staff and the administration before moving ahead to select a system.

A detailed strategy for EHR system selection is beyond the scope of this chapter; however, there are many points in the process where the healthcare epidemiologist should be at the table.

When the goals, needs, and priorities for information management are established, other clinical leaders and administrative or IT managers may neglect to include the need for capabilities for population or cohort data analysis, or tools for outbreak investigation.

When evaluating possible EHR vendors, the healthcare epidemiologist should understand the system's potential capabilities: Is the system designed for direct physician use? If so, where are sites of use in the institution? Is there evidence that the system meets clinical needs? What are the speed and flexibility of the system? Have physician suggestions been incorporated into the system? What is the scope and design of the EMR and the capability for a longitudinal record? Does it offer inpatient and outpatient applications? Are there a central database and a knowledge base, and who will maintain them? What are the methods for data capture? What are the interfacing capabilities and communication protocols in the system? What standardized terminologies and messaging standards does the system use? Is the system Web enabled, and does it support browser applications in all of its applications? Does this system capture financial data and true cost data? Will there be a clinical data warehouse, and how can it be queried? Does the system allow patients to directly access their own records? Does the system offer order entry, and what provisions are there for electronic signatures and security?

In summary, healthcare epidemiologists of the future will have a much broader mission both in the inpatient and outpatient settings as the healthcare reform process moves forward and as clinical information is computerized. Not only will healthcare epidemiologists be more effective in managing infection control issues in a timely and real-time basis, but their experience and background will make them invaluable in managing outcomes information in all aspects of healthcare delivery, especially as care moves to the outpatient arena. Future healthcare epidemiologists must be computer literate, as they will either adapt to the electronic revolution in healthcare or become a victim of it.

HEALTH INFORMATION TECHNOLOGY GLOSSARY

Admission–discharge–transfer (ADT) The registration data that are the core component of a hospital information system that maintains and updates the hospital census.

Application program A computer program designed to accomplish a user-level task.

ARRA The American Recovery and Reinvestment Act of 2009, federal legislation driving economic stimulus and recovery in the United States that includes a significant focus on health information technology and meaningful use of information by healthcare providers (see HITECH).

Artificial intelligence The branch of computer science concerned with endowing computers with the ability to simulate intelligent human behavior, both cognitive and perceptual.

ASCII American Standard Code for Information Interchange; the world standard code for representing characters (all the upper and lowercase Latin letters, numbers, punctuation, etc.) as binary numbers used on computers, terminals, printers, etc. In addition to printable characters, the ASCII code includes control characters to indicate carriage return, backspace, etc.

Application service provider (ASP) A service delivery model where the application is run on remote computer systems maintained by a vendor and the client/end user accesses the service(s) remotely (usually via the Internet) (see also cloud computing).

Bandwidth The maximum amount of data per second that can be transmitted across a telecommunications line or received by a network interface. T1 speed = 1.544 Megabits per second.

Biomedical computing The use of computers in biology or medicine.

Biomedical engineering An area of engineering concerned primarily with the research and development of medical instrumentation and medical devices and the application of engineering methods and technology to biomedical science.

Bit A digit that can assume the values of either 0 or 1. Shorthand for *b*inary dig*it*.

Browser A client program that is used to look at various kinds of Internet resources. For example, Firefox/Mozilla, Microsoft Internet Explorer, Google Chrome, Opera, etc.

Continuity of Care Document (**CCD**) An XML-based markup standard that defines the encoding, structure, and semantics of a clinical summary document for a patient.

Clinical Document Architecture (CDA) An XML-based markup standard that defines the encoding, structure, and semantics of clinical documents.

Byte A sequence of eight bits. The amount of memory space needed to store one character, which is usually eight bits.

Central processing unit (CPU) The "brain" of the computer. The CPU executes a program stored in main memory by fetching and executing instructions in the program.

Client A computer that receives services from another computer (known as a server), or (on multitasking operating systems) a process that receives services from another process. The system (software running on a piece of hardware) that initiates the process or requests services in a client/server architecture (see Server).

Client/server A style of distributed computing that enables several local area network–based PCs or workstations (known as clients) to share access to a more powerful server computer. With this approach, processes are divided between two systems that work together to perform a task, such as retrieving information from a database.
Clinical data repository A database containing information from numerous sources, optimized for review of individual patient data (see Clinical data warehouse).
Clinical data warehouse A data repository that encompasses enterprise-wide data on many topics with data often drawn from multiple source systems in the institution that has been optimized for display and analysis of aggregate data, reporting, and data mining.
Clinical decision support system A computer-based system that assists physicians in making decisions about patient care.
Clinical prediction rule A rule, derived from statistical analysis of clinical observations, that is used to assign a patient to a clinical subgroup with a known probability of disease.
Cloud computing A type of distributed client-server computing generally via the Internet where applications and data reside in a remote data center (or cloud) often via the ASP model.
Cognitive science Area of research concerned with studying the processes by which people think and behave.
Consulting system A computer-based system that develops and suggests problem-specific recommendations based on user input (see Critiquing system).
Computerized provider order entry (CPOE) The process or system by which healthcare providers have direct computer access to enter and process their clinical orders. This is a core component of most electronic medical record systems.
Critiquing system A computer-based system that evaluates and suggests modifications for plans or data analyses already formed by a user (see Consulting system).
Data mining A technique that uncovers new information and relationships by systematically examining existing information in an existing data set.
Decision support system An information processing system or subsystem designed specifically to address the information needs of decision makers often within a larger application. Decision support systems evolved from database and management information systems.
Distributed computing A collection of independent computers that share data, programs, and other resources.
Domain A named subnetwork of the Internet defined by an institution or its components—for example, idsociety.org
Electronic health record An electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards and that can be created, managed, and consulted by authorized clinicians and staff, across more than one healthcare organization.
Electronic medical record An electronic record of health-related information on an individual that can be created, gathered, managed, and consulted by authorized clinicians and staff within one healthcare organization *(27)*.
Enterprise system A system that spans or is designated for use by an entire institution (usually reserved for larger institutions—e.g., a hospital or corporation).
EHR-Laboratory Interoperability and Connectivity Specification (ELINCS) A standard for defining laboratory and electronic clinical data promoted by the California Healthcare Foundation.
Ethernet A type of local area network originally developed by Xerox Corporation. Communication takes place by means of radio frequency signals carried by a coaxial cable. Most Ethernet systems today use the transport protocol called TCP/IP (see TCP/IP).
Expert system A program that symbolically encodes concepts derived from experts in a field and uses that knowledge to provide the kind of problem analysis and advice that the expert might provide. Specifically, a computer system designed to capture the skills and factual knowledge of one or more individuals. A program that uses a set of rules to construct a reasoning process that can reach conclusions and generate new data.
FAQ Frequently asked question. Documents that contain and answer the most asked questions on a particular subject. A popular heading on many Internet sites.
FTP File transfer protocol. The name of a program that transfers files from one computer to another on the Internet and on other TCP/IP networks (see Internet and TCP/IP).
Gateway A link between two or more computer networks.
GUI Graphical user interface. A way of communicating with the computer by manipulating icons (pictures) and windows with a mouse as opposed to a textual user interface (TUI), which requires typed commands.
Heuristic A rule of thumb; a cognitive process used in learning or problem solving.
Health information exchange (HIE) An organization or system for exchanging healthcare data across a region or set of cooperating institutions.
Health Information Technology for Economic and Clinical Health (HITECH) Act A component of the ARRA of 2009 promoting EHR/EMR adoption and meaningful use.
Health Level Seven (HL7) A standard format for defining clinical data for exchange that is frequently used by commercial applications.
HTML Hypertext markup language. The coding language used to create hypertext documents on the World Wide Web (WWW) (see WWW).
HTTP Hypertext transport protocol. A formal program for moving hypertext files across the Internet (see Internet).
Hypertext A formal way of creating documents so that information can be connected in many different ways rather than in a simple sequential manner as in books. Any text that links to other documents; words or phrases in a document that can be chosen and that cause another document to be retrieved and displayed.
Inference engine A computer program that embodies one or more general-purpose problem-solving algorithms that are largely independent of any specific domain. Inference engines draw conclusions by performing simple logical operations on knowledge bases and the information supplied by users.
Information Organized data or knowledge that provides a basis for decision making.
Information science The field of study concerned with issues related to the management of both paper-based and electronically stored information.

Integrated The state where two or more computer systems or applications have been closely tied together for both data and function sharing.
Interfaced The state where two or more computer systems or applications have direct links established to transfer data.
Internet An immense worldwide network of networks, connecting computers at universities, research labs, hospitals, offices and other commercial settings, private homes, and military sites.
IP Address A network address under the Internet protocol (IP) composed of four numbers (0–255) separated by periods that designates a unique location on the Internet.
Knowledge Relationships, facts, assumptions, heuristics, and models derived through the formal or informal analysis (interpretation) of data.
Knowledge base A collection of stored facts, heuristics, and models that can be used for problem solving.
Knowledge engineering The art of formalizing knowledge. Typically, the term is used in reference to building expert systems.
Laboratory information system (LIS) A computer-based information system that supports laboratory functions for collecting, verifying, and reporting test results.
Local area network (LAN) A network for data communication that connects multiple nodes, all typically owned by a single institution and located within a small geographic area. A system of network software and hardware components used to connect a group of end stations via wire or fiber optic cable. A single LAN segment connects from one to several hundred end stations, usually in the same building. A large organization may have a thousand or more LAN segments and tens of thousands of end stations.
Logical Observation Identifiers Names and Codes (LOINC) A nomenclature system for uniquely identifying laboratory and clinical observations for data exchange.
Mainframe computer A large computer designed to manage large amounts of data and complex computing tasks. A mainframe computer can be utilized by hundreds or even thousands of users. The term also describes the memory storage and computing part of a large computer system, as opposed to input or output devices, such as video monitors, keyboards, or printers.
Meaningful use A term coined with the release of the HITECH Act that encompasses the definition of information utilization for compliance with federal requirements for the use of electronic health information systems and Medicare/Medicaid claims payments.
Medical informatics A field of study concerned with the broad range of issues in the management and use of biomedical information, including medical computing and the study of the nature of medical information.
National Council on Prescription Drug Programs (NCPDP) A national standards organization and their protocols for representing pharmacy and medication data.
Network A set of computers that are connected together using standard communications protocols. A collection of hardware, such as printers, modems, servers, and clients, that enables users to store and retrieve information, share devices, and exchange information (see Local area network and Wide area network).
Nursing information system (NIS) A computer-based information system that supports nurses' professional duties in clinical practice, nursing administration, nursing research, and education.
Open architecture An approach to computing systems that assumes heterogeneous mixture of applications and host computers, systems, and databases, which are minimally interfaced with one another by means of de facto conventions and standards.
Open server A network server that can accommodate multiple operating systems and myriad software products. In addition, an open server can be used in numerous hardware configurations, because it is not dependent on proprietary standards.
Picture archiving and communications system (PACS) An enterprise system for storing, managing, and sharing radiology and other clinical images across a network.
Patient monitor An instrument that collects and displays physiologic data, often for the purpose of watching for and warning against life-threatening changes in physiologic state.
Patient monitoring Repeated or continuous measurement of physiologic parameters for the purpose of guiding therapeutic management.
Personal health record An electronic record of health-related information on an individual that conforms to nationally recognized interoperability standards and that can be drawn from multiple sources while being managed, shared, and controlled by the individual.
Pharmacy information system (PIS) A computer-based information system that supports the medication verification and delivery workflows that take place inside the pharmacy.
RAID Redundant array of inexpensive disks. A method of storing data on multiple hard disk drives for faster access and/or greater reliability. Currently, there are six officially defined levels, each designed for a specific kind of application.
Regional Health Information Organization A health information organization that brings together healthcare stakeholders within a defined geographic area and governs HIE among them for the purpose of improving health and care in that community.
Remote Installation Services (RIS) A system for installing or updating software on remote systems for a given institution or network. This allows centralized administration of remote systems.
Server A computer that provides services to another computer (called the client). On multitasking machines, a process that provides services to another process (see Client).
Service-oriented architecture A methodology/set of design principles for loosely coupling services from various sources into an integrated architecture.
Short message service (SMS) A standard for exchange of short text messages between telecommunications devices such as mobile phones.
Systematized Nomenclature of Medicine—Clinical Terminology (SNOMED CT) A systematic computer-interpretable medical vocabulary defining diseases, diagnoses, and other medical terms.
Standards The creation of common protocols for communication between different computer systems including

electronic communication and data exchange. Examples include ASTM, HL7, ISO, and MEDEX.

Tablet PC A personal computer that has a pen-based or touch interface usually with an optionally available keyboard. Many models are also fully functional laptops.

TCP/IP Transmission control protocol/Internet protocol. A standard format for transmitting data in packets from one computer to another. It is used on the Internet and various other networks (see Internet).

Telnet A command on the Internet and other TCP/IP networks that allows one to use their computer as a terminal on another computer. The command allows a user to log in from one Internet site to another (see Internet and TCP/IP).

Terminal A computer that is dependent on a single host computer for its accessibility and capability.

Three-tier architecture A client/server architecture in which the screen presentation, database, and software programs run separately on the client, host computer, and one or more application servers, respectively. This division of labor allows information to be processed more quickly and facilitates distribution of data across wide area networks.

TUI Textual user interface. A way of communicating with a computer through typed commands. For example, DOS or Unix.

URL Uniform resource location. The standard method to give the address of a resource on the Internet that is part of the WWW (see Internet and WWW).

Vaporware Software promised by a vendor that never materializes (an exceedingly common occurrence).

Wide area network (WAN) A set of widely separated computers connected together. Long-distance telecommunication links and networks that connect local area networks and end stations.

Wireless LAN A local area network in which the computers communicate by radio signals. Also called WiFi.

Workstation A computer that is connected to a network of host and server computers and has enough local processing power to run local applications and to interface with the hosts and servers.

World Wide Web (WWW) A worldwide standard Internet protocol for sharing and interlinking documents and applications using hypertext transmission protocol (http) and other standards.

eXtensible Markup Language (XML) A standard language for defining and encoding structured data for transmission.

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SECTION IV
Epidemiology and Prevention of Healthcare-Associated Infections of Organ Systems

CHAPTER 17

Healthcare-Associated Infections Related to the Use of Intravascular Devices Inserted for Short-Term Vascular Access

Angela L. Hewlett and Mark E. Rupp

BACKGROUND AND CLINICAL SIGNIFICANCE

Short-term vascular catheters are vitally important medical devices that are ubiquitously used in acute care settings. Over 150 million intravascular devices are purchased yearly in the United States, including 7 million central venous catheters (CVCs). Unfortunately, despite recent significant reductions in the incidence of IV catheter–related infections (*1*,2), they continue to result in substantial morbidity and excess economic cost. Although most studies that account for severity of illness have not found central line–associated bloodstream infection (CLA-BSI) to be independently associated with mortality (*3*,*4*,5), they do extend hospitalization by approximately 1 week (5) and result in excess attributable cost that ranges from $7,288 to $29,156 per episode *(6)*. However, CLA-BSIs due to more virulent pathogens such as *Staphylococcus aureus* or *Candida albicans* are associated with greater morbidity and mortality than less virulent microbes such as *Staphylococcus epidermidis (7,8)*.

There is a growing recognition that many, if not most, CLA-BSIs are preventable through the use of existing technology and clinical practice techniques, and there is increasing pressure to eliminate preventable CLA-BSI. Many states now require public reporting of hospital-specific CLA-BSI rates *(9)*. The Centers for Medicaid and Medicare Services (CMS) no longer reimburses hospitals for excess costs associated with CLA-BSI *(10)* and the Department of Health and Human Services has recently targeted CLA-BSI for a 75% reduction within 5 years *(11)*. These efforts have focused unprecedented scrutiny on CLA-BSI rates and fueled additional efforts to develop products and clinical techniques to prevent CLA-BSI.

EPIDEMIOLOGY

The National Healthcare Safety Network (NHSN) collects data on the incidence of healthcare-associated infections (HAIs) in the United States, including those related to the use of intravascular devices *(12)*. The NHSN data are expressed as the risk of a CLA-BSI per 1,000 CVC days. The CLA-BSI rates from data collected from 2006 to 2008 are presented in Table 17-1. The risk of infection varied according to the type of ICU or inpatient ward setting, as well as the birth weight of the infant in neonatal ICUs. Burn units were found to have the highest rate of infection (5.5 per 1,000 catheter days) and pediatric medical ICUs had the lowest rate of infection (1.3 per 1,000 catheter days) *(12)*. CLA-BSI rates are influenced by multiple factors including patient-related factors (severity and type of illness), catheter-related factors (catheter type and conditions under which the catheter was placed), and institutional factors including academic affiliation of the institution and bed size (13). It should be noted that the NHSN data may overestimate the true risk of CLA-BSI, because some bloodstream infections may be due to an unrecognized source

TABLE 17-1

National Healthcare Safety Network Central Line–Associated BSI Rates (2006–2008)

Location	*Pooled Mean*[a]
Critical Care Units	
Burn	5.5
Medical cardiac	2.0
Medical major teaching	2.6
Medical all others	1.9
Medical/surgical major teaching	2.1
Medical/surgical all others ≤15 beds	1.5
Medical/surgical all others >15 beds	1.5
Pediatric medical	1.3
Pediatric medical/surgical	3.0
Surgical	2.3
Surgical cardiothoracic	1.4
Inpatient Wards	
Medical	1.5
Medical/surgical	1.2
Pediatric medical	1.8
Pediatric medical/surgical	3.1
Rehabilitation	0.8
Surgical	1.4

[a]Per 1,000 catheter days.

of infection that is unrelated to the CVC (13,*14*). In spite of these issues the risk-adjusted rates reported by NHSN are utilized by various types of facilities for benchmarking.

The European Centre for Disease Prevention and Control (ECDC) reported data from 695 hospitals in 12 European countries in 2007, which included 4,718 episodes of ICU-acquired bloodstream infections. These data indicate that ICU-acquired bloodstream infections occurred on average in 3% of patients staying more than 2 days in these ICUs, with 56% of these infections being catheter associated *(15)*. The incidence of CLA-BSI in limited-resource countries has been investigated in a comprehensive review and is reported to range from 1.6 to 44.6 cases per 1,000 central line days in adult and pediatric ICUs *(16)*. The International Infection Control Consortium (INICC) reported a CLA-BSI rate of 7.6 per 1,000 CVC days in INICC ICUs *(17)*. These rates are higher than the rate reported by NHSN for the United States, which may be secondary to the lack of infection control resources in these developing countries. However, one study found the incidence of CLA-BSI in non-US and US hospitals to be similar in an international group of hospitals with similar infection control practices *(18)*.

The type of intravascular device inserted markedly contributes to the risk of catheter-related bloodstream infections. Peripheral venous catheters are rarely associated with bloodstream infections. However, peripheral venous catheters are by far the most commonly used intravascular device, so the burden of bloodstream infections due to peripheral venous catheters may be more substantial than is commonly appreciated (19). Phlebitis is the most common complication associated with peripheral venous catheters and may represent inflammation rather than infection, but when phlebitis is present, the risk of subsequent bloodstream infection may be increased *(20)*.

Studies show that midline catheters are associated with lower rates of infection than CVCs *(21)*. Peripherally inserted central venous catheters (PICCs) have traditionally been utilized to administer medications in the outpatient setting, and have been shown to have a low infection rate *(22)*. However, the use of PICCs is currently becoming more common in the inpatient setting. Infection rates in PICC lines inserted into high-risk hospitalized patients are associated with an infection rate similar to that of CVCs *(23)*.

CVCs account for the vast majority of catheter-related bloodstream infections, causing an estimated 90% of these infections *(20)*. Factors associated with increased risk of CLA-BSI include prolonged hospitalization, prolonged duration of catheterization, heavy microbial colonization at the insertion site or the catheter hub, internal jugular catheterization, neutropenia, prematurity, total parental nutrition, and substantial care (excessive manipulation) of the catheter *(24)*. An increased risk of CLA-BSI has been observed with catheters with multiple lumens in observational studies, but a randomized trial did not observe a difference in infection risk between single lumen and triple lumen catheters *(25)*.

The risk associated with site selection for CVC insertion has received particular attention in the medical literature. It has been suggested that the subclavian site is the preferred site of insertion in order to minimize the CVC infection risk, and femoral catheterization has been shown to be an independent risk factor for CLA-BSI *(14)*. However, data on the optimal insertion site are conflicting, with some studies demonstrating a higher incidence of CLA-BSI when the femoral site is used, while others showing a higher incidence of CLA-BSI when the jugular site is used (*26,27,28*,29). One study showed that infection rates did not differ according to insertion site when experienced operators inserted the catheters, strict sterile technique was utilized, and trained ICU nursing staff performed catheter care *(30)*. Another study involving patients requiring short-term dialysis vascular access demonstrated that the jugular site may be preferred over the femoral site in patients with a high body mass index *(31)*. In contrast, several studies have demonstrated that the femoral site may be preferred in certain patients, especially those with tracheostomy *(32–34)*. Pediatric studies have shown that placement of catheters at the femoral site in children have a low incidence of mechanical complications and that infection rates are equivalent to that of catheters placed at other sites *(35–37)*. Careful consideration of the risks and benefits of placing a CVC at the recommended site should be weighed against the risks of mechanical complications, the experience of the person inserting the catheter, and patient-specific factors like the presence of open wounds, obesity, or anatomic deformity (13).

PATHOGENESIS

A comprehensive discussion of the pathogenesis of CLA-BSI is beyond the scope of this chapter and interested readers are directed to recent reviews *(38,39)*. Briefly, the pathogenesis of intravascular catheter infections includes

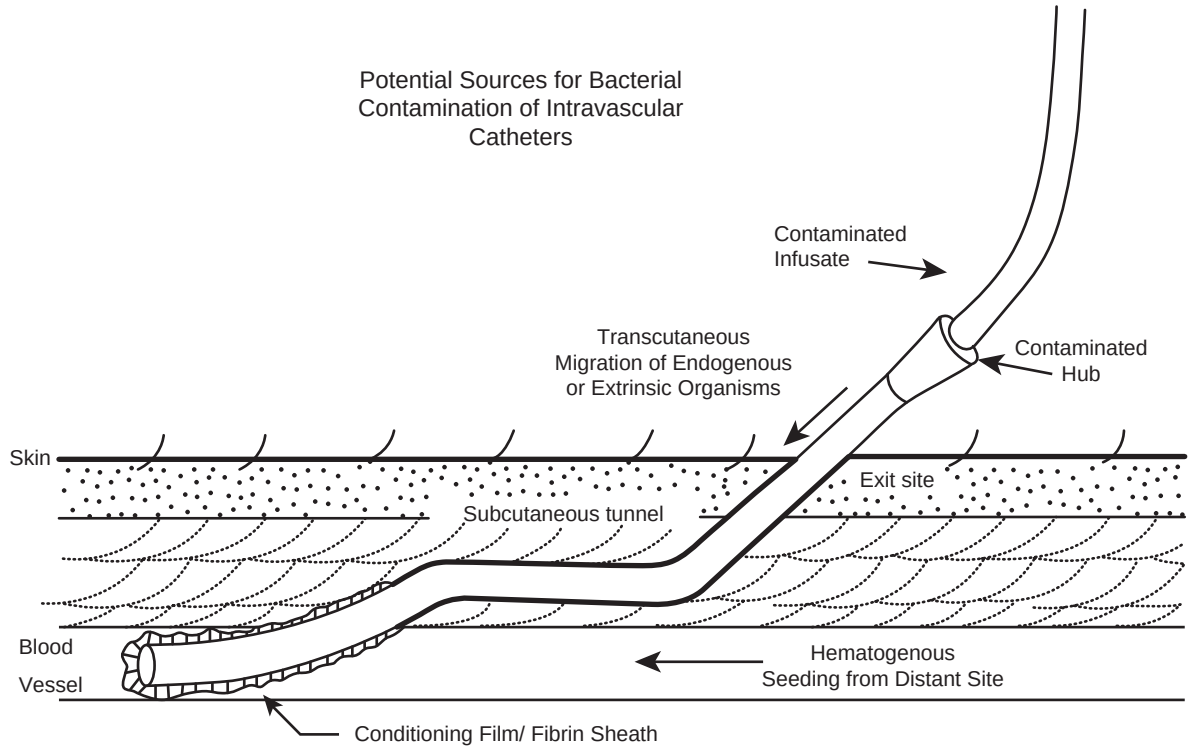

FIGURE 17-1 Pathogenesis of intravascular catheter–related infection. Routes by which microbes gain access to the intravascular catheter and initiate an infection are illustrated. Short-term catheters are most frequently colonized via the transcutaneous route, while longer-term catheters become infected via hub contamination. (From Rupp ME, Infections of intravascular catheters. In: Crossley KB, Archer GL, eds. *The Staphylococci in human disease*. New York, NY: Churchill Livingstone, 1997:381, © Elsevier [1997]).

complex interactions between the microbe, the catheter and what is infused through the catheter, and the host. Microbial factors include the presence of various polysaccharide and proteinaceous adhesions, and the ability to proliferate and elaborate biofilm. Catheter variables involve biomaterial composition, device design, and surface coatings. Host factors include such items as underlying illness, condition of the skin, local commensal flora, and site of catheter insertion.

Figure 17-1 illustrates the routes by which microbes gain access to the catheter. For short-term, nontunneled, CVCs, it appears that most infections are caused by microorganisms from the patient's skin that track via the external surface of the catheter *(40)*. The longer a catheter remains in place, the more likely it is that a break in aseptic practices takes place and microbes gain access to the hub of the catheter and migrate via the luminal surface *(41,42)*. Rarely do catheters become infected via hematogenous seeding or via infusion of intrinsically contaminated infusate *(43)*. Once the microbes gain access to the catheter, they interact with the conditioning film that is comprised of host plasma proteins and blood cellular elements that quickly coat the catheter surface after insertion, and they adhere, proliferate, and elaborate biofilm *(44)*. Figure 17-2 illustrates the appearance of a 1-day old, experimentally induced *S. epidermidis* biofilm-associated catheter infection. Physical and nutritional conditions differ from one portion of the biofilm to another and various populations of microbes are found, including rapidly growing cells at the macrocolony–blood interface as well as metabolically quiescent, antibiotic-resistant, persister cells in deeper portions of the biofilm *(45)*. Because of associated cost and morbidity and because successful treatment of biofilm-associated catheter infections often requires removal of the catheter, it behooves us to apply stringent measures to prevent these infections in the first place.

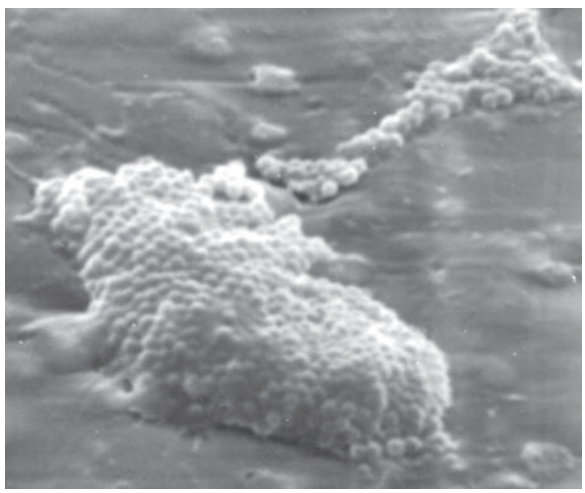

FIGURE 17-2 Intravascular catheter–associated infection. Scanning electron micrograph of the surface of an intravascular catheter demonstrating a *S. epidermidis* biofilm 24 hours after the catheter was experimentally infected *in vitro*. (Reproduced from Rogers KL, Fey PD, Rupp ME. Epidemiology of coagulase-negative staphylococci and infections caused by these microorganisms. In: Crossley KB, Jefferson KK, Archer GL, Fowler VG Jr, eds. *Staphylococci in human disease*. 2nd ed. Oxford, UK: Wiley-Blackwell, 2009:313, with permission).

MICROBIOLOGY

The 2008 NHSN Annual Update report contains data on pathogens associated with HAIs and the associated antimicrobial resistance patterns reported between January 2006 and October 2007 *(46)*. Overall 463 hospitals reported one or more HAIs, resulting in a total of 28,502 HAIs including 10,064 (35.3%) cases of CLA-BSI.

According to the NHSN data, gram-positive cocci remain the most common cause of CLA-BSI. Coagulase-negative staphylococci are the most frequent causative microorganism in both adult and pediatric patients, causing 34.1% of the cases of CLA-BSI in the hospital setting *(46–48)*. Other pathogens that cause CLA-BSI include *Enterococcus* sp. (16%), *Candida* sp. (11.8%), and *S. aureus* (9.9%). Gram-negative bacilli like *Klebsiella* sp., *Escherichia coli*, *Enterobacter* sp., *Pseudomonas* sp., and *Acinetobacter* sp. account for 17.7% of CLA-BSI according to NHSN data.

Antimicrobial resistant microorganisms are commonly implicated in CLA-BSI infections. Data from NHSN indicate that 56.8% of *S. aureus* isolates are resistant to oxacillin (MRSA), and 36.4% of Enterococci are vancomycin resistant (VRE). Resistance amongst gram-negative microorganisms is also emerging, with 27.1% of *Klebsiella pneumoniae* isolates demonstrating resistance to third generation cephalosporins, and 23% of *Pseudomonas aeruginosa* isolates demonstrating resistance to carbapenems such as imipenem and meropenem.

CLINICAL MANIFESTATIONS

Signs and symptoms related to intravascular device infections vary depending on whether the infection is localized or systemic. Local catheter infections include those at the exit site, tunnel infections, and phlebitis. Exit site infections commonly manifest with evidence of localized inflammation including erythema, warmth, tenderness, and purulent discharge. An infected CVC tunnel may demonstrate similar inflammatory signs extending along the tunneled portion of a tunneled catheter. Phlebitis is inflammation of the veins associated with a catheter. It typically involves peripheral catheters, and often presents with signs of local inflammation. Phlebitis may represent a localized infection or a chemical irritation of the vein due to the catheter material or drugs administered. Localized infections may lead to a systemic catheter infection, but are not a reliable predictor of such infections *(49)*.

Systemic catheter infections typically present with signs of systemic infection, including fever, chills, and hemodynamic instability. Other signs may include altered mental status, catheter dysfunction, and complications of bloodstream infections such as endocarditis.

DIAGNOSIS

Initial diagnosis of catheter-related bloodstream infection involves examining the catheter site for local signs of infection and obtaining blood cultures. Since the symptoms and signs of CLA-BSI are nonspecific, microbiologic evidence is necessary to establish that the catheter is the source of the infection. Diagnostic methods to identify CLA-BSI can be divided into methods that require removal of the catheter and methods that do not necessitate removal of the catheter *(50)*.

One diagnostic technique that does not require removal of the catheter involves obtaining paired blood cultures (one from the catheter and one through a peripheral vein) prior to initiation of antimicrobial therapy (*50*,51). When possible, these cultures should be drawn by a phlebotomy team *(52)*. A definitive diagnosis of CLA-BSI can be made if the blood culture drawn through the catheter yields a colony count that is at least threefold greater than that of the culture obtained from the peripheral vein (51,*53*,*54*). If a peripheral blood culture is not possible, two quantitative blood cultures obtained through two catheter lumens in which the colony count for the blood sample drawn through one lumen is at least threefold greater than the colony count for the blood sample obtained from the second lumen is suggestive of CLA-BSI (51). One study demonstrated that obtaining blood samples from all catheter lumens may help to establish a diagnosis of CLA-BSI *(55)*. However, this has not been clearly documented in the literature, and the possible advantages must be weighed against the additional time required, expense, and possibility of contributing to healthcare-associated anemia. If there is purulent material present at the catheter exit site, this should also be sent for Gram stain and culture *(56)*.

Differential time to positivity (DTP) is a method that involves obtaining blood cultures from the catheter and a peripheral vein simultaneously, and comparing the amount of time it takes for the cultures to become positive. Blood cultures should be obtained prior to initiation of antibiotic therapy when DTP is used. CLA-BSI can be diagnosed definitively when the blood culture obtained through the catheter becomes positive at least 2 hours earlier than the culture obtained through the peripheral vein (*57*,*58*,59).

When the catheter is removed for suspected CLA-BSI, catheter tip cultures should be performed. However, catheter tip cultures should not be performed routinely if CLA-BSI is not suspected *(60)*. In order to satisfy the definition of CLA-BSI the same microorganism must be isolated from one percutaneous blood culture and from a culture of the catheter tip (51). If the catheter is a pulmonary artery (PA) catheter, the introducer tip should be cultured *(27)*. If a subcutaneous port is removed for suspected CLA-BSI, the catheter tip and the port reservoir should be cultured *(61)*. Growth of >15 colony-forming units (CFU) from a 5-cm segment of the catheter tip by semiquantitative (roll-plate) culture or growth of $>10^2$ CFU from a catheter by quantitative (sonication) broth culture reflects significant catheter colonization (51,*60*,*62*,63).

PREVENTION

Efforts to prevent infections due to short-term intravascular catheters can be broadly divided into two categories: (a) clinical practice measures associated with insertion and care of catheters and (b) technologic innovations. Guidelines for prevention of intravascular catheter-related infections were recently updated (13) and key recommendations are summarized in Tables 17-2 and 17-3. Table 17-2 summarizes clinical practice measures that are broadly recommended in almost all clinical settings. Table 17-3

TABLE 17-2

Summary of Recommended Clinical Practices for Prevention of Short-Term Intravascular Catheter–Related Infection

1. *Education, Training, and Staffing*
   - Healthcare workers who insert and maintain intravascular catheters should be adequately trained and their knowledge should be periodically assessed regarding the indications for catheter use and proper insertion and care procedures (*81*,*82*,83).
   - Appropriate nursing staffing levels should be maintained in the ICU *(84,85)*.
2. *Catheter Type and Site Selection*
   - Catheters and site of insertion should be selected based on the intended purpose, duration of use, potential complications, and patient specific factors.
   - In general, the femoral vein should be avoided for central venous access, particularly in obese patients *(27,31)*.
3. *Insertion Technique*
   - Perform hand hygiene at appropriate time points (before and after palpating insertion site; before and after inserting, accessing, or dressing an intravascular catheter) *(86)*.
   - Use maximal sterile barrier precautions, including a cap, mask, sterile long-sleeve gown, sterile gloves, and a head-to-toe sterile body drape (87).
   - Prepare the skin with a ≥0.5% concentration chlorhexidine-based preparation before CVC insertion and with catheter dressing changes (88).
   - Do not administer systemic antimicrobial prophylaxis before insertion or during use of an intravascular catheter to prevent catheter infection *(89)*.
4. *Site Care*
   - Use sterile gauze or a sterile, transparent, and semipermeable dressing to cover the catheter site; monitor catheter sites regularly, and change the dressing if it becomes damp, loosened, or visibly soiled *(90,91)*.
   - Do not submerge the catheter or catheter site in water. Showering is permitted if the catheter and catheter connector device can be protected with an impermeable cover *(92)*.
5. *Replacement of CVCs and Administration Sets*
   - Promptly remove an intravascular catheter that is no longer required for patient care (2).
   - Do not routinely replace CVCs or routinely change catheters using guidewire exchanges to prevent infection (*79*,93).
   - Replace continuously used administration sets between 4 and 7 d *(94–96)*.
   - Replace tubing used to administer blood, blood products, or fat emulsions within 24 h of initiating the infusion and replace tubing used to administer propofol infusions every 6–12 h *(97)*.
6. *Needleless Intravascular Catheter Systems*
   - Access ports should be adequately disinfected with an appropriate disinfectant (70% alcohol, chlorhexidine, iodophore, povidone-iodine) that is applied correctly.
   - Needleless, mechanical connector valves should be used with caution as some particular valves or types of valves may be associated with an increased risk of infection *(98,99)*.

covers technologic innovations and devices designed to minimize the incidence of CLA-BSI that should be considered in conjunction with clinical practice. Most authorities believe that it is important to first emphasize clinical practice measures and then introduce technologic innovations if clinical practice measures are not successful in minimizing the incidence of CLA-BSI. New devices and other technologic approaches may be particularly useful in populations that are at high risk of CLA-BSI (e.g., persons receiving long-term parenteral nutrition, burn patients). Comparative effectiveness research to establish which device or technique is most cost effective is particularly needed in this clinical area.

IMPLEMENTATION OF PREVENTIVE AND PERFORMANCE MEASURES

Unfortunately, despite the presence of a good foundation of knowledge in the epidemiology and pathogenesis of intravascular catheter infections and the presence of evidence-based measures to prevent infection, widespread implementation of well-supported preventative measures has been suboptimal *(64,65)*. Recently, substantial success has been observed in prevention of CLA-BSI through a combination of specific insertion and maintenance procedures into a "prevention bundle" (2,*66,67*). In addition, through use of an insertion compliance checklist and ongoing surveillance and reporting, the gains in these programs have been sustainable *(68)*. Compliance with the insertion bundle can be optimized by conveniently providing all necessary equipment in an all-inclusive catheter insertion kit or on an easily accessible cart *(66)* and bedside personnel should be empowered to stop a nonemergent procedure if breaks in aseptic technique are observed.

Oftentimes, CVCs are inserted in the operating room, interventional radiology suite, emergency department, or general patient care ward, and efforts to ensure appropriate insertion and care of CVCs should be performed in all of these settings. In many acute care hospitals and long-term acute care hospitals, 25% to 30% of patients have CVCs *(69)* and therefore it is important to perform surveillance outside the ICU setting. In order to accurately measure institutional performance, standardized definitions of infection should

TABLE 17-3

Summary of Technologic Innovations Recommended to Minimize the Risk of Short-Term CVC-Associated infection

1. *Coated/Impregnated CVCs*
   - Use a chlorhexidine/silver sulfadiazine or minocycline/rifampin-impregnated CVC if the CVC is expected to remain in place at least for 5 d (*100*,*101*,102,*103*).
2. *Dressings*
   - Use a chlorhexidine-impregnated sponge dressing for patients >2 mo of age (*104*,105).
3. *Patient Bathing*
   - Use 2% chlorhexidine-impregnated washcloths or a 2% chlorhexidine solution to bathe patients on a daily basis (106,*107*).
4. *Prophylactic Antimicrobial Lock Solution*
   - A variety of antibiotic and antiseptic solutions can be utilized to flush or lock catheter lumens to prevent CLA-BSI. This technique has primarily been utilized on long-term catheters in patients with a history of recurrent CLA-BSI. The lock solution should not interact with the catheter material *(108–110)*.
5. *Antibiotic/Antiseptic Ointments*
   - Povidone iodine, bacitracin/neomycin/polymyxin B, or mupirocin ointment can be applied at the catheter insertion site to prevent central line–associated bloodstream infection *(111,112)*. This technique has primarily been used on long-term hemodialysis catheters. If this technique is used, the ointment should not interact with the catheter material. Concern regarding catheter material interactions, selection for fungal pathogens, and development of antimicrobial resistance has discouraged wider use of this technique.
6. *Other Promising Technologic Innovations that are in Development or do not Currently have Sufficient Clinical Data to Support a Recommendation*.
   A. Coated catheters:
      - Silver/platinum/carbon (silver iontophoretic) *(103)*
      - Rifampin-miconazole *(103)*
      - Active iontophoresis *(113)*
      - Numerous surface modifications and coatings in laboratory investigation

   B. Dressings and catheter securement devices
      - Chlorhexidine-impregnated gel pad dressing *(114)*
      - Silver-impregnated dressing
      - Sutureless catheter securement device

   C. Caps/connectors
      - Silver-impregnated mechanical connector valve *(115)*
      - Antiseptic barrier cap/hub

be utilized *(70)* and unit-specific infection rates should be expressed as CLA-BSI per 1,000 catheter days. Benchmark rates can be used to measure relative performance *(1,12)*. In addition to outcomes measures, process measures such as compliance with CVC insertion guidelines, checklist completion, documentation of daily catheter assessment, compliance with site care recommendations, and compliance with catheter access procedures should be monitored *(24)*. Up-to-date process and outcomes measures should be reported frequently to both senior hospital leadership as well as bedside clinicians *(24)*.

Pulmonary Artery Catheters

PA catheters are complex intravascular devices that are utilized for hemodynamic monitoring of critically ill patients. A meta-analysis demonstrated a higher rate of catheter-related bloodstream infection with PA catheters (3.7 per 1,000 catheter days) when compared with unmedicated, nontunneled CVCs (2.7 per 1,000 catheter days) (19). One prospective study of 297 Swan–Ganz PA catheters found a high incidence of local catheter-related infection (21.8%) but a low incidence of catheter-related bacteremia (0.7%) *(27)*. Another study of 164 PA catheters in cardiac surgery patients demonstrated an 11.6% incidence of PA catheter colonization and a 0.6% incidence of catheter-related bacteremia *(71)*. The risk of PA catheter-related infection increases with the duration of catheterization, cutaneous colonization of the insertion site, insertion into the internal jugular vein, and insertion in the operating room with less stringent barrier precautions *(27,61,72)*.

Arterial Catheters

Arterial catheters, most frequently inserted in the radial or femoral artery, are frequently used in critical care settings in order to monitor blood pressure and obtain arterial blood for blood gas determinations. Compared to CVCs, there are few data examining the risk of infections associated with arterial catheters and, traditionally, arterial catheters have been regarded as low-risk devices. However, more recently, there is growing recognition that arterial catheters pose a substantial risk for infection (19,*73,74*). In a review of 14 studies of arterial catheters, Maki et al. (19) noted a mean rate of arterial catheter-related bloodstream infection of 1.7 per 1,000 catheter days (95% CI 1.2–2.3). When the femoral site is utilized for arterial catheterization,

catheters are more likely to become colonized and there is a greater risk of bacteremia due to gram-negative bacilli than when the radial site is used *(75)*. However, a meta-analysis did not note a significant difference in the rate of bloodstream infection when comparing catheterization at the femoral, radial, and axillary sites *(76)*. Other factors that have been implicated as increasing the risk of infection include the duration of catheterization and utilization of a cut-down method for catheter placement.

The use of full sterile barrier precautions has not been shown to decrease the risk of arterial catheter related BSI *(77,78)*. Similar to CVCs, most evidence does not favor routinely changing arterial catheters to prevent infection *(79,80)*. In order to prevent arterial catheter–associated infections, the following measures should be followed (13):

- Avoid the femoral artery site for catheter insertion.
- Barrier precautions consisting of a minimum of a cap, mask, sterile gloves, and small sterile fenestrated drape should be utilized.
- Do not routinely replace arterial catheters to prevent infection and remove arterial catheters as soon as they are not needed.
- Use disposable transducer assemblies and replace them at 96-hour intervals.
- Minimize manipulation of the catheter and pressure working system and keep all components of the system sterile.

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CHAPTER 18

Healthcare-Associated Infections Related to Use of Intravascular Devices Inserted for Long-Term Vascular Access

Anne-Marie Chaftari and Issam Raad

Long-term intravascular devices (IVDs) have become indispensable in the modern medical care of chronically ill patients such as cancer patients, patients with renal failure requiring chronic hemodialysis, or patients requiring organ or bone marrow transplantation. In the 1960s and 1970s, treatment of cancer patients through a small peripheral venous catheter was often complicated by extravasation of vesicant chemotherapeutic agents and thrombosis of peripheral veins, which limited the use of parenteral anticancer chemotherapy. Long-term silicone central venous catheters (CVCs) allowed the extended, safe use of anticancer chemotherapeutic agents as well as the potential for appropriate use of total parenteral nutrition (TPN) fluids, blood products, and other intravenous therapeutic agents. For patients with short bowel syndrome, long-term CVCs have become the only source for nutritional support through TPN. Similarly, patients requiring hemodialysis who have had prior failure of arteriovenous fistulas or shunts become totally dependent on intravascular catheter–related access for their hemodialysis. In all of these clinical situations, the long-term CVC becomes an essential device for the maintenance of life.

There is no standard agreed-upon definition for long-term catheters in terms of the duration of catheterization. Sherertz defined long-term catheters as those with a duration of placement of an average of >8 days. Rather than using an average duration, we have defined this term in a previous study to signify catheters that remain in place for >30 days. We also defined short-term catheterization by duration of placement of <10 days, and intermediate catheterization by duration of placement ranging between 10 and 30 days *(1)*.

Long-term IVDs can be categorized into one of three groups: (a) nontunneled long-term CVCs (such as peripherally inserted central catheters [PICCs] or subclavian CVCs such as Hohn catheters); (b) cuffed and tunneled catheters (such as Hickman/Broviac, Groshong, and tunneled Uldall catheters); and (c) implanted subcutaneous central venous ports.

NONTUNNELED CATHETERS

Traditionally, it was assumed that the only method of maintaining long-term intravascular access in chronically ill patients was through surgically implantable CVCs such as the tunneled catheters and implantable ports. Over the last decades, nontunneled long-term silicone CVCs (particularly PICCs) have become more accepted as a cost-effective form of intravascular access. In addition, these catheters could be maintained for a long period, up to 400 days, without complications (2). Nontunneled long-term catheters consist of two types: long-term nontunneled subclavian catheters and PICC lines. Nontunneled subclavian catheters are inserted percutaneously via the subclavian vein into the superior vena cava, in the outpatient nonsurgical setting. The advantage of these catheters is that they are associated with low cost, because their insertion does not require the use of an operating room or a special surgical technique *(3)*. In addition, these catheters can be exchanged over a guidewire, and the removed intravascular segment may be cultured if a catheter infection is suspected or if a new catheter needs to be inserted. These catheters are available as single-, double-, or triple-lumen cannulas.

The PICC lines are becoming widely used, particularly for outpatient long-term central venous therapy, such as patients requiring intravenous home antibiotics for osteomyelitis or endocarditis, cancer patients, or patients requiring TPN delivery. These catheters are usually inserted in the antecubital space, via the cephalic or basilic vein, and advanced into the central venous system. These catheters are very cost-effective, because they can be inserted in the outpatient clinic by a trained infusion therapy nurse and do not require a physician for their insertion. These catheters can be maintained for an average of 3 months and are associated with a low infection rate and cost (2). However, their main disadvantage is a high rate of aseptic thrombophlebitis related to mechanical contact *(4)*. Traditionally, many of these catheters were made of silicone, although

over the last decade, most PICCs are power injectable made of polyurethane and hence allow the use of contrast material for diagnostic imaging.

TUNNELED CATHETERS

In 1973, Broviac et al. (5) described the first surgically implanted tunneled catheter to be used in pediatric patients requiring long-term TPN. Later, Hickman et al. (6) described another long-term tunneled catheter for cancer patients requiring bone marrow transplantation. These catheters are usually tunneled under the skin for several inches until they reach the cannulated vein. Tunneled catheters have a Dacron cuff that is located in the proximal subcutaneous segment 5 cm from the exit insertion site. After insertion, the Dacron cuff becomes enmeshed with fibrous tissue, hence anchoring the catheter and creating a tissue interface mechanical barrier against the migration of skin microorganisms along the external intracutaneous pathway. Tunneled catheters usually exit the body midway between the nipple and the sternum. Another vascular access catheter is the Groshong, which, unlike the Hickman/Broviac, is thin walled and has two slit valves adjacent to a rounded closed end that remains closed unless fluids are being infused or blood is being drawn. This decreases the risk of intraluminal blood clotting or infusion of air when the catheter is not in use. Hence, this type of catheter does not require daily heparin flushes, but rather is flushed with saline on a weekly basis.

IMPLANTABLE PORTS

To eliminate the migration of skin microorganisms from the skin insertion site in externalized catheters along the intracutaneous pathway, the surgically implanted subcutaneous central venous ports were developed where the whole catheter, including the metallic port, is placed beneath the skin *(7)*. Hence, implantable ports consist of a metal/titanium or plastic port placed beneath the skin and connected to a catheter that enters the cannulated vein. Ports are usually placed in a subcutaneous pocket on the upper chest or, less often, in the antecubital area of the arm (peripheral port). Ports are available as single- or double-lumen catheters with or without Groshong valves and can be accessed as needed with a steel needle.

EPIDEMIOLOGY

The bloodstream infection (BSI) rates associated with long-term CVCs should be reported using catheter-days as the denominator. The Centers for Disease Control and Prevention (CDC) recommends that rates of central line-associated bloodstream infections (CLABSI) be expressed per 1,000 device-days. This recommendation takes into consideration the varying risks of CLABSI over time for the different types of CVCs. According to Crnich and Maki (8), although the rates of CLABSI per 100 CVCs used are usually higher for long-term devices, the risk per 1,000 catheter-days is usually considerably lower than that for short-term CVCs. Previous studies showed that the average infection rate for long-term CVCs in cancer patients ranged from 1 to 1.5 episodes per 1,000 catheter-days (*9,10*,11,*12*). Assuming this rate and the fact that three million long-term CVCs are inserted annually in the United States (with an average dwell time of 100 days), the estimated annual number of episodes of catheter-associated bacteremia that occur in the United States related to the use of these catheters in cancer patients is between 300,000 and 450,000.

Several studies have compared the efficacy of tunneled catheters (such as Hickman/Broviac catheters) with implantable ports. Mueller et al. *(13)*, in a prospective, randomized study, compared the complications of the two types of long-term catheters and found no significant difference in infection rates between the two types of devices. Similarly, Keung et al. *(14)* conducted a retrospective study of infectious complications in 111 long-term CVCs. Multivariable analysis revealed no significant difference in infection rates between tunneled catheters and implantable ports. On the other hand, there are several studies that suggest that ports may be associated with lower infection rates. Mirro et al. *(15)* evaluated 266 tunneled catheters and 93 implantable ports in children with cancer, and showed that, when all causes of failure were analyzed including infectious complications, ports had a significantly longer duration of use than tunneled catheters. In a prospective observational study conducted at Memorial Sloan-Kettering on 1,630 long-term CVCs (923 tunneled catheters and 707 ports), Groeger et al. *(16)* found that the incidence of infection per device per day was 12 times greater with the tunneled catheter than with ports. Therefore, these data might suggest that ports are associated with a lower infection rate than tunneled catheters, even though they are not conclusive. In addition, the data should be analyzed with caution because there could be confounding variables, such as the various uses of the catheters (including the use of TPN), duration of neutropenia, and thrombotic complications that were not taken into consideration.

There are very few data in the literature comparing tunneled with nontunneled long-term CVCs in terms of infection rates. In a prospective randomized study, Andrivet et al. *(17)* showed that the infection rate associated with nontunneled subclavian silicone CVCs was not different from that related to tunneled silicone catheters. However, the lack of a difference could be related to the small sample size. In a prospective study evaluating nontunneled long-term CVCs at the M. D. Anderson Cancer Center, we determined that the infection rate for PICC lines and nontunneled subclavian CVCs was 1.4 per 1,000 catheter-days, which was comparable to what was described for Hickman catheters in the literature (2). At the M. D. Anderson Cancer Center, the cost of insertion of nontunneled catheters, including the chest x-ray postinsertion and other related fees, is in the range of $1,190 to $1,326 as compared with more than $6,502 for the Hickman tunneled CVC. The cost of placing an implantable port at our institution is about $7,076. Given the comparable durability of all long-term catheters, the potential marginal difference in infection rates might not justify the wide difference in cost between the tunneled catheters and ports on the one hand and the nontunneled CVC (PICC lines and nontunneled subclavian catheters) on the other.

PATHOGENESIS

Microbial adherence and colonization of long-term catheters is the by-product of the interaction of several factors: (a) host-derived proteins, (b) microbial factors, (c) catheter material, and (d) iatrogenic factors.

After insertion, a thrombin sheath covers the internal and external surfaces of the catheter, which is rich in host proteins *(18,19)*. These proteins include fibronectin, fibrinogen, laminin, thrombospondin, and collagen *(20–24)*. *Staphylococcus aureus* binds strongly to fibronectin and fibrinogen, whereas coagulase-negative staphylococci (CNS) bind strongly to fibronectin *(20,21)*. In addition, *Candida albicans* has been shown to bind well to fibrin *(25)*.

Biofilm formation represents the microbial factor involved in the enhancement of adherence of microorganisms to catheter surfaces. Microorganisms, such as CNS, *S. aureus*, and even *Candida parapsilosis*, have the potential of undergoing intrinsic phenotypic changes that result in the expression of several enzymes that lead to the production of an exopolysaccharide, thus causing the biofilm to form *(26–31)*. Microorganisms embed themselves in this layer of biofilm (or microbial slime), and hence protect themselves from antimicrobial agents such as glycopeptides *(32)*. Other microbial factors, such as hydrophobicity and the surface charges of microorganisms, contribute to the adherence to catheter materials such as silicone *(33,34)*. Hydrophobic staphylococcal microorganisms adhere better to silicone surfaces of which most long-term catheters are made than to the polyurethane or Teflon surfaces of short-term catheters.

The material from which the catheters are made plays a role in the adherence of microorganisms to the catheter surface. The physical characteristics of the catheter surfaces, including hydrophobicity, surface charges, irregularities, and defects on the catheter surface and the thrombogenicity of the catheter surface, contribute to the process of microbial adherence *(3,35)*. Several investigators have shown, for example, that *Staphylococcus* and *Candida* species adhere better to polyvinyl chloride catheters than to Teflon catheters *(36,37)*. Sherertz et al. *(38)* have demonstrated in a rabbit model that silicone catheters are easier to infect with *S. aureus* than polyurethane, Teflon, or polyvinyl chloride catheters. This was also shown by Vaudaux et al. *(39)*, who demonstrated that indwelling silicone catheters, after being removed from patients, were more prone to *S. aureus* adherence than were polyurethane or polyvinyl chloride catheters. This was related to the fact that silicone catheters tend to have a direct toxic effect on neutrophils, alter neutrophil chemotaxis, and cause a localized depletion of complement *(40,41)*.

Iatrogenic factors associated with medical interventions in high-risk patients entail a higher risk of colonization of catheter surfaces. These consist of the use of TPN fluids and lipid emulsions, interleukin-2, and long-term hemodialysis *(3,35)*. TPN has been associated with higher rates of infection in tunneled catheters *(42)*. The 25% dextrose and the lipid emulsions have been associated with microbial growth, particularly *Candida* species and *Malassezia furfur* *(35)*. In addition, interleukin-2 has also been shown to predispose to catheter colonization and infection by staphylococcal microorganisms *(43,44)*. It is postulated that interleukin alters neutrophil chemotaxis toward staphylococcal microorganisms, and hence leads to a higher degree of colonization of catheter surfaces with these microbial agents. Finally, chronic hemodialysis patients have a high rate of nasal carriage of *S. aureus*, ranging from 30% to 65% *(45–47)*. Hemodialysis patients who are chronic carriers of *S. aureus* have a threefold higher risk of contracting catheter-related *S. aureus* BSI when compared with noncarriers *(48)*. The majority (more than 90%) of *S. aureus* infections in carriers are caused by the same type as that carried in the nares *(45)*.

The most common microorganisms causing catheter-associated infections in long-term CVCs are CNS, *S. aureus*, and yeasts (49). This is related to the fact that staphylococci are skin microorganisms. In addition, staphylococci and *Candida* adhere well to host proteins found on catheter surfaces and tend to form a microbial biofilm *(25–31)*. This is in contrast to gram-negative microorganisms, such as *Escherichia coli* and *Klebsiella pneumoniae*, that do not adhere well to fibronectin and fibrin and are not known to produce a biofilm. Other microorganisms that have been associated with long-term CVC infections are *Bacillus* species, *Corynebacterium* species, *Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, micrococcus, Achromobacter, rapidly growing mycobacteria, and various other fungal microorganisms such as *M. furfur* and *Fusarium oxysporum (50)*.

For long-term catheters, the lumen seems to be the major site of colonization and source of CLABSIs. This has been shown for catheters used for long-term hemodialysis and for CVCs used for TPN and cancer treatment *(51–53)*. Previous investigators highlighted the hub as the most common source for long-term catheter–related bloodstream infections (CR-BSIs) *(51,54)*. However, for short-term catheters with an average duration of <8 days, the skin seems to be the major source, followed by the hub/lumen *(55,56)*. The relative contribution of contaminated infusate, hematogenous seeding from a remote infected source, or extension from a contiguous site of infection seems to be low even in long-term catheters. Using semiquantitative scanning electron microscopy studies, we have determined that the extent of biofilm formation and colonization is greater on the external surface of short-term catheters (<10 days of catheterization) than the internal surface *(1)*. However, for catheters that remain in place for >30 days, this phenomenon is reversed with greater biofilm formation and ultrastructural colonization in the lumen of the catheter versus the external surface.

Electron microscopy studies have shown that colonization is universal *(1,57)*. It involves all CVCs within 24 hours of insertion *(57)*. However, although colonization is universal, only a few catheters are associated with infection. There is a quantitative relationship between the number of microorganisms (particularly free-floating microorganisms) on the catheter and the risk of BSIs. Sherertz et al. *(58)* studied 1,610 CVCs and found that the greater the number of microorganisms retrieved from the catheters by sonication, the greater the risk of BSI. Therefore, infection could be a function of whether the microorganisms on the catheter surface, particularly those that are free-floating, exceed a certain quantitative threshold due to various risk factors outlined above.

MANIFESTATIONS AND DEFINITIONS

The clinical manifestations of a CLABSI for long-term catheters consist of systemic manifestations such as fever and chills, which are nonspecific, particularly in the immunocompromised patient. Clinical evidence of a local infection at an exit site, tunnel, or port pocket would be necessary to suggest the catheter as the source of the BSI. However, for PICC lines, local catheter site inflammation consisting of erythema and phlebitis could be aseptic in nature and reflect a local mechanical irritation of the vein due to the insertion of a large catheter in the relatively small basilic or cephalic veins (2). Therefore, local catheter-related infection or systemic CLABSI should be defined in terms of clinical manifestations associated with microbiologic data implicating the catheter as the source of the infection (Tables 18-1 and 18-2). The following definitions were proposed in a recent guideline by the Infectious Diseases Society of America (IDSA) (59):

1. Local catheter infection: Local catheter infection could exist in different forms, depending on the type of catheter (nontunneled or tunneled implantable port). However, in the presence of positive results of a blood culture, it would be classified as CLABSI (59,60).
   a. Exit-site infection: erythema, tenderness, or induration within 2 cm of the catheter exit site, may be associated with other signs and symptoms of infection such as fever or purulent drainage emerging from the exit site.
   b. Pocket infection: purulent exudate in the subcutaneous pocket containing the reservoir of the port or erythema and necrosis of the skin over the reservoir of a totally implantable device.
   c. Tunnel infection: erythema, tenderness, and induration in the tissues overlying the catheter and >2 cm from the exit site.
2. Systemic catheter infection: BSI could either be
   a. Infusate-related: with the concordant growth of a microorganism from infusate and from percutaneously obtained blood cultures with no other identifiable source of infection.
   b. Central line–related:
      i. Bacteremia or fungemia in a patient who has an IVD and >1 positive blood culture result obtained from the peripheral vein, clinical manifestations of infection (e.g., fever, chills, and/or hypotension), and no apparent source for BSI (with the exception of the catheter).
      ii. For the definitive diagnosis of CLABSI or CR-BSI as defined by the IDSA (59), one of the following should be present:
         1. the isolation of the same microorganisms (species) from a semiquantitative (>15 colony-forming units (CFU)/catheter segment) or quantitative (>102 CFU/catheter segment) catheter tip culture and from at least one percutaneous blood culture
         2. simultaneous quantitative cultures of blood drawn, one from a catheter hub and the other from a peripheral vein with a ratio of >3:1 CFU/mL (catheter vs. peripheral blood)
         3. differential time to positivity (DTP) of 2 hours (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 hours earlier than a culture of simultaneously drawn peripheral blood of equal volume).

TABLE 18-1

Definitions of Colonization, Phlebitis, and Local Central Line–Associated Infections

Type of Central Line–Related Infection	*Definitions*
Catheter colonization	Significant growth of one microorganism by quantitative or semiquantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub, in the absence of simultaneous clinical symptoms
Phlebitis	Induration or erythema, warmth, and pain or tenderness along the tract of a catheterized or recently catheterized vein
Exit-site infection	Purulent drainage from the catheter exit site, or erythema, tenderness, and induration within 2 cm of the catheter exit site
Tunnel infection	Erythema, tenderness, and induration of the tissues overlying the catheter and more than 2 cm from the exit site
Pocket infection	Purulent exudate in the subcutaneous pocket containing the device or erythema, tenderness, induration, and necrosis of the skin over the pocket

However, quantitative blood cultures are not widely available for a definite diagnosis of CR-BSI. According to the CDC, a CLABSI can be diagnosed in a patient who has a central line that was in place at the time of, or within 48 hours before, onset of bacteremia in the presence of any one of the following:

a. A recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site.
b. A common skin contaminant cultured from two or more blood cultures drawn on separate occasions within two days of each other and at least one of the following clinical signs or symptoms: fever (>38°C), chills, or hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site.

Most CR-BSIs are uncomplicated. However, with virulent microorganisms such as *S. aureus*, *C. albicans*, and *P. aeruginosa*, deep-seated infections can occur, particularly catheter-related septic thrombosis, which consists of

TABLE 18-2

Diagnosis of Intravascular Catheter–Related Bloodstream Infection[a]

IDSA 2009 Definition of Intravascular Catheter–Related Bloodstream Infection (CR-BSI)	*CDC Definition of Central Line–Associated Bloodstream Infections (CLABSI)[b]*
A. A definite CR-BSI diagnostic method sparing the catheter requires one of the following to be present: 1. The same organism is cultured from two quantitative blood cultures samples drawn, one from a catheter hub and the other from a peripheral vein with a 3:1 ratio (the catheter hub is at least threefold greater than the colony count from blood obtained from a peripheral vein) 2. The same organism is cultured from two blood cultures samples drawn, one from a catheter hub and the other from a peripheral vein with a differential time to positivity (DTP) of 2 h (same pathogen detected from a blood sample drawn from a catheter hub at least 2 h before it is detected in a blood sample obtained from a peripheral vein) B. A definite CR-BSI diagnostic method implicating catheter removal requires that the same organism is cultured from at least one percutaneous blood culture and from a culture of the catheter tip	Patient has a central line that was in place at the time of, or within 48 h before, onset of bacteremia with any one of the following: 1. A recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site 2. A common skin contaminant cultured from two or more blood cultures drawn on separate occasions within 2 d of each other and at least one of the following clinical signs or symptoms: fever (>38°C), chills, or hypotension and signs and symptoms and positive laboratory results are not related to an infection at another site

[a]According to the Infectious Diseases Society of America (IDSA) 2009 guidelines for the diagnosis and management of intravascular catheter–related infections and to the CDC definition for CLABSI.
[b]Centers for Disease Control and Prevention (CDC) definition of CLABSI does not require catheter removal.

CR-BSI with an infected thrombus *(61–63)*. The clinical course of septic thrombosis is characterized by occasional swelling above the site of the thrombotic vein and persistent BSI on antimicrobial therapy even after the removal of the catheter. Other deep-seated infections associated with complicated catheter-related bacteremias and fungemias consist of endocarditis, osteomyelitis, and retinitis in the case of candidemia *(61,62)*.

DIAGNOSIS

Catheter-related infections are often overdiagnosed, resulting in unnecessary antimicrobial therapy and wasteful removal of the CVC. Misdiagnosis is often the result of relying on false-positive microbiologic data, such as positive blood cultures from the CVC or clinical data such as catheter-site inflammation/phlebitis associated with PICC lines in the absence of other confirmatory data. Therefore, the diagnosis of these infections is often difficult and should be the result of integrating clinical and microbiologic findings. A positive nonquantitative blood culture drawn through the CVC with a concurrent negative peripheral blood culture should be interpreted with extreme caution. Bryant and Strand *(64)* demonstrated that 93% of such cultures are often contaminated with microorganisms that colonize the hub or the lumen, and hence do not reflect an infection. This is particularly true for skin microorganisms such as CNS. It has been demonstrated that the positive predictive value of a single positive blood culture for CNS ranges from 4.1% to 26.4% *(65–68)*. Therefore, prior to initiating antimicrobial therapy and considering whether the catheter should be removed, a single positive blood culture yielding a skin microorganism should be interpreted in light of associated clinical and microbiologic data. Because CVCs are universally colonized, a positive blood culture from the CVC could reflect intraluminal or hub colonization. Therefore, attention should be paid to other laboratory findings suggestive of BSI and which consist of (a) multiple positive blood cultures of skin microorganisms (60), (b) quantitative blood cultures revealing a high colony count (>15 CFU/mL of blood) or time to positivity of <20 hours for blood culture growing CNS (69,*70*), and (c) the same microorganisms isolated from the quantitative catheter culture and peripheral blood culture (59). All three of these factors should be considered to reflect a catheter-related infection in the setting of concurrent signs of infection such as fever and chills with no other apparent source for the infection other than the catheter.

Before or after removal of the catheter, the diagnosis should be made based on the interplay of clinical and microbiologic findings. The infection is initially suspected when there is a positive blood culture in a patient with a CVC with clinical signs of infection, such as fever and chills, and no other apparent source for the BSI, such as pneumonia, urinary tract infection, intra-abdominal infection, or surgical site infection (Table 18-2). This type of BSI has been termed primary BSI. In this case, the primary BSI is a probable CLABSI. The diagnosis becomes definitive in the presence of either confirmatory clinical or microbiologic data.

Clinical findings are unreliable for establishing the diagnosis of IVD-related infection because of their poor sensitivity and specificity. However, clinical data consisting of (a) local inflammation, such as catheter exit-site inflammation or tunneled/port inflammatory signs (Tables 18-1 and 18-2)—the presence of purulence at the insertion

site, particularly in patients with *S. aureus* bacteremia, is diagnostic of catheter-related bacteremia—and (b) systemic signs of infection, such as fever and chills, that persist despite appropriate antimicrobial therapy for the BSI but resolve with catheter removal should increase the suspicion for CLABSI *(71)*.

Confirmatory microbiologic data may be available prior to catheter removal. The three best-studied methods to determine the diagnosis prior to catheter removal are simultaneous quantitative blood cultures from the CVC and a peripheral vein, DTP, and, for nontunneled catheters, quantitative cultures of the skin at the exit site (*59*,*68*,69,*70–84*). In the former case, the diagnosis of CR-BSI is often suggested when the number of colonies isolated from a quantitative blood culture obtained from the catheter is at least threefold more than that quantitated from a peripheral venipuncture blood culture *(73–78)*. DTP is a method that was shown in cancer patients to be a simple and reliable tool for *in situ* diagnosis of catheter-related bacteremia. Blot et al. *(81,82)* defined DTP as the difference in time necessary for the blood cultures drawn from a peripheral vein and through the catheter to become positive. When DTP was >120 minutes, this diagnostic method was shown to be highly sensitive (100%) and specific (96.4%) for the diagnosis of CR-BSI *(81)*. Blot et al. *(82)* concluded that using DTP as a diagnostic technique is mainly of value for patients requiring long-term catheterization. Another large prospective study conducted by our group confirmed that DTP of >120 minutes was highly suggestive of CR-BSI associated with the use of both short-term and long-term CVCs *(83)*. Semiquantitative and quantitative catheter cultures are not very helpful in the setting of long-term CVC because they require the removal of the CVC in order to diagnose CR-BSI. The roll-plate semiquantitative culture method is most commonly used for culturing catheters *(85)*. However, this method is limited in that it cultures only the external surface of the catheter and may not retrieve microorganisms that are well embedded in the biofilm on the catheter surface. The fact that this method does not quantitate microorganisms from the lumen of the catheter is important for long-term indwelling catheters where colonization is mostly luminal. In a study of long-term catheters (nontunneled CVC and PICC lines) at the M. D. Anderson Cancer Center, the sensitivity of the roll-plate technique was 45% compared with 72% for the sonication technique for making the diagnosis of catheter colonization or catheter-related infection by culture of the intravascular segment of the catheter *(1)*. Quantitative catheter cultures, particularly sonication, which retrieves microorganisms from the external and internal surfaces, have been shown to be of higher diagnostic value than the roll-plate technique, particularly for long-term CVC with predominantly luminal colonization *(1,86,87)*. If semiquantitative or quantitative catheter cultures are not done, then a clinical response to catheter removal within 24 hours, after failure of antimicrobial therapy to resolve the infection, with the catheter *in situ*, is highly suggestive of CR-BSI *(88)*.

If the bacteremia or fungemia persists after catheter removal in spite of the use of appropriate antimicrobial agents, then one has to determine whether the patient has a deep-seated catheter-related infection, such as right-sided endocarditis or septic thrombosis *(61,62)*. In these situations, a venogram would be useful to rule out septic thrombosis, and a transesophageal echogram might be useful to detect valvular vegetations suggestive of endocarditis.

PREVENTION

Effective preventive strategies for long-term CVC-related infections should be based on an understanding of the pathogenesis of these infections. Because luminal colonization is the major source of BSIs in long-term catheters, preventing colonization of the external surface of the catheter during the early-phase postinsertion will not decrease the overall rate of infection. One such example is the use of the silver-impregnated cuff, which was shown to interrupt the intracutaneous migration of microorganisms and to decrease the risk of short-term catheter colonization and infection *(55)*. However, this silver-impregnated cuff has failed to protect against infections in long-term tunneled Hickman catheters. Measures that decrease the risk of colonization of the lumen of the catheter have been shown to be of benefit in decreasing the risk of catheter-associated infection for long-term CVCs *(89)*. However, some of the preventive measures suggested for prevention of long-term catheter–associated infections have limited data to support their use with respect to this type of catheter (Table 18-3).

Maximal Sterile Barriers

A prospective randomized study was conducted to test the efficacy of maximal sterile barriers in reducing infections associated with long-term nontunneled subclavian silicone catheters with a mean duration of placement of approximately 70 days *(90)*. Maximal sterile barrier precautions (which involve wearing sterile gloves and gown, a cap, and

TABLE 18-3

Measures for the Prevention of Long-Term Catheter–Related Infections

A. Traditional measures:
   a. Education of healthcare workers on vigilant catheter care
   b. Skilled infusion therapy team
   c. Hand hygiene
   d. Chlorhexidine cutaneous antisepsis
   e. Use of maximal sterile barrier precautions during CVC insertion
   f. Use the subclavian vein as the preferred insertion site and avoid femoral insertions
   g. Removal of unnecessary CVCs
B. Novel technology:
   i. Strongly recommended or well supported by evidence:
      a. Antimicrobial coating of catheters
      b. Flush solutions/antimicrobial catheter lock
      c. Chlorhexidine sponges
      d. Topical antibiotics at the insertion site
   ii. With limited supporting evidence:
      a. Antimicrobial hubs and connectors

using a large drape during insertion of the catheter) were compared with routine procedures (which involve wearing only sterile gloves and use of a small drape). Maximal sterile barrier precautions decreased the risk of catheter-related bacteremia from 0.5 per 1,000 catheter-days to 0.02 per 1,000 catheter-days. Long-term catheters consisted of nontunneled subclavian CVCs and PICC lines. A recent multicenter prospective randomized clinical trial conducted in Japan failed to demonstrate better prevention of CLABSI by maximal sterile barrier precautions compared with standard sterile barrier precautions (which involves the use of sterile gloves and a small drape during insertion of CVC) in surgical inpatients; however, this study was underpowered and might not negate the possible benefit of the maximal sterile barrier precautions *(91)*.

Hand washing, maximal sterile barrier precautions, skin cleansing using chlorhexidine, avoiding the femoral site if possible, and removing unnecessary catheters represent the five evidence-based procedures recommended by the CDC for having the greatest effect on the rate of CR-BSI and the lowest barriers to implementation (92,93). Although the five bundle elements remain the mainstay of protection against CLABSI associated with short-term CVC used in critically ill patients, its efficacy has not been studied during the insertion of long-term IVDs. Furthermore, its implementation is not easily enforceable, requires continuous educational training and compliance assessment for sustained efficacy, is usually associated with high cost and poor compliance, and does not completely prevent infection.

Skilled Infusion Therapy Team

In addition to decreasing the catheter-related infection rate by five- to eightfold, an experienced infusion therapy team has been shown to be cost-effective. Most of the studies were done with relatively short-term catheters (94–98). However, we have reported the finding that the duration of placement of nontunneled, noncuffed silicone catheters (mean duration of catheterization of 109 days) could be prolonged to approach that of the tunneled Hickman catheter with a very low infection rate of 1.4 per 1,000 catheter-days at the M. D. Anderson Cancer Center (2). This was attributed, at least in part, to the presence of a skilled infusion therapy team at our institution.

Tunneling

Tunneling of catheters is considered a standard of care for the prevention of long-term CLABSI. Because tunneled catheters have been associated with long durability and low infection rates, it has been assumed that tunneling decreases the risk of catheter-related infections and is the only safe option for the maintenance of long-term externalized silicone catheters. A prospective, randomized study evaluating the effect of tunneling on long-term silicone catheters was conducted by Andrivet et al. *(17)*, wherein the catheters were used in immunocompromised patients. The risk of catheter-related bacteremia associated with tunneled as compared with nontunneled catheters was 2% and 5%, respectively. The difference was not significant, probably due to the relatively small number of patients in each group (107 and 105 patients, respectively). In another study involving short-term polyurethane catheters placed in the internal jugular vein of critically ill patients, tunneled catheters were associated with a statistically significantly lower rate of catheter-related bacteremia than nontunneled catheters, suggesting that tunneling may decrease the risk of infection *(99)*. A prospective randomized multicenter trial showed that BSIs were four times less likely to originate from minocycline and rifampin (M-R)-impregnated, nontunneled, long-term catheters than from tunneled catheters (100). The cost saving related to simple insertion of a nontunneled M-R CVC at M. D. Anderson Cancer Center when compared to a tunneled, uncoated, long-term silicone CVC is at least $2,500. This cost saving is restricted only to insertion cost and does not include the added cost saving associated with the reduction of CLABSI related to the use of M-R CVC versus tunneled, uncoated CVC (100). The use of a M-R-impregnated, long-term CVC may help obviate the need for surgically implantable catheters (100).

Ports

The lowest rate of CR-BSI has been associated with the use of surgically implanted subcutaneous central venous ports. In a review by Crnich and Maki (8), in which they evaluated the results of 13 prospective studies of subcutaneous central venous ports, the pooled mean of CR-BSI rates associated with ports was at a low 0.2 per 1,000 catheter-days (95% confidence interval (CI) 0.1–0.2) (8). Another recent systematic review of 200 published prospective studies on different IVDs showed that all types of IVDs were associated with IVD-related BSI (101). Ports are especially useful for intermittent venous access needed for short durations such as with periodic chemotherapy administrations.

Antiseptic Dressings

A chlorhexidine-impregnated hydrophilic polyurethane foam dressing, which can be pressed firmly onto the skin at the catheter insertion site and then covered with a transparent polyurethane dressing, was shown to reduce site skin colonization as well as epidural catheter colonization *(102)*. It also prevented infection at the site of orthopedic traction pins in an animal model *(103)*. The chlorhexidine-impregnated sponge dressings were evaluated in a multicenter trial involving six neonatal ICU patients, where they were found to be similar to gauze and tape combined with periodic skin disinfection with 10% povidone-iodine, in preventing skin colonization and CR-BSI *(104)*. However, the use of these chlorhexidine dressings was associated with 15% incidence of dermatotoxicity in low birth weight neonates (<1,000 g). Another multicenter, prospective randomized controlled trial, demonstrated that the use of chlorhexidine gluconate–impregnated sponges used for intravascular catheter dressings in critically ill adult patients decreased the risk of major catheter-related infections by 60% despite a low baseline infection rate *(105)*.

A prospective randomized controlled trial showed that the use of chlorhexidine-impregnated wound dressings significantly reduced the incidence of central line–related infections in adult cancer patients with long-term CVC (106).

Intraluminal Antibiotic Locks

This prophylactic measure consists of flushing and filling the lumen of the catheter with antimicrobial agents and leaving the solution to dwell in the lumen of the catheter for 2 to 12 hours. Although heparin has become widely used

as an antithrombotic agent to maintain catheter patency, it has been shown to enhance staphylococcal biofilm formation when used at the relevant concentration of 1,000 U/ml used in catheters lock (107).

Various antimicrobial agents have been used as antimicrobial locks, often following an infection in a surgically implanted catheter in order to treat the infection without removal of the catheter *(108,109)*. Among the antimicrobial agents used were vancomycin, gentamicin, ciprofloxacin, cefazolin, erythromycin, nafcillin, ceftriaxone, clindamycin, fluconazole, and amphotericin B. Vancomycin in combination with heparin has been used as a daily flushing solution of tunneled CVCs and has been reported to significantly decrease the frequency of catheter-related bacteremia caused by vancomycin-susceptible gram-positive microorganisms colonizing the lumen *(110)*.

A meta-analysis of seven prospective randomized controlled trials showed that a vancomycin heparin lock or flush solution reduces the risk of BSI in high-risk patients with long-term CVCs *(111)*. However, with the emergence of resistant microorganisms, it is prudent to avoid using antibiotics that are commonly used in the therapy of BSIs (such as beta-lactam antibiotics, vancomycin, quinolones, and aminoglycosides) for prophylaxis against catheter infections. This is particularly true for vancomycin which has been shown to have little to no antimicrobial activity against microorganisms embedded in biofilm on catheter surfaces *(112–114)*.

Chelating agents such as ethylene diaminetetraacetic acid (EDTA) or citrate possess anticoagulation properties and enhance the activity of antimicrobials in eradicating bacteria and fungi embedded in biofilm *(115–120)*. A novel catheter flush solution consisting of low concentrations of minocycline and ethylenediaminetetraacetic acid (EDTA) has been developed. Minocycline is not commonly used in the treatment of systemic infections and does not have cross-resistance with vancomycin or beta-lactam antibiotics against resistant gram-positive bacteria. A flush solution of minocycline and EDTA (M-EDTA) was shown to have broad-spectrum and often synergistic activity against methicillin-resistant staphylococci, gram-negative bacilli, and *C. albicans*, and was found to prevent CR-BSIs in several complicated, high-risk patients *(121)*. Also, in a rabbit model, M-EDTA lock solution succeeded more than heparin alone and heparin–vancomycin in preventing catheter colonization, CR-BSI, and phlebitis in all of the study animals ($p < .01$) *(122)*. In that study, the M-EDTA lock solution also prevented tricuspid endocarditis, as did the heparin–vancomycin lock solution, more effectively than heparin alone ($p \leq .06$).

In a prospective randomized trial involving patients with long-term hemodialysis CVCs, M-EDTA flush solution significantly reduced rates of catheter colonization ($p = .005$) (123). Also, in another prospective pediatric cohort study, M-EDTA was used as a lock solution in 14 pediatric cancer patients with ports (124). There were no CR-BSIs, thrombotic events, or adverse events associated with the use of M-EDTA flush solution over a total of 2,073 catheter-days in comparison with a rate of 2.23 infections per 1,000 catheter-days in a control group that received heparin flush solution.

C. albicans is the most common fungal pathogen associated with colonization and biofilm formation on the surface of indwelling medical devices *(125,126)*. Ethanol has a potent anticandidal biofilm activity, anticoagulant property, and could be synergistic when combined with other antibiotics in lock solution *(127–129). In vitro* studies have shown the efficacy of ethanol, alone or in combination with other agents in preventing and eradicating biofilm formation *(127–129)*. A recent randomized clinical trial showed a nonsignificant reduction of CLABSI in patients receiving 70% ethanol locks compared to those receiving 0.9% NaCl locks for 15 minutes per day *(130)*. In addition, drug-related toxicities such as feeling of discomfort, facial redness or flushing, drowsiness, and alcohol taste were significantly higher in the patients receiving 70% ethanol lock compared to placebo. Hence, ethanol locks when used alone particularly at high concentrations might not be very useful for the prevention of CLABSIs. Although small clinical trials have shown promising results *(131–133)*, large prospective, randomized, controlled trials are needed to evaluate the role of ethanol (particularly lower concentration of 25%–50%) in combination with other agents such as biofilm-penetrating antimicrobials and chelator agents in the prevention and treatment of CLABSI *(128)*.

Taurolidine, a derivative of the amino acid taurine, is an antimicrobial agent, which in high concentrations (250–2,000 μg/mL) has inhibitory as well as cidal activities against many microorganisms *(134)*. The use of taurolidine lock solution reduced the rate of CR-BSI associated with the use of hemodialysis CVCs *(135)* and other long-term CVCs *(136)*. A combination of taurolidine and citrate-based catheter lock solution (Neutrollin; Biolink Corp., Norwell, MA) reduced bacterial counts in a catheter model by more than 99% *(137)*. The microorganisms affected included *S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. faecalis*, and *C. albicans*. Taurolidine–citrate significantly reduced biofilm on silicone disks in modified Robbins devices more than heparin treatment (by 4.8 logs vs. 1.7 logs, $p < .01$).

In a multicenter, prospective, randomized controlled trial in adult patients with end-stage renal disease receiving hemodialysis through a cuffed and tunneled CVC, Maki et al. demonstrated that a novel lock solution containing sodium citrate, methylene blue, and parabens significantly reduced the rate of CLABSI when compared to a heparin lock (0.24 vs. 0.82 infections per 1,000 catheter-days, respectively, with a relative risk of 0.29 [95% CI: 0.11–0.70]; $p = .005$) and provided a similar protection against thrombosis compared with heparin (138).

The issue of resistance developing with a wide use of prophylactic antibiotic lock solutions needs to be investigated thoroughly. However, currently, the CDC guidelines for the prevention of intravascular catheter-related infections do not recommend the routine use of prophylactic antibiotic lock solutions. The guidelines recommend the use only in special circumstances, such as in treating a patient with a long-term cuffed or tunneled catheter or port who has a history of multiple CLABSIs despite optimal maximal adherence to aseptic techniques (92).

Antimicrobial Coating of Catheters

Antimicrobial coating of catheters has been shown to be effective in reducing the rate of catheter-related infection in short-term polyurethane catheters. By coating the external surface of catheters with chlorhexidine plus silver

sulfadiazine (CH-SS), Maki et al. *(139)* showed that this combination did decrease the risk of colonization by nearly 50% and decreased the risk of catheter-related bacteremia by at least fourfold. A meta-analysis analyzed the results of 12 studies investigating the efficacy of catheters impregnated with CH-SS *(140)*. According to this analysis, the mean duration of catheterization with CH-SS catheters was between 5.1 and 11.2 days, and hence their efficacy is only proven for short-term catheterization. A second generation of catheters impregnated with CH-SS, in which the catheters are impregnated both externally and internally, significantly reduced catheter colonization more than uncoated catheters, but failed to reduce the risk of CR-BSI in two prospective randomized trials *(141,142)*. In a prospective, randomized multicenter study when CVCs impregnated with M-R on their external and internal surfaces were compared with first-generation CH-SS catheters, they were shown to be 12 times less likely to be associated with CR-BSI and three times less likely to be colonized. It was shown that the risk of catheter colonization was reduced by threefold and the risk of CLABSIs was reduced from 5% to 0%. Among catheters that remained in place for more than 7 days, the rate of CLABSI was significantly higher for catheters impregnated with CH-SS than for catheters impregnated with M-R (6.4% vs. 0.7%, respectively, $p = .01$) *(143)*. Another prospective randomized clinical trial comparing 182 long-term silicone CVCs impregnated with M-R to 174 nonimpregnated catheters showed that M-R catheters were safe and efficacious in preventing CRBSI in cancer patients. In this study, the rate of CLABSI was 0.25 per 1,000 catheter-days with the M-R-impregnated catheters versus 1.28 per 1,000 catheter-days with the nonimpregnated catheters ($p = .003$) (144). As previously mentioned, a randomized controlled trial showed that long-term nontunneled M-R-impregnated CVCs prevented CLABSI more effectively and at a lower cost than tunneled CVCs (100). A recent study conducted over a 7-year period demonstrated that M-R CVCs significantly decrease the rate of CLABSI in critically ill patients *(145)*.

Several meta-analyses demonstrated the effectiveness of antimicrobial catheters impregnated with CH-SS or M-R in preventing CLABSI (*146*,*147*,148). M-R CVCs outperform the antiseptic catheters and are preferred when long periods of catheterization are expected (148). The M-R CVCs were shown to have an antimicrobial activity with a half-life of 25 days against *S. epidermidis* compared to 3 days for CH-SS CVCs (149). In a randomized controlled trial, CH-SS CVCs did not decrease the rate of CLABSIs in patients with hematologic malignancies who had a mean duration of catheterization of 20 days (150).

Despite the significant evidence from multiple randomized controlled trials and several meta-analyses proving the efficacy of M-R-impregnated CVCs in decreasing CLABSI, concerns exist about the potential emergence of resistance to M-R developing with the prolonged use of such devices (151). *In vitro* exposure of gram-positive bacteria to rifampin and minocycline in combination did not lead to the emergence of resistance (152,153). In randomized clinical trials, no evidence of antibiotic resistance bacteria was noted after the use of M-R-impregnated catheters (*143*,144,*154,155*). A 7-year experience of extensive use of M-R CVC exceeding 0.5 million catheter-days demonstrated the lack of emergence of resistance to tetracycline or rifampin among clinical isolates of *S. aureus* and CNS on a hospital-wide level and in the intensive care unit *(145)*.

Currently, the CDC guidelines for the prevention of intravascular catheter-related infections recommend the use of antimicrobial CVC in adults whose catheter is expected to remain in place for more than 5 days, if rates of CR-BSI remain above the goal set by the individual institution after implementing aseptic techniques, including maximal sterile barrier precautions (92).

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CHAPTER 19

Healthcare-Associated Bloodstream Infections

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Healthcare-associated bloodstream infections (HA-BSIs) are a significant and continuing problem in our present-day healthcare system. A variety of factors, including central venous catheterization, predispose patients toward development of infections involving the bloodstream. Pathogens causing these infections vary according to the primary site of infection and a variety of patient factors. Preventive efforts are generally directed at the primary site of invasion. This chapter summarizes general issues related to healthcare-associated bacteremia. More specific information can be found in chapters covering specific primary infections and pathogens.

INCIDENCE AND IMPACT

HA-BSIs are increasing in prevalence and result in significant morbidity, mortality, and economic cost. From 1975 to 1998, the proportion of healthcare-associated infections accounted for by BSIs increased from 5% to 17% *(1,2)*. McGowan and Shulman *(3)* noted from 1975 through the early 1990s that the rate of HA-BSI increased dramatically from approximately 2 to 4 episodes/1,000 discharges to 15 to 20 episodes/1,000 discharges. A recent review of data from the US Nationwide Inpatient Sample estimated the rate of HA-BSI at 21.6 episodes/1,000 admissions *(4)*. It is estimated that each year in the United States between 250,000 and 500,000 patients experience a HA-BSI and between 30,000 and 100,000 die from these infections *(4,5)*. A recent encouraging development has been a decrease in methicillin-resistant *Staphylococcus aureus* (MRSA) HA-BSIs *(6)*. The reason for this decline is not clear but possible explanations include changes in *S. aureus* epidemiology, the impact of hospital policies designed to decrease MRSA transmission, and widespread efforts to decrease rates of central venous catheter (CVC) infection.

The crude mortality associated with HA-BSI varies in published reports from 5% to 58% and depends on the microbial etiology and the underlying condition of the patient *(3)*. Over a 7-year observational period from 1995 to 2002, the Surveillance and Control of Pathogens of Epidemiological Importance (SCOPE) investigators analyzed over 24,000 cases of HA-BSI from 49 medical centers, and noted a crude mortality rate of 27%, ranging from 21% for coagulase-negative staphylococci to 40% for *Candida* sp. (7). However, attributable mortality is more difficult to ascertain. In some studies that controlled for confounding variables such as severity of illness, BSI was not noted to increase mortality *(8,9)*, while other investigators noted substantial increased mortality *(10,11)*. HA-BSIs result in dramatic increases in economic cost. The length of hospital stay is extended by 1 to 4 weeks at a cost of up to $40,000 per survivor *(10–14)*. There is no doubt that HA-BSI is a very significant problem associated with the current healthcare system and that efforts to better understand and prevent this problem are well warranted.

CLASSIFICATION AND DEFINITIONS

Although the definition of hospital-acquired BSI appears clear-cut, the application of the definition is, at times, confusing. HA-BSI is typically defined as the demonstration of a recognized pathogen in the bloodstream of a patient who has been hospitalized for >48 hours. BSIs can be further categorized as primary or secondary. When a microorganism isolated from the bloodstream originated from a healthcare-associated infection at another site (urinary tract, surgical site, etc.), the infection is classified as a secondary BSI. Conversely, primary BSIs occur without a recognizable focus of infection elsewhere. It should be noted, that BSIs stemming from intravascular catheters are classified as primary infections.

The Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) previously defined BSI as "laboratory-confirmed BSI" or "clinical sepsis" *(15)*. However, the category of clinical sepsis, which applied to infants and neonates, is no longer considered an NHSN event for BSI (16). NHSN laboratory-confirmed primary BSI must meet at least one of the following criteria:

Criterion 1: Patient has a recognized pathogen cultured from one or more blood cultures *and* microorganism cultured from blood is *not* related to an infection at another site.

Criterion 2: Patient has at least *one* of the following signs or symptoms: fever (>38°C), chills, or hypotension (systolic pressure ≤90 mm Hg) *and* signs and symptoms and positive laboratory results are *not* related to an infection at another site *and* common skin contaminant (e.g., diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative

staphylococci, viridans group streptococci, *Aerococcus* sp., or *Micrococcus* sp.) is cultured from *two* or more blood cultures drawn on *separate* occasions.

Criterion 3: Patient ≤1 year of age has at least *one* of the following signs or symptoms: fever (>38°C rectal), hypothermia (<37°C rectal), apnea, or bradycardia *and* signs and symptoms and positive laboratory results are *not* related to an infection at another site *and* common skin contaminant (e.g., diphtheroids, *Bacillus* sp., *Propionibacterium* sp., coagulase-negative staphylococci, viridans group streptococci, *Aerococcus* sp., or *Micrococcus* sp.) is cultured from *two* or more blood cultures drawn on *separate* occasions.

Although ambiguity is generally not encountered in evaluating patients with positive blood cultures, it is important to note that there is potentially wide practice variation with regard to procurement of blood cultures, and thus bias can be introduced when comparing rates of BSI from institution to institution or unit to unit *(17)*. In general, it is felt that clinicians in the United States are very liberal in their ordering of blood cultures, and it is doubtful that many clinically significant episodes of bacteremia escape detection. However, differentiating true, clinically significant BSI from blood culture contaminants can, at times, offer a challenge to clinicians. This is discussed in greater detail in subsequent sections.

Another issue that has complicated the definition of HA-BSI is the blurring of the distinction between healthcare-associated and community-acquired infections as many therapies traditionally used only in hospitalized patients are now performed routinely in the outpatient setting. Multiple studies have attempted to better define this new category of BSI usually defined as HA-BSI. Friedman et al. *(18)* observed that of 504 consecutive BSIs detected at an academic medical center and two associated community hospitals, 37% were considered healthcare-associated. Likewise, Siegman-Igra et al. *(19)* noted that 39% of 604 BSIs occurring in settings traditionally classified as community-acquired could be more accurately classified as healthcare-associated. An analysis of over 6,600 BSIs from a national database classified 55.3% of these infections as healthcare-associated using the criteria of first positive culture within 2 days of admission and any of the following: transfer from another healthcare facility including nursing home, receiving chronic hemodialysis, prior hospitalization within 30 days, and currently on immunosuppressive medication or with metastatic cancer (20). It has been noted that HA-BSIs have similar mortality rates to HA-BSI and are more likely to be due to drug-resistant pathogens including MRSA and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae (19,21)*. Table 19-1 summarizes the characteristics of BSI associated with different patient groups. These findings have significant implications for empiric antimicrobial treatment choices as patients with HA-BSI have been noted to be more likely to receive initially inadequate therapy, likely due to higher rates of resistant pathogens *(22)*. Further research is needed to better delineate this category of patients and their unique risk factors and characteristics.

CLINICAL MICROBIOLOGY AND DIAGNOSTIC TECHNIQUES

The diagnosis of BSI is dependent on the capacity to recover microbes from the blood. Most large laboratories utilize various automated blood culture systems that are reasonably comparable and are often continuously monitored. These automated systems have been reviewed elsewhere *(23)*, and an extensive discussion is beyond the scope of this chapter. In considering the reliability of recovery of nonfastidious microbes, issues with appropriate procurement likely outweigh the type of system used.

Several factors regarding blood culture reliability and contamination should be emphasized:

TABLE 19-1

Classification, Pathogens, and Outcomes from 6,697 Bacteremic Patients

Microorganism/Outcome	*CAB No. (%) (n = 2,524)*	*HCAB No. (%) (n = 3,705)*	*HAB No. (%) (n = 468)*
Gram positive	1,110 (44)	1,810 (48.9)[a]	229 (48.9)
MSSA	354 (14)	672 (18.1)[a]	92 (19.7)[a]
MRSA	95 (3.8)	280 (7.6)[a]	47 (10)[a]
Gram negative	1233 (48.9)	1603 (43.3)[a]	179 (38.2)[a]
Escherichia sp.	635 (25.2)	723 (19.5)[a]	32 (6.8)[a]
Klebsiella sp.	146 (5.8)	231 (6.2)	29 (6.2)
Pseudomonas sp.	57 (2.3)	117 (3.2)	15 (3.2)
Candida sp.	22 (0.9)	32 (0.9)	15 (3.2)[a]
Mortality	253 (10.0)	551 (14.9)[a]	70 (15.0)[a]
LOS, days, mean	6.0	6.0	10.0
Total charges, $, median	15,278	15,288	30,340

[a]$p < .01$ compared to CAB.
CAB, community-acquired BSI; HCAB, healthcare-associated BSI; HAB, hospital-acquired BSI; MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*.
(From Shorr AF, Tabak YP, Killian AD, et al. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S. database. *Crit Care Med* 2006;34:2588–2595.)

Skin Preparation and Culture Technique

Inadequate skin preparation has been reported to be the most frequent cause of culture contamination *(24)*. A variety of products are available for skin preparation. Several studies have found that use of iodine tincture results in lower rates of contamination when compared to povidone iodine, which is thought to be due to the shorter drying time and rapidity of antimicrobial activity associated with the alcohol containing iodine tincture *(25–27)*. Similarly, a number of trials have observed that skin disinfection with alcoholic chlorhexidine resulted in fewer contaminated blood cultures than povidone iodine *(28,29)*. However, Calfee and Farr (30) observed no significant differences in contamination rates among four different skin antiseptics including povidone iodine, povidone iodine with 70% alcohol, isopropyl alcohol, and tincture of iodine. Studies comparing tincture of iodine and alcoholic chlorhexidine have noted no difference and both have very low rates of contamination *(31,32)*. Based on these studies, guidelines published by both the Infectious Disease Society of America and the American College of Critical Care Medicine recommend using either alcohol alone, chlorhexidine with alcohol, or tincture of iodine for skin decontamination *(33,34)*. Following appropriate skin preparation, if the blood vessel must be palpated, it should be done with a sterile glove. A new needle should be utilized for each attempt at venipuncture *(35)*. Blood should be promptly inoculated into culture bottles following disinfection of culture bottle top septums as they are not sterile. While a meta-analysis suggested the practice of changing needles between procurement of blood and inoculation of blood culture bottles decreased the rate of contamination from 3.7% to 2.0%, it is generally believed the risk of needle stick injury outweighs the benefit of this practice *(34,36)*.

Blood Volume Sampled

To maximize the diagnostic yield from blood cultures, an adequate amount of blood must be sampled. In many cases, the concentration of microorganisms in the bloodstream is ≤1 colony-forming unit (CFU)/mL, and therefore 10 to 20 mL of blood should be sampled to reliably detect bacteremia *(37,38)*. Mermel and Maki *(39)* calculated that the yield from blood cultures in adults increased 3% per milliliter of blood obtained. Unfortunately, the inadequate sampling of blood volume is frequent in many clinical centers *(39)*. Interestingly, inadequate blood volume has also been associated with increased rates of culture contamination *(40)*.

Timing and Number of Blood Cultures

The optimum time to draw blood cultures is when the number of microbes in the bloodstream is greatest, which unfortunately is 1 to 2 hours before the onset of symptoms *(41)*. Therefore, it is recommended to obtain blood cultures as soon as symptoms occur and preferably before antimicrobials are administered. Although it is common to wait 30 to 60 minutes between obtaining culture sets, Li et al. *(42)* found no advantage associated with this practice. The practice of drawing blood cultures with fever spikes does not appear to increase yield either *(43)*. Previous literature suggested that two to three blood cultures obtained over a 24-hour period could detect >99% of all bacteremias *(44,45)*. More recent literature suggests that three to four blood cultures over a 24-hour period may be necessary to detect >99% of bacteremias and recent guidelines have recommended this practice, particularly in the critically ill (*34*,*43*,46,*47*). Issues regarding repetitive blood cultures, the utility of anaerobic cultures, blood-to-broth ratios, and other clinical microbiology issues have been reviewed elsewhere *(48–50)*.

Sites for Obtaining Blood Cultures

Although it is generally recommended to avoid obtaining blood for cultures via intravascular catheters because of concern for contamination, the ease of vascular access, minimization of patient discomfort, and consideration of the catheter as a source of infection has made this a common clinical practice. Multiple studies have evaluated the utility of blood cultures drawn from catheters for the detection of BSI and a recent systematic review summarized their findings (*51*,*52*,53). Obtaining blood cultures from catheters increases the sensitivity for detection of bacteremia but is associated with increased isolation of contaminants and decreased positive predictive values. The sensitivity of a single blood culture from either a CVC or peripheral site is not considered adequate for detection of bacteremia and paired blood cultures from both sites are indicated if a blood stream infection is suspected *(33)*. A variety of new diagnostic techniques have been developed to evaluate the source of fever/bacteremia in patients with CVCs including semiquantitative superficial cultures, differential time to positivity and differential quantitative blood cultures *(54–56)*. These techniques, which are described in greater detail in Chapters 15 and 16, are based on the premise that patients with a catheter-associated infection have a greater burden of bacteria in blood drawn from the intravascular catheter than in blood drawn from the periphery. Recently published guidelines on the diagnosis of CVC infection consider both differential time to positivity and quantitative blood cultures acceptable methods for the diagnosis of CVC-related BSI *(33)*. Therefore, if clinicians are using catheter-drawn blood for culture, it should be paired with a sample drawn peripherally and the sites and times of procurement should be clearly documented.

INDICATIONS FOR BLOOD CULTURES

Indications for blood cultures are not standardized, but should be obtained as a routine study whenever there is a realistic possibility of a HA-BSI. Fever is generally the most common clinical marker for serious healthcare-associated infection, and blood cultures are usually included in the evaluation of fever in hospitalized patients. However, it should be noted that fever may be absent during episodes of bacteremia in certain patient populations such as the elderly, neonates, immunocompromised hosts, and persons with end-stage renal disease. Changes in mental status or functional status may be the most prominent findings associated with bacteremia in elderly patients or patients with renal dysfunction *(35,57)*. Likewise, bacteremia in neonates is often manifested by lethargy, feeding intolerance, apnea, cholestasis, and temperature instability rather than fever *(58,59)*.

If a BSI is identified by blood culture, it is generally not necessary to repeat blood cultures after appropriate treatment has been initiated. Patients who fail to improve despite appropriate antimicrobial therapy should have repeat blood cultures performed to assess for persistence of infection. Also, in the evaluation of *S. aureus* HA-BSI, many authorities would recommend repeating blood cultures to help assess whether a patient has endocarditis or other deep-seated staphylococcal infection. An exception to this practice are BSIs due to *Candida* species that require repeat blood cultures to document clearance and determine length of therapy *(60)*.

MICROBIAL ETIOLOGY OF HEALTHCARE-ASSOCIATED BSI

The microbial profile of HA-BSI has changed markedly over the past several decades in response to changes in patient population and antibiotic use. Throughout the 1970s, Enterobacteriaceae were the most common cause of HA-BSI *(61)*. During the 1980s, a relative decrease in bacteremia due to *Escherichia coli* and *Klebsiella pneumoniae* was observed, whereas the contribution due to coagulase-negative staphylococci, enterococci, and *Candida albicans* increased *(62)*. These changes were attributed to the widespread use of antibiotics with activity against Enterobacteriaceae and the increased utilization of indwelling medical devices, particularly intravascular catheters. Banerjee et al. *(63)*, reporting on secular trends in healthcare-associated primary BSIs during the 1980s, found that, depending on the type of hospital studied (small, ≤200 beds; large, ≥500 beds; teaching vs. nonteaching), the rate of bacteremia due to coagulase-negative staphylococci skyrocketed by 161% to 754% *(63)*. Similarly, enterococcal bacteremia increased by 120% to 197% and *Candida* sp. fungemia increased by 75% to 487% *(63)*. Another trend observed during the 1980s was a shift toward more antibiotic-resistant pathogens. Increased prevalence of antibiotic-resistance was observed in *Pseudomonas aeruginosa* and *Enterobacter cloacae* resistant to third-generation cephalosporins, *S. aureus* and coagulase- negative staphylococci resistant to methicillin, and enterococci resistant to high levels of aminoglycosides *(62)*.

These trends continued in the 1990s. Figure 19-1 illustrates the distribution of over 14,000 bloodstream isolates from the CDC's National Nosocomial Infection Surveillance (NNIS) hospitals from 1990 through 1996 *(64)*. BSI accounted for approximately 14% of healthcare-associated infections with gram-positive cocci including coagulase-negative staphylococci, *S. aureus*, and enterococci responsible for 56% of all HA-BSIs *(64)*. Unfortunately, since the mid-1990s, due to limitations in time and personnel resources, fewer and fewer hospitals participated in the hospital-wide surveillance component of the NNIS system and it was discontinued in 1999. However, the NNIS system continued to track healthcare-associated infections from targeted surveillance in intensive care units (ICUs). There was little change in the relative rank order of bloodstream isolates observed in ICU patients from 1990 to 1999. Table 19-2 summarizes this information (65). Pathogens varied by type of ICU with gram-negative pathogens such as *Enterobacter* sp. or *P. aeruginosa* causing BSI more frequently in burn ICUs than other types of ICUs (11.2% and 9.5%, respectively), whereas BSI due to *S. aureus* and coagulase-negative staphylococci occurred with greater frequency in coronary care and cardiothoracic ICU patients (23.2% and 42.7%, respectively) than in other ICUs (65).

NNIS has transitioned into the NHSN in the last decade and while NHSN includes a much larger number of institutions, it no longer reports HA-BSI data. Data on HA-BSIs has been less frequent as both national surveys and literature reports have focused on the syndromes responsible for HA-BSIs such as intravascular catheter infections, pneumonia, and UTI. Some literature has been published including a nationwide surveillance study (SCOPE) that described over 24,000 HA-BSIs from 1995 to 2002 (7). The gram-positive pathogens coagulase-negative staphylococci, *S. aureus*, and enterococci were most common in both ICU and non-ICU settings (62.5% and 59.3%, respectively). Coagulase-negative staphylococci, *Enterobacter* sp., *Serratia* sp., *Acinetobacter baumannii*, and *Candida* species were more common in the ICU while *S. aureus*, *Klebsiella* sp., and *E. coli* were more common in the general ward ($p < .001$). A notable finding in this study was the high incidence of BSIs due to *Candida* species, accounting for nearly 10% of HA-BSIs and increasing significantly from 8% in 1995 to 12% in 2002 ($p < .001$, trend analysis). *C. albicans* was the most common species isolated (54%) and *C. glabrata* (19%), *C. parapsilosis* (11%), and

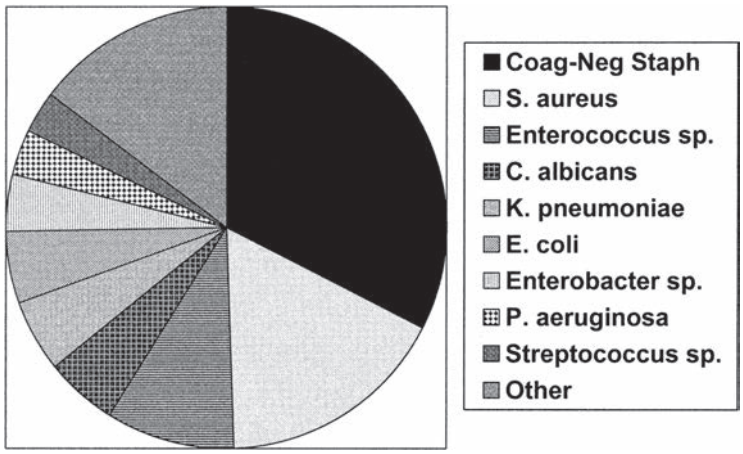

FIGURE 19-1 Microbial etiology of healthcare-associated bloodstream infection from 1990 to 1996.

TABLE 19-2

Pathogens Isolated from Intensive Care Unit (IC) Healthcare-Associated Bloodstream Infections, National Nosocomial Infections Surveillance Report (NNIS), 1992–1999 (*n* = 21,943)

Pathogen	*Number (%)*
Coagulase-negative staphylococci	8,181 (37.3)
Enterococcus sp.	2,967 (13.5)
S. aureus	2,758 (12.6)
C. albicans	1,090 (5.0)
Enterobacter sp.	1,083 (4.9)
P. aeruginosa	841 (3.8)
K. pneumoniae	735 (3.4)
E. coli	514 (2.3)
Other	3,774 (17.2)

(Reprinted from National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1990–May 1999, issued June 1999. *Am J Infect Control* 1999;27:520–532, with permission from Elsevier.)

C. tropicalis (11%) were also frequently isolated (7). Other centers have noted similar trends with candidal BSIs making up 10% or more of HA-BSIs (66,*67*,*68*). Some institutions have recently described a reemergence of gram-negative pathogens causing HA-BSIs. In a tertiary care center in the US from 1999 to 2003 the number of BSIs caused by gram-negative microorganisms significantly increased from 15.9% to 24.1% ($p < .001$) while infections due to coagulase-negative staphylococci and *S. aureus* decreased over the same time period ($p < .007$) (66). These findings have not been described nationally, but in some centers gram-negative pathogens have eclipsed gram-positives as the most common microorganisms causing HA-BSIs *(69,70)*. Factors possibly contributing to the increase in gram-negative pathogens include improved practices in the placement and maintenance of CVCs leading to decreased line-related gram-positive infections, increasing resistance in gram-negative isolates, and the emergence of microorganisms such as *A. baumannii* as major pathogens in the ICU. These trends in the etiology of HA-BSIs are described in Table 19-3.

As previously mentioned, during the 1980s a trend was observed indicating that HA-BSIs were increasingly being caused by antibiotic-resistant pathogens. This trend continued in the 1990s and worsened in the first decade of the 21st century. Klevens et al. *(71)* compared NNIS microbiologic data for the period 1990–1994 to 2000–2004 and noted significant increases in MRSA BSIs (27.0–54.1%), ceftazidime-resistant *P. aeruginosa* pneumonias (16.6–22.7%), and ciprofloxacin-resistant *E. coli* urinary tract infections (UTIs) (0.9–9.8%). The most recently published data from the NNIS system, summarizing bacterial isolates from ICU and non-ICU inpatient areas from January 1998 to June 2004, indicate an alarming prevalence of antimicrobial resistance *(72)*. These data are shown in Table 19-4. Using data from the SCOPE study that included HA-BSI from 49 hospitals from 1995 to 2002, Wisplinghoff et al. (7) described significant increases in the isolation of MRSA (22–57%), ceftazidime-resistant *P. aeruginosa* (12–29%), and vancomycin-resistant *Enterococcus faecium* (47–70%). The rise of resistant pathogens is a global phenomenon as a survey of over 81,000 BSI from three continents noted 2- to 3-fold higher rates of MRSA (38.5%), vancomycin-resistant enterococci (13.3%), ESBL *Klebsiella* sp. (24.6%), and multidrug-resistant *P. aeruginosa* (9.0%) in HA-BSIs compared to community BSIs *(73)*.

TABLE 19-3

Pathogens Isolated from Healthcare-Associated Bloodstream Infections, 1989–2003

	Cockerill et al. (85) 1989–1992, n = 9,109	*Lark et al. (47a) 1994–1997, n = 404*	*Wisplinghoff et al. (7) 1995–2002, n = 24,179*	*Corona et al. (77)[a] 2002–2003, n = 1,266*
Coagulase-negative staphylococci	10.4	27.3	31.3	26.9
S. aureus	18.4	15.4	20.2	24.3
Enterococcus sp.	6.2	10.4	9.4	10.8
E. coli	11.1	5.8	5.6	6.7
Candida sp.	14.0	5.8	9.0	7.6
Viridans streptococci	3.2	5.2	NR	NR
Pseudomonas sp.	4.3	5.0	4.3	9.9
Klebsiella sp.	5.2	3.0	4.8	8.5
Enterobacter sp.	3.8	2.6	3.9	5.9
Other GNR	6.2	2.4	3.0	8.2
Other	17.2	6.2	8.5	NR
Polymicrobic	NR	19.5	13.2	NR

Values represent percentage of total bloodstream isolates for pathogen in specific study.
[a]Total percentage >100% as more than one microorganism may be reported as cause of bacteremia.
NR, not reported; GNR, gram-negative aerobic rods.
(Data from references *7*,47a, *47, 77*, and *85*.)

TABLE 19-4

Prevalence of Antimicrobial-Resistant Phenotypes Among Healthcare-Associated Pathogens Isolated in CDC's National Nosocomial Infection Surveillance System From January 1998 to June 2004

Antimicrobial-Resistant Pathogens	*Mean Percentage Exhibiting Resistance Phenotype in ICU and Non-ICU Patients*	
	ICU	*Non-ICU*
MRSA	52.9	46.0
Methicillin-resistant coagulase-negative staphylococci	76.6	65.7
Vancomycin-resistant enterococci	13.9	12.0
Fluoroquinolone-resistant *P. aeruginosa*	34.8	27.7
Imipenem-resistant *P. aeruginosa*	19.1	12.3
Ceftazidime-resistant *P. aeruginosa*	13.9	8.8
Pipercillin-resistant *P. aeruginosa*	17.5	11.6
Cef3-resistant *Enterobacter* sp.	27.7	21.0
Cef3-resistant *K. pneumoniae*	6.2	5.8
Fluoroquinolone-resistant *E. coli*	7.3	8.2

MRSA, methicillin-resistant *S. aureus*; Cef3, third-generation cephalosporin.
(Reprinted from National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470–485, with permission from Elsevier.)

SOURCES OF BACTEREMIA

Most episodes of primary or laboratory-confirmed HA-BSI without an obvious source are thought to be due to intravascular catheters. These infections are discussed in depth in Chapters 17 and 18. Prior to the widespread use of intravascular catheters, HA-BSIs were largely secondary to infections at other sites. During the 1960s and 1970s, approximately 75% of HA-BSIs were secondary to surgical site infections, intra-abdominal infections, infections of the urinary tract, pneumonia, or skin and soft tissue infections *(74,75)*. Approximately two-thirds of these infections were due to aerobic, gram-negative bacilli *(74)*. As previously mentioned, in more recent years primary BSI has become more prevalent and staphylococci and enterococci have become more prominent pathogens. Pittet and Wenzel (76) noted that from 1981 to 1992 the proportion of HA-BSIs classified as primary BSIs increased from 51% to 71%. Over the same time period, the proportion of HA-BSIs due to coagulase-negative staphylococci increased from 12% to 30% and those due to aerobic gram-negative rods fell from 52% to 29%. SCOPE study data from 1995 to 2002 classified 77% of HA-BSIs as primary with 31% of primary BSI attributed to infections of intravenous catheters (7). UTIs and lower respiratory tract infections were other common sources of BSI (6.5% and 6%, respectively). Corona et al. (77) described HA-BSIs in 26 different countries and classified 58.3% as primary with 45% of primary BSIs being catheter-related. Other frequent sources of BSI included the respiratory tract (15.4%), gastrointestinal tract (8.9%), and wound infections (5.7%). While infections of intravenous catheters are the most common source of device-related HA-BSI other sources may be more common in specific populations. In the elderly and those undergoing urologic procedures, infections due to urinary catheters are the most common source of BSIs *(78)*.

Rates of bacteremia vary due to the pathogen and site of infection. For example, although healthcare-associated UTIs are common and account for 30% to 40% of healthcare-associated infections, they result in secondary bacteremia in only 0.4% to 4% of cases *(79–81)*. The rate of bacteremia secondary to healthcare-associated UTI appears to be higher with pathogens such as *Serratia marcescens* (16%) and is lowest in low virulence microorganisms such as coagulase-negative staphylococci (1.8%) *(82)*. Allen et al. *(61)* found that bacteremia was associated with 3.3% of healthcare-associated UTIs, 6.2% of surgical site infections, and 8.6% of lower respiratory tract infections. Petti et al. *(83)* recently noted in a community hospital setting that 9.1% of surgical site infections were associated with bacteremia. *S. aureus* surgical site infection was associated with an almost 3-fold increased rate of bacteremia compared to other microbes *(83)*. Table 19-5 characterizes the relative contribution of various sites to overall rates of secondary bacteremia (7,76,77,*84*).

Two additional trends in the microbiology of HA-BSI should be noted. First, a significant proportion of BSIs are due to multiple microorganisms with up to 15% to 20% of HA-BSIs being polymicrobic *(85,86)*. Pittet and Wenzel (76) observed from 1980 to 1992 that polymicrobic HA-BSIs increased from 8 episodes/10,000 patient-days to approximately 20 episodes/10,000 patient-days, which equated to a rise from 11% to 14%. Polymicrobic infections are more common in elderly patients *(87)*, neonates *(88)*, patients with underlying gastrointestinal disorders or on parenteral nutrition *(89,90)*, and patients with underlying malignancies *(91)*. Polymicrobial BSIs are also frequent in patients with candidemia. Klotz et al. *(92)* found 24% of patients with candidemia also had synchronous bacteremia and 3% had more than one species of *Candida* present *(92)*. In addition, polymicrobic infections are more likely to be associated with mortality than monomicrobic infections *(93)*. A second trend is that along with an increase in HA-BSIs due to yeast, a shift in the microbiology of yeast has occurred. Increasingly, non-albicans *Candida* sp. are being recovered from blood cultures. Edmond et al. *(94)* noted that half of *Candida* BSIs were due to species other than *C. albicans*, and in 34 medical centers throughout North America and Latin America, 46% of 306 episodes of candidemia were due to non-albicans species of *Candida* (95). Similar trends were seen in NNIS system hospitals and a large multicenter database (PATH Alliance database) *(96,97)*. The increasing prevalence of non-albicans

TABLE 19-5

Relative Contribution of Anatomic Sites to Overall Healthcare-Associated Bloodstream Infection (7,76,77,84)

Study (Author, Reference, No. of Subjects, Years of Study)				
Site Responsible for BSI	***Mylotte et al. (84) n = 1,365, 1979–1987***	***Pittet and Wenzel (76) n = 3,464, 1980–1992***	***Wisplinghoff et al. (7) n = 24,179, 1995–2002***	***Corona et al. (77) n = 1266, 2003–2003***
Primary	34.1	59	77	58.3
Intravascular catheter	—	—	24	26.3
Intra-abdominal	5.5	2.0	—	8.9
Urinary tract	21.2	8.3	6.5	3.2
Lower respiratory tract	13.4	12	6.0	15.4
Skin/soft tissue	—	—	—	1.7
Surgical site	4.4	10	—	4.7
Other	19.1	—	—	4.6

species as a cause of HA-BSI has been attributed to the increased use of imidazole antifungal agents and CVCs *(67,98)*.

HEALTHCARE-ASSOCIATED BSI IN SPECIFIC PATIENT POPULATIONS AND CIRCUMSTANCES

HA-BSIs are more common in certain patient populations. Healthcare-associated infections in many of these specific groups of patients (elderly, neonates, ICU patients, burn patients, etc.) are discussed more thoroughly in other chapters of this text. The following is a concise summary of issues related more specifically to HA-BSIs.

Elderly and Long-Term Care

Older age (>65 years old) has been noted as a predisposing factor for healthcare-associated bacteremia and an indicator for worse outcome (99,*100–102*). Some authors have reported that the rates of BSIs per hospitalization in the elderly appear to be increasing, but others noted no change in ICU BSI incidence over 18 years *(102,103)*. Incidence rates of BSI increase with age and are highest in the most aged population *(104)*. Mortality rates also increase with age and hospital mortality has been reported to exceed 50% in patients over 75 years *(102)*. Mylotte et al. (99) reviewed the literature on BSIs in nursing home residents and estimated the incidence of BSI to be approximately 0.3 episodes/1,000 patient-days with mortality ranging from 18% to 35%. Staphylococcal species including *S. aureus* (12–24%) and coagulase-negative staphylococci (10–24%) are the most common cause of HA-BSI in the elderly, but *E. coli* is the single most common pathogen (9–32%) *(102,104,105)*. MRSA BSIs are more common among those older than 65 but other forms of resistance (vancomycin-resistant enterococci and ESBL-producing pathogens) have not been associated with increasing age *(73)*. Intravascular devices are the most common source of BSIs (14–41%) followed by the urinary tract (8–25%), lung (8–14%), and abdominal sources (7–11%) *(102,105,106)*.

Neonates and Pediatrics

General considerations regarding healthcare-associated infections in neonates and pediatric patients are discussed thoroughly in Section VI (Chapters 48–52). Previously BSI rates in these patients were generally higher than the adult population, but more recent data suggest a decrease in the rate of HA-BSI among children and neonates to near adult levels *(107)*. Neonatal BSI, during the initial period after birth, is most often a result of infection of the birth canal or maternally acquired microbes. Late-onset BSIs are usually due to healthcare-associated microorganisms. BSI is the most commonly observed healthcare-associated infection in neonates in the NHSN system and is estimated to account for 40% of infections depending on birth weight category *(5,107)*. Low birth weight is a major risk factor for HA-BSI with each 100 g decrease in birth weight conferring an additional 9% risk of BSI *(108)*. The U.S. National Institute of Child Health and Human Development documented that late-onset BSI was commonly due to the healthcare-associated pathogens coagulase-negative staphylococci (55%), *S. aureus* (9%), enterococci (5%), and *Candida* sp. (7%) *(109,110)*. A recent development has been the spread of MRSA to neonates. NNIS data from 1995 to 2004 showed a 308% increase in MRSA infections in neonatal ICUs *(111)*. Primary BSI is the most common source of HA-BSI in neonates with up to 85% of BSIs considered primary (*108*,112). Intravascular catheter use is the major risk factor for primary BSI in neonates, and data from the NHSN system from 2006 to 2008 documented BSI rates ranging from 1.9/1,000 CVC days to 3.9/1,000 CVC days, depending on birth weight classification *(107)*. Lastly, administration of certain therapies strongly increases the risk of bacteremia due to specific pathogens. For example, fungemia due to *Malassezia furfur* is seen almost exclusively in infants receiving intravenous lipids *(113)*.

Among nonneonatal pediatric patients BSIs were responsible for 21% to 34% of healthcare-associated infections depending on the age of the patient *(114,115)*. Risk factors for HA-BSI among children are similar to adults and include the use of CVCs and other invasive devices, but more unusual risk factors such as the presence of a genetic syndrome have also been reported to increase the

TABLE 19-6

Pathogens Isolated from Healthcare-Associated BSI in Neonates and Children ≤16 Years, 1995–2001, *n* = 3558

	Percentage of Isolates		
Pathogen	***Age <1 y***	***Age 1–5 y***	***Age >5 y***
Coagulase-negative staphylococci	46.3	39.0	31.0
Enterococci	9.1	7.1	12.6
Candida sp.	9.3	8.2	10.5
S. aureus	8.4	10.3	12.4
Klebsiella sp.	5.8	5.2	6.5
E. coli	5.4	3.2	3.4
Enterobacter sp.	5.1	4.1	5.1
P. aeruginosa	2.4	5.4	5.3
Streptococcus sp.	2.3	5.2	4.5

(From Wisplinghoff H, Seifert H, Tallent SM, et al. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. *Pediatr Infect Dis J* 2003;22:686–691, with permission.)

risk of a BSI *(114,116)*. Similar to the experience observed in adult patients, the most frequently recovered pathogens are coagulase-negative staphylococci, enterococci, and *S. aureus*; *Enterobacter* sp. and *P. aeruginosa* are the most commonly observed gram-negative pathogens, and *C. albicans* is responsible for around 10% of pediatric HA-BSIs (112,*115*,*117*). Table 19-6 summarizes the pathogens found most commonly in neonatal and pediatric HA-BSIs (112).

ICU Patients

ICU patients account for a disproportional share of healthcare-associated infections compared to other patients. Despite only making up 5% to 10% of all hospital beds, a national survey of 49 institutions found 51% of all HA-BSIs occurred in the ICU (7). A large multicenter study in France, noted the risk of HA-BSI was 12-fold greater in ICU patients than in ward patients *(118)*. (For an extensive description of ICU-associated HA-BSI, see several recent reviews and studies that will be briefly discussed herein (119,*120–123*)). Table 19-7 summarizes observations from several studies concerning ICU BSI. The rate of HA-BSI in ICU patients has been increasing and is primarily due to intravascular catheters, lower respiratory tract infections, and intra-abdominal infections. A multicenter trial matched ICU HA-BSI cases on severity of underlying illness and risk-exposure time and noted that HA-BSIs were associated with a 3-fold increase in mortality *(123)*. Overall mortality is approximately estimated at 40%. Similar to HA-BSI throughout the hospital, the gram-positive cocci are the most frequent etiology and most often associated with line-associated or primary BSI. Gram-negative pathogens are more frequently present in lower respiratory tract, urinary tract, and surgical infections *(123)*. In a surgical ICU population Mainous et al. *(124)* noted that enterococci were the most common cause of HA-BSI. Polymicrobic infections are observed in 10% to 20% of bacteremic patients. The prevalence of polymicrobic infections depends on the ICU setting and is most common in surgical ICUs that care for a larger number of patients with intra-abdominal infections *(10,118,121)*.

Multidrug-resistant pathogens, particularly gram-negative microorganisms are an increasing problem in hospitals and resistance rates are higher in the ICU than the general ward *(73)*. These microorganisms are important not only for their infection control implications, but their presence impacts empiric therapy choices and patient outcomes. MRSA and multidrug-resistant *P. aeruginosa* were associated with increased mortality in primary BSI and hospital-acquired pneumonia, respectively, when compared to sensitive microorganisms of the same species *(125)*. The reason for increased mortality from resistant microorganisms may be inadequate initial therapy. A retrospective review of over 5,700 patients with septic shock, including 2,300 with BSI, noted inappropriate therapy (i.e., therapy not active against the pathogen) was given in 19.9% of cases and was associated with a 5-fold reduction in survival *(126)*. In contrast, Corona et al. (77) prospectively evaluated >1,700 ICU patients with BSI and found that initial receipt of ineffective therapy did not alter patient outcomes, but increasing age, severity of illness and immunosuppression were associated with increased mortality. Blot et al. *(127)* reviewed their experience in ICU patients with HA-BSI due to gram-negative bacteria and noted no increased association with mortality in relation to antimicrobial resistance. Similarly, no increase in mortality was observed in patients with HA-BSI due to ESBL-producing Enterobacteriaceae in comparison to those with bacteremia due to non–ESBL-producing strains *(128)*. Similar findings have been noted in patients with resistant gram positive infections such as VRE suggesting that underlying patient factors have the dominant effect on patient outcomes *(129)*. Determining the clinical significance of antimicrobial resistance is difficult as severely ill patients who are more likely to be colonized with resistant pathogens, and many studies that evaluate resistance have not controlled for the severity of underlying disease and further more definitive studies are still needed.

A. baumannii is an increasingly important gram-negative pathogen in the ICU. Healthcare-associated infections due to *A. baumannii* occur late in hospitalization (16–26 days after admission on average), most often involve the respiratory tract and intravascular catheters, and are typically multi-drug resistant (7,*130*,*131*). Risk factors independently associated with *A. baumannii* BSI have included immunosuppression, prior antibiotic therapy, unscheduled hospital admission, respiratory failure, prior ICU sepsis, previous *A. baumannii* colonization, cardiovascular failure, and the invasive procedure index *(130,131)*.

Neutropenia/Oncology Patients

It has long been known that patients with underlying oncologic diseases and/or neutropenia are more likely to experience HA-BSI *(132–134)*. These conditions are discussed more fully in Chapters 57 and 59. Rates of BSI vary based on the type of malignancy and the intensity of chemotherapy with patients with hematologic malignancies at a greater risk of HA-BSI than patients with solid tumors *(135)*. Gram-positive pathogens, most commonly coagulase-negative staphylococci, have

TABLE 19-7

Healthcare-Associated Bloodstream Infections in ICU Patients

Author/Reference/ Year(s)	*No. BSI*	*Rate of BSI (per 1,000 ICU admissions)*	*Source of BSI (%)*	*Mortality (%)*	*Comment*
Crowe et al. *(121)*, 1985–1996	315	Increased from 17.7 (1985) to 80.3 (1996)	IVC 24.5, LRTI 39.7, GI 7.3, UTI 4.1, SSI 2.2, CNS 5.1, Unk 8.9	44.4	Single ICU
Valles et al. *(120)*, 1993	590	36	IVC 37.1, LRTI 17.5, GI 6.1, UTI 5.9, SSI 2.4, Unk 28.1, Other 2.9	41.6	Multicenter study, length of ICU stay for patients with BSI 28.5 days
Edgeworth et al. *(122)*, 1971–1995	486	Increased from 17.4 (1971–1975) to 38 (1991–1995)	IVC 62, LRTI 3, GI 6.9, UTI 2.4, SSI 3, Unk 22.5, Other 2.9	Decreased from 44% (1971–1975) to 31% (1991–1995)	Single ICU
Garrouste-Orgeas et al. *(123)*, 1997–2004	232	71	Primary 32.7, IVC 20.2, LRTI 16.4, SSI 9.9, UTI 2.6, Other 18.1	61.6%	Multicenter study, BSI increased mortality 3-fold over severity matched control patients

IVC, intravenous catheter; LRTI, lower respiratory tract infection; GI, gastrointestinal/intra-abdominal; UTI, urinary tract infection; SSI, surgical site/skin, soft tissue infection; CNS, central nervous system; Unk, unknown.

replaced gram-negative pathogens as the most frequently isolated etiologic agents *(136,137)*. This is likely due to the increased use of intravascular catheters and widespread use of prophylactic agents directed at gram-negative microorganisms for patients with neutropenia *(136,138)*. Risk factors for development of BSI in this population include hematologic malignancy, cytotoxic chemotherapy resulting in neutropenia and mucositis, graft versus host disease in bone marrow transplant patients, and the presence of intravascular catheters or other invasive devices (*132*,*134*,*139*,140).

Cirrhosis/Chronic Liver Disease

Patients with cirrhosis are predisposed to a variety of infectious complications including bacterial peritonitis and HA-BSI *(141)*. Campillo et al. *(142)* studied 200 cirrhotic patients in whom 194 episodes of bacterial peritonitis and 119 episodes of BSI were documented over a 5-year period; 93.3% of these infections were healthcare-associated, and *S. aureus*, specifically MRSA, was the most commonly observed pathogen, responsible for 39.5% of cases. The mortality rate was 49.5% for patients with healthcare-associated BSI versus 23.8% for patients with community-acquired BSI *(142)*.

Burn Patients

Thermal injury destroys the barrier function of the skin and is often complicated by burn wound infection and bacteremia *(143)*. *S. aureus*, particularly MRSA is the most frequent pathogen encountered in BSI in burn patients, followed by *P. aeruginosa* and other healthcare-associated gram-negative bacilli *(144–146)*. Enterococci and *Candida* have become more problematic in more recent years *(144–146)*.

Spinal Cord Injury Patients

HA-BSI in spinal cord injury patients is largely secondary to UTI (25–47%), infected pressure sores (19%), and pneumonia (9%) *(147,148)*. Resistance to antibiotics is common in this population with up to 65% of patients having resistant pathogens including MRSA and multidrug-resistant gram-negative bacilli *(149)*. Predisposing conditions include indwelling urinary catheters, ventilator dependency in quadriplegics, and pressure sores. Prevention of BSI requires prevention of the primary infectious complications associated with spinal cord injury. HA-BSIs in patients with spinal cord injuries are discussed more fully in Chapter 56.

Hemodialysis

Over 300,000 persons are maintained on hemodialysis in the United States. These patients experience BSI at a rate of approximately 0.6 BSI/1,000 patient-days, which equates to approximately 65,000 BSIs per year *(150)*. Approximately 80% of BSIs in hemodialysis patients are related to vascular access and 20% are secondary to infections at other sites, most frequently UTI and lower respiratory tract infections *(17)*. Primary BSI is much more likely in patients whose vascular access is achieved through intravascular catheters than those with arteriovenous fistula or synthetic grafts. Klevens et al. *(5)* summarized data reported by 32 dialysis centers to NHSN in 2006 and noted rates of BSI per 100 patient-months based on the type of access is as follows: fistula (0.5), graft (0.9), permanent central line (4.2), and temporary central line (27.1). Primary HA-BSI in hemodialysis patients is described more fully in Chapter 63.

Solid Organ Transplant Patients

Healthcare-associated infections in solid organ transplant recipients are discussed in detail in Chapter 58. A few specific issues regarding HA-BSI are as follows:

Renal Prior to the widespread use of posttransplant antibiotics, 50% to 70% of renal transplant patients developed UTI with a 40% incidence of bacteremia *(151)*. Although prophylactic antibiotics have significantly reduced the incidence of UTI to 5% to 10%, UTI remains responsible for 40% to 60% of episodes of bacteremia in kidney transplant patients *(152,153)*. Gram-negative bacilli are responsible for between 60% and 80% of bloodstream isolates, with *E. coli*, *Pseudomonas* sp., *Klebsiella* sp., and other Enterobacteriaceae most prominently represented *(152,153)*.

Liver HA-BSI occurs in approximately 10% of liver transplant recipients *(153)*. The most common source of BSIs is intravascular catheters and is predominantly due to gram-positive cocci *(153,154)*. HA-BSIs due to gram-negative bacilli have been increasing in frequency and are usually secondary to intra-abdominal or biliary tract infections *(155–157)*. Antibiotic-resistant pathogens including MRSA, VRE, and ESBL-producing gram-negative bacilli are being increasingly described as significant pathogens following liver transplantation and are associated with significant morbidity and mortality *(153,155)*.

Small Bowel Healthcare-associated bacteremia is a common complication of small-bowel transplantation with approximately 80% of small-bowel recipients developing at least one bacterial infection within the first 2 months after transplant *(158)*. Intravascular catheter and intra-abdominal infections are the most common sources in this patient group *(158,159)*. BSIs also occur in patients with organ rejection due to altered permeability of the small-bowel allograft *(160)*.

Lung Approximately 10% to 25% of lung transplant recipients experience a BSI within the year after transplant with pulmonary and line-related BSI being most common *(153,161,162)*. MRSA, *P. aeruginosa*, and *A. baumannii,* and *Candida* species are commonly observed pathogens *(153,161,162)*.

Heart HA-BSI occurs in roughly 10% of heart transplant recipients and most commonly stems from a pulmonary, intravascular catheter, or surgical site source *(153,163)*.

Pancreas HA-BSI occurs in 10% to 20% of pancreatic transplant patients *(153,157,164)*. Surgical site infections, line-related BSI, and UTIs (particularly in kidney-pancreas transplant patients) are the most common identifiable sources for bacteremia.

Transient Bacteremia

A large variety of medical procedures can result in transient bacteremia. Although many of these episodes might not be considered "healthcare-associated" in a strict classification scheme, they would oftentimes qualify as "healthcare-associated" bacteremia. In most instances, transient healthcare-associated bacteremia does not result in significant infection due to efficient host defense mechanisms designed to filter and interdict circulating pathogens. However, in some groups of patients, transient bacteremia can result in infection. Roberts et al. *(86)* noted that 7% of almost 2,000 positive blood cultures were due to transient bacteremia; 71.6% of these episodes were due to gram-positive cocci (39% coagulase-negative staphylococci, 23% viridans streptococci). Transient bacteremia has been well documented to result from dental procedures. Although tooth brushing and tooth flossing cannot usually be considered a healthcare-associated source, they result in transient bacteremia in up to 86% of patients *(165–167)*. Similarly, tooth extraction results in a very high percentage of patients experiencing transient bacteremia *(168,169)*, and antibiotic prophylaxis is recommended to prevent endocarditis in patients at high risk for developing this condition *(170)*. Numerous other procedures have been documented to result in transient bacteremia and occasional infection and include endotracheal intubation *(171,172)*; lachrymal duct probing *(173)*; burn wound manipulation *(174)*; gastrointestinal endoscopy, including gastroscopy, scleral therapy, sigmoidoscopy, colonoscopy, esophageal dilatation, and polypectomy *(175–180)*; chorionic villous sampling *(181)*; nephrostomy tube manipulation *(182)*; minor dermatologic surgery *(183,184)*; urologic endoscopy and transurethral prostatic resection *(185)*; replacement of intrauterine contraceptive devices *(186)*; barium enema *(187)*; and percutaneous liver biopsy *(188)*. The significance of bacteremia in most of these settings is debatable, and the rationale for and benefits of antibiotic prophylaxis is often minimal *(170,189,190)*.

BLOOD CULTURE CONTAMINATION OR PSEUDOBACTEREMIA

Pseudobacteremia, false-positive blood cultures, and blood culture contamination all refer to the problem in which microbes from a site outside the bloodstream are introduced into the sample of blood obtained for culture. This is a widespread phenomenon and occurs in 1% to 5% of cultures even under optimal conditions and up to 50% of positive cultures may represent contamination *(24,48,191,192)*. The implications of blood culture contamination are significant and include increased cost due to additional cultures and tests needed to investigate culture positivity, unnecessary antibiotics, side effects and toxicity due to the antibiotics, increased length of hospital stay and inappropriate admission to the hospital. The total excess cost associated with blood culture contamination was $4,385/patient in one study and $4,100/patient in another *(26,193)*.

Differentiating contamination from true bacteremia must be done clinically by consideration of the microbe recovered from the blood, clinical presentation, number and source of positive cultures (line vs. peripheral), and incubation time to positivity. It should be noted, however, that discounting single positive cultures with skin flora microbes (coagulase-negative staphylococci) may lead to misdiagnosis in up to 25% of clinically significant bacteremic episodes due to these microorganisms, particularly in patients with CVCs (*35*,53). Measures to prevent contamination were discussed in the section on clinical microbiology (see also Chapter 9).

PREVENTION OF HEALTHCARE-ASSOCIATED BACTEREMIA

The prevention of HA-BSI requires prevention of intravascular catheter infections and other sites of infection (pneumonia, UTI, wound infection, etc.). Prevention of infection associated with intravascular catheters is best achieved by having catheters inserted in the least infection prone site (subclavian vein) by trained personnel using appropriate precautions (full sterile barrier precautions) and effective skin antisepsis (chlorhexidine). Additionally, great care must be exercised in accessing the catheters and in routine site care. The combination of these interventions into a standardized protocol has been shown to be highly effective *(194)*. These measures are discussed in detail in Chapters 17 and 18 and both the CDC Hospital Infection Control Practices Advisory Committee (HICPAC) and The Society for Healthcare Epidemiology of America (SHEA) have published guidelines addressing these practices *(195)*.

Similarly, to prevent urinary catheter–associated infection and the potential complication of HA-BSI both CDC HICPAC and SHEA have recently published evidenced based guidelines recommending that urinary catheters should be used only when necessary, inserted with careful attention to aseptic technique, carefully maintained, and removed as soon as possible *(196,197)*. The use of antiseptic-bonded urinary catheters has shown promise in prevention of healthcare-associated UTI, although further research is needed to clarify the role of coated catheters and their routine use is not currently recommended *(80,196–198)*. These preventive measures are discussed in greater detail in Chapter 20.

Prevention of healthcare-associated and hospital-acquired pneumonia requires a multidisciplinary approach designed for the provision of appropriate care to patients receiving mechanical ventilation and other high-risk groups. Both the CDC HICPAC and SHEA have issued guidelines for the prevention of healthcare-associated pneumonia and ventilator-associated pneumonia *(199,200)*. Strategies advocated include minimizing the use and duration of invasive ventilation, minimizing contamination of respiratory equipment, following rigorous hygiene and infection control practices, preventing aerodigestive colonization with pathogens, and taking steps to prevent subsequent aspiration of these pathogens (see also Chapter 22).

Prevention of surgical site infections requires careful attention to preoperative risk factor reduction, timely administration of prophylactic antibiotics, aseptic surgical technique, and appropriate wound care. A more comprehensive discussion can be found in Chapter 21 and the CDC HICPAC and SHEA guidelines *(201,202)*.

Specific recommendations for prevention of healthcare-associated infection and, hence, secondary bacteremia can be found throughout this text in sections detailing specific infections and specific patient populations and care settings.

PREDICTION MODELS FOR HEALTHCARE-ASSOCIATED BSI AND CHALLENGES FOR THE FUTURE

Clinicians tend to make decisions regarding diagnosis and prognosis based on overall clinical judgment and anecdotal experience. Unfortunately, the inability of physicians to accurately predict the presence of bacteremia has been noted *(203)*. Therefore, investigators have attempted to develop quantitative predictive models to assist clinicians in their recognition of bacteremic patients. HA-BSIs are associated with a variety of risk factors, many of which have been previously discussed, such as age, use of intravascular catheters, underlying diseases and conditions, severity of illness, and healthcare worker understaffing. Taking many of these factors into account, a number of investigators have developed predictive models *(204–207)*. In general, these models are not specific for HA-BSI, and their clinical utility remains unknown. Recently, as our understanding of the pathogenesis of sepsis has improved, a number of investigators have attempted to correlate various proinflammatory markers and other factors with bacteremia and outcome in several patient populations *(208,209)*. One of the most promising markers is the molecule procalcitonin. Procalcitonin elevations are predictive of systemic bacterial infection and elevations in procalcitonin have been found useful in the prediction of BSIs *(210–212)*. The combination of clinical predictive models with biomarkers such as procalcitonin, particularly if coupled with electronic decisions support, holds the most promise for predicting BSI. These markers and models have not been specifically applied to patients with healthcare-associated infections, and further validation is required.

HA-BSIs will likely remain a significant medical problem as the number of high-risk patients and the use of invasive devices continues to increase. Increased numbers of outpatient surgical procedures, shorter hospital stay, utilization of outpatient intravenous infusion services, and expanding populations of hemodialysis patients, residents of long-term care facilities, and immunocompromised hosts will influence the occurrence of BSI. Healthcare epidemiologists will continue to be challenged with the question of how to operate surveillance systems to monitor HA-BSI in the rapidly changing healthcare arena. It is encouraging to note that an improved understanding of the pathogenesis, predisposing risk factors, and underlying causes of HA-BSI has led to numerous evidence-based interventions that have had a significant impact on healthcare-associated infection rates. Future work will hopefully lead to further improvement in prevention and detection of this ongoing problem.

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CHAPTER 20

Healthcare-Associated Urinary Tract Infections

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Urinary tract infections (UTIs) are the most common healthcare-associated infections in both acute care hospitals and long-term care facilities, accounting for about 40% of all healthcare-associated infections and constituting a major source for healthcare-associated septicemia and related mortality. The rates of healthcare-associated UTIs are similar in both adult and pediatric patients *(1)*, and nearly all such infections are associated with urinary tract instrumentation. In acute care hospitals, the vast majority of UTIs occur in patients with temporary indwelling bladder catheters; the remaining ones are usually related to cystoscopy and other urologic procedures. The costs for the prevention, detection, treatment, and complications of these infections add significantly to the nation's healthcare bill.

The catheterized urinary tract is also a model of the growing problem of infections related to the placement of a foreign body in a patient's tissues. So-called device-associated infections are important both because of their high frequency and expanding number of different types of devices, and because they appear to be the most preventable of all healthcare-associated infections *(2)*. Their prevention depends on the oldest and most basic tenets of infection control as well as on the promise of technologic advances to develop safer instruments *(3)*. By virtue of being device-related and the most common healthcare-associated infection, catheter-associated UTIs (CA-UTI) are also increasingly a focus of the patient safety movement.

Urinary catheters are characterized by site of insertion (e.g., urethral, suprapubic, or nephrostomy) and by duration of use (e.g., intermittent or indwelling). Modern catheters are typically manufactured of latex rubber, silicone- or Teflon-coated latex rubber, or solid silicone, and come in a bewildering variety of types and sizes *(4)*. The indwelling Foley catheter with a retention balloon was first developed in 1927 by Frederick E. B. Foley to control bleeding in patients after transurethral prostatectomy *(5,6)* and is still essential to modern medical care. It is used today to drain the functionally or anatomically obstructed urinary tract, to control drainage in incontinent patients, and to obtain precise measurement of urinary output (7). Although the most mundane of invasive devices, it is the single most frequent cause of healthcare-associated infection. Major questions regarding its use and care—not to mention alternatives to its use—remain unanswered.

Infections associated with urinary catheters occur in both endemic and epidemic circumstances; common-source outbreaks are infrequent, although an estimated 15% of endemic infections occur in clusters, presumably from cross-infection *(8)*. Most TIs—whether endemic or epidemic—are asymptomatic, and removal of the catheter is usually curative. The usually benign nature of catheter-associated UTIs and the perception that they are easily treated by antibiotics may inhibit aggressive measures for both their prevention and their recognition.

Nevertheless, today's complacency of clinicians toward the continued high occurrence of UTIs should not diminish recognition of the remarkable achievements of the last several decades in their prevention. Indeed, this is one of the most successful chapters in the history of infection control. In the past, UTIs were generally accepted as an inevitable consequence of indwelling bladder catheterization. However, in the 1950s, the effectiveness of closed sterile urinary drainage, which had first been proposed by Cuthbert Dukes at London's St. Mark's Hospital more than 30 years earlier (9), was finally established. Its introduction proved a landmark in infection control (*10,12*,13). Commercially available systems for closed drainage into sterile plastic bags now enable the prevention of UTIs in 70% to 85% of patients with temporary indwelling catheters (*14*,15,16,*17*).

The benefits of closed drainage systems have not been fully documented because routine surveillance of healthcare-associated infections did not exist before the 1970s. Furthermore, current surveillance methods that focus on catheter days are a recent development. According to a recent National Healthcare Safety Network (NHSN) report, healthcare-associated UTI rates ranged from 0.4 to 6.6 per 1,000 urinary catheter-days for the 10th to 90th percentile in medical/surgical intensive care units at major teaching hospitals *(18)*. Thus, in contrast to the era prior to closed drainage systems, even in severely ill patients the use of closed sterile drainage, when properly maintained, currently prevents infection in the overwhelming majority of patients in whom this device is placed for short-term use.

The challenge of preventing UTIs has multiplied with changes in the character of hospitalized populations. These changes are often enumerated: the increased numbers of patients with advanced age and more severe underlying illnesses, the emergence of specialized units for the care of

critically ill patients, the increased use of multiple invasive devices, the growing population of immunosuppressed patients, and the expanding use of organ transplantation. Such factors may have increased both the use of indwelling catheters and the susceptibility of catheterized patients to infection. Even today, despite significant progress, virtually all patients with chronic indwelling bladder catheters are continuously infected. Moreover, as a result of the extensive use of broad-spectrum antimicrobial agents and the emergence of multiply resistant pathogens, patients with urinary catheter–associated UTIs also harbor an increasingly formidable reservoir of antibiotic-resistant pathogens *(19–22)*.

All urinary catheters may induce UTIs, but indwelling catheters have additional hazards; for example, they may also obstruct the periurethral glands, producing urethritis, epididymitis, or urethral stricture. Paul Beeson (23) was one of the first, in 1958, to advise caution in the use of urinary catheters: "At times, the catheter is indispensable for therapy and there are many good indications for its use. Nevertheless, the decision to use the instrument should be made with the knowledge that it involves the risk of producing serious disease which is often difficult to treat." Many investigators, stimulated by Beeson's admonition and the controversy it aroused, have added to our knowledge of the pathogenesis, epidemiology, and prevention of these infections. Although the remaining problems should not be underestimated, the grounds for optimism have been summarized by Calvin Kunin *(24)*: "In the current era of magnificent biotechnological advances, we should be able to solve the apparently simple but very important problem of draining the urinary bladder without producing infection."

EPIDEMIOLOGY

Catheter Use

The problem of healthcare-associated UTI appears to be deceptively simple: the major extrinsic risk factor is the use of a device that bypasses host defense mechanisms and allows microorganisms to grow in normally sterile body sites. Yet, the pathogenesis is far more complex than is implied by a purely mechanical model, and the epidemiology of the use and complications of urinary catheters is today understood only in its broad outlines.

The relative neglect of this problem by investigators undoubtedly reflects the low importance assigned to UTIs both by clinicians and by infection control programs. Indeed, in 2001, Jarvis *(25)* reported no epidemics of UTIs among 114 healthcare-associated outbreaks that the Centers for Disease Control and Prevention (CDC) investigated on-site in the previous decade *(25)*. Although this could suggest that the CDC did not elect to participate for various reasons or that individual hospitals simply did not request the CDC's help, underreporting or failures of surveillance are also likely explanations.

Healthcare-associated UTIs present unique challenges for epidemiologists. Because endemic UTIs occur throughout the hospital and because healthcare-associated epidemics often involve multiple sites of infection, epidemic rates of catheter-associated UTIs may not be readily apparent unless they involve an unusual microbial species *(26)*. Indwelling urinary catheters are used in nearly all hospital nursing units, unlike ventilators and many other devices. For this reason, healthcare-associated UTIs have complex behavioral and social determinants.

Duration of indwelling catheterization is the most important risk factor for the development of catheter-associated infection. Overall, the mean and median durations of catheterization in acute care hospitals are 2 and 4 days, respectively, and catheters are removed within 7 days in nearly 70% of patients *(27)*. Although the prevalence of infection increases steadily with extended durations of catheterization, the daily incidence of newly acquired infection is relatively constant during closed drainage, at least for the first 10 days, with 2% to 16% of previously uninfected patients acquiring infection each day (28,29). Infection becomes nearly universal by 30 days. Nonetheless, this is a dramatic improvement over open drainage systems, for which universal infection followed just 4 days after insertion *(30)*.

Thus, the principal benefit of closed drainage has been to delay, if not prevent, the onset of infection. True prevention begins by avoiding unnecessary catheter use. Catheters that must be used should be removed at the earliest possible time. Unfortunately, epidemiologists have not fully exploited the potential of these simple principles. Studies in many countries suggest that more restrictive policies for catheter use would be beneficial *(31–45)*. Though patterns of use in other countries may differ from those in the United States, investigators in Denmark and Sweden determined that indwelling catheters were used in 13% of patients and 12% of hospital days, respectively, and there was great variation between hospitals for the same type of nursing service *(32,33)*. Catheter usage is most prevalent in ICUs; data from NHSN that examine utilization of urinary catheters indicate that 54% to 90% of all ICU days in medical/surgical intensive care units at major teaching hospitals involve the use of a urinary catheter, in the lowest 10th percentile to the 90th percentile, respectively, of reporting hospitals *(18)*. A study in Israel suggested that patients with intermediate durations of catheterization (7–30 days) and who are catheterized for the indications of obstruction or incontinence are a high-risk group that may benefit most from intervention *(35)*. Such patients had a higher daily risk (8.6%) of acquiring infection even during the early period of catheterization. In Canada, an investigation of overutilization of indwelling urinary catheters in a large tertiary-care hospital found that 20.3% of patients admitted via the emergency room were catheterized upon admission *(36)*. Furthermore, 50% of catheters were inserted for unjustifiable reasons and 60% of those patients who subsequently developed UTI did not meet the study's criteria for justifiable catheterization. Another study found that 21% of catheterized medical patients did not have any initial indication for placement of the urinary catheter and that continued catheterization was unjustified in 47% of patient-days studied *(37)*.

Other recent studies have produced similar findings. For example, 10.7% of patients on a medical service had an indwelling urinary catheter inserted within the first 24 hours, with 91% having been placed in the emergency room and 38% deemed inappropriate *(38)*. Another study

of emergency department patients found appropriate indication for catheter placement correlated with documentation of a physician order in the chart; only 52% were deemed appropriate in those without orders versus 73% to 82% with orders *(46)*. In a point prevalence study from Spain, only 22% of patients had a correct indication with adequate drainage systems *(39)*.

Lack of awareness of the presence of an indwelling catheter is a further problem. One group found that physicians were not aware of the catheter status in 28% of their patients and in as many as 41% of those whose catheterization was judged inappropriate *(40)*. Thus, physicians appear to discount the importance of the urinary catheter, leading to overuse and misuse, for example, for inappropriate indications such as nursing staff convenience. In a study of patients with urinary incontinence, 37.5% were catheterized even though 55.5% of these were previously incontinent before admission to hospital and had managed this problem by other noninvasive methods. The decision to catheterize was made by physicians in 31.7% and by nursing staff in 37.3% *(41)*. Recent studies directed at prevention of unnecessary catheter use have shown some success of nursing education as a means to reduce the use of urinary catheters. Reinforcing strict adherence to approved indications and use of alternatives to bladder catheterization in non-ICU settings were associated with decreased overall incidence of healthcare-associated UTI through reduction in catheter use. CA-UTI incidence in those with bladder catheters did not change *(44)*. Less comprehensive approaches to reduce duration of urinary catheter use, such as simple reminder systems, have been shown to reduce the median duration of catheter use in an ICU setting from 5 to 4 days *(47)*, without an effect on infection rates. However, a recent meta-analysis of stop orders and reminders for removal of urinary catheters concluded that both approaches appear to reduce rates of infection *(48)*.

All the above studies emphasize that catheter use is frequently inappropriate; inattention to both the proper indications for catheter use and the catheter status in patients appears to be an important factor. Potential solutions include the implementation of hospital-wide protocols for catheter insertion and continued usage, such as allowing removal of a catheter by a nurse without a physician's order, and systems for computer-based order entry of indwelling catheters *(42,43)*.

Magnitude of the Problem

Incidence and Costs From a broad epidemiologic perspective, the problem of catheter-associated infections acquires force from the magnitude of the population affected. Each year, 3 to 6 million of the 33 million patients admitted to acute care hospitals in the United States receive indwelling catheters. It has been estimated that about 15% to 25% of patients in general hospitals have a catheter inserted sometime during their stay *(49)*, and that the prevalence of urinary catheters has increased over recent decades *(50)*. The problem encompasses many different medical specialties, local practice patterns, and geographical differences. For example, in a French urology department, 52.4% of the patients received indwelling catheters and the incidence of catheter-related UTI was 13% *(51)*. By contrast, in a pediatric population, healthcare-associated UTI was the fifth most common healthcare-associated infection and only 50% of patients with healthcare-associated UTIs had urethral instrumentation *(52)*. According to an older estimate performed by the CDC, there were 2.39 healthcare-associated UTIs per 100 hospital admissions in 1975 to 1976 *(53)*. Recent NHSN reports provide data on both catheter-associated UTI and urinary catheter utilization rates for a variety of patient settings. For the category of medical/surgical inpatient wards, the largest single category, the pooled mean data suggest that urinary catheters were utilized in 22% of patient days and infection developed in 5.9 patients per 1,000 catheter days *(18)*. In 1992, the CDC estimated that more than 900,000 healthcare-associated UTIs occurred in the United States, and that the resulting extra charges exceeded $600 million *(54)*. This represented nearly 14% of the total charges for healthcare-associated infections, estimated to be $4.5 billion.

These figures, however, may markedly understate the actual costs of UTIs, since they are based on decades-old estimates of an expected increased length of stay of only 1 day and extra charges of $680 (1992 dollars) for each UTI. Moreover, charges reflect cost shifting, and therefore are an inaccurate measure of true costs. Using attribution methods in a case-referent study of true costs at the Salt Lake City LDS Hospital from 1990 to 1992, the mean attributable difference in length of stay for patients with healthcare-associated UTIs was 3.8 days, and the mean increase in hospital costs was $3,803 *(55)*. If this is representative of all US hospitals, the true national cost of healthcare-associated UTIs is likely to be more than $3 billion.

In the managed care environment, costs are a financial loss to healthcare institutions. Thus, market forces should revive interest in preventing all healthcare-associated infections, including UTIs. Based on a theoretical model, the extra costs were estimated for each symptomatic healthcare-associated UTI to be at least $676 and for each catheter-associated bacteremia to be $2,836 *(56)*. Another study estimated the mean costs of a healthcare-associated UTI to be $589, with the lowest costs associated with infections caused by *Escherichia coli* and higher costs with infections caused by other gram-negative bacilli and yeasts *(57)*. The substantially lower estimates in this study as compared to other earlier retrospective studies were attributed to cost-containment measures implemented in the era of managed care as well as to the availability of newer oral antimicrobials with activity against gram-negative pathogens. Additional economic incentive for hospitals in the United States to reduce rates of healthcare-associated UTI due to urinary catheter use has recently come in the form of a change in reimbursement policy from the federal government *(58)*. Under revised policy, additional payments for certain complications from medical care that are deemed "reasonably preventable" will be curtailed *(59)*.

Mortality The extent of mortality attributed to catheter-associated UTIs is still uncertain since these infections might be effect modifiers or simply markers of high mortality from other causes. The most generally acknowledged cause of death is related to bacteremia, which occurs in 0.3% to 3.9% of patients with healthcare-associated

catheter-associated UTIs *(60–62)*. Secondary bacteremia from a urinary source is generally considered unequivocal evidence of an invasive UTI. However, when a blood culture was obtained immediately after urethral catheterization from patients with sterile bladder urine, 6.5% were positive *(63)*. Therefore, transient bacteremia secondary to urinary tract instrumentation can be a source of a remote infection, perhaps at the site of an implanted prosthetic device.

As many as 35,000 cases of bacteremia secondary to healthcare-associated catheter-associated UTIs occur each year in the United States. Even though the crude case-fatality rate perhaps exceeds 30%, the mortality rate attributed specifically to bacteremic UTI in one large retrospective study was 12.7% *(61)*. According to this estimate of the attributable mortality, as many as 4,500 deaths occur in the United States each year from healthcare-associated UTIs, but most of these deaths may occur in patients with serious underlying disease processes.

The true mortality rate from bacteremic UTIs for the United States in recent years is also undoubtedly lower than such extrapolations from studies in large tertiary care hospitals. In 1992, the CDC estimated that UTIs directly caused only 932 of the 19,027 deaths from healthcare-associated infections but contributed to an additional 6,500 of 58,092 deaths associated with healthcare-associated infections in US hospitals *(54)*. To appreciate recent advances, consider that, before closed drainage systems were used, Martin et al. (64) estimated that 31,000 deaths occurred in US hospitals each year because of urinary catheter-related bacteremia. This study serves as the principal evidence that closed drainage markedly lowered the mortality rate and suggests that further reductions will be achieved only with great difficulty.

Additional mortality may nonetheless occur from causes unrelated to bacteremia. One study, using logistic regression analysis in a large hospital population, suggested that the actual mortality rate of healthcare-associated UTIs is significantly higher than estimates based on the incidence of bacteremia *(65)*. Acquisition of catheter-related UTI predicted a nearly threefold increase in mortality that was not completely explained by clinical sepsis, documented bacteremia, or underlying disease. If this study is representative of all US hospitals, the actual excess mortality associated with catheter-related infections could be as high as 56,000 deaths per year in acute care hospitals. Possible support for this conclusion also came from observations of women with long-term catheters in whom the incidence of death during fevers of suspected urinary origin was 60 times the incidence during afebrile periods *(66)*. A more recent retrospective study of over 25,000 patients with indwelling urinary catheters, and at least 4 days of hospitalization, documented a relative risk, by multivariate logistic regression modeling, of 1.37 for death among those patients who developed UTI *(67)*.

Morbidity Indwelling urinary catheters pose a risk for many infective and noninfective complications. Catheter-related infection can spread to any site in the urinary tract and can predispose patients to perinephric, vesical, and urethral abscesses as well as epididymitis, prostatitis, orchitis, and vesicoureteral reflux. The overall incidence of these complications is unknown, although 20% to 30% of patients with asymptomatic catheter-induced UTIs may develop local or systemic symptoms *(56,60)*.

Infection may also have a role in other complications of catheterization. Bladder and renal stones, hemorrhagic pseudopolyps of the bladder *(68,69)*, and squamous metaplasia and carcinoma of the bladder *(70)* have all been associated with UTIs in patients with long-term or chronic indwelling catheters. Accidental inflation of the catheter balloon in the posterior urethra has caused minor hematuria and subsequent urethral stricture as well as periurethral abscesses, sepsis, and death *(71)*. Neglect of long-term catheters, usually in patients who are discharged from the hospital with an indwelling catheter, can lead to bladder gangrene, perforation, and peritonitis *(72–74)*. Among noninfectious complications of indwelling urethral catheterization, some cardiovascular surgery units have reported that urethral ischemia during cardiopulmonary bypass caused urethral strictures that could be prevented by the use of silicone rather than latex catheters *(75)*.

Healthcare-associated UTIs may also be a source for other healthcare-associated infections. In one large study, 40% of UTIs occurred in patients with multiple healthcare-associated infections, but the incidence of autoinfection secondary to the urinary site was not evaluated *(76)*. In a study of patients in a university hospital in Spain, an indwelling urinary catheter used for more than 3 days more than doubled the risk of developing bacteremia *(77)*. A more recent study from Spain investigating bacteremia occurring within 30 days of solid organ transplantation found UTI was the most common identifiable cause, in 27% of cases, with *E. coli* being the most common bacteria isolated *(78)*. Healthcare-associated UTIs can be the source for 10% to 15% of healthcare-associated bloodstream infections *(61,62,79)*. A recent study identified 350 cases of healthcare-associated UTI-related bloodstream infection over a 9-year period at a large academic medical center, predominantly among patients with immunosuppression, liver, or kidney disease *(80)*. Healthcare-associated *Staphyloccocus aureus* UTI among residents of a long-term care facility was found to be associated with bacteremia in 13%; among the cohort 82% had recent urinary catheterization *(81)*.

Surgical site infection secondary to a healthcare-associated UTI has been documented as a cause of major morbidity with an attack rate of 2.3 secondary surgical site infections per 100 surgical patients with healthcare-associated UTIs *(82)*. Two reports confirm an increased rate of surgical site infections and allograft dysfunction in renal transplant recipients with healthcare-associated UTIs *(83,84)*, whereas others have demonstrated associations between UTIs and infections of prosthetic heart valves *(85,86)*, total hip replacements *(87,88)*, and central venous catheters *(89)*. Rare complications such as gram-negative endocarditis and septic discitis may also complicate urosepsis of healthcare-associated origin *(90,91)*.

Consequences of Antimicrobial Use The indication for antibiotic therapy of healthcare-associated UTIs in acute care settings is a subject of debate and controversy. Nonetheless, treatment of symptomatic UTIs is virtually universal. In one report, among 1,233 patients with healthcare-associated UTIs, only a single patient

was not treated *(92)*. Yet, routine therapy increases not only drug costs but also adverse drug reactions and the emergence of antibiotic-resistant microorganisms. These adverse consequences have not been fully evaluated in epidemiologic studies, although antibiotic use during catheterization influences the patterns of microbial species causing healthcare-associated UTIs. The changing nature of UTIs at one medical center in the last decade was reflected by significant increases in the proportion of certain uropathogens such as yeasts, *Klebsiella pneumoniae,* and group B streptococcus *(93)*. Antibiotic use was probably largely responsible for these changes. Other reports, such as one that tied the emergence of multidrug-resistant *K. pneumoniae* to prophylactic use of trimethoprim–sulfamethoxazole in patients with indwelling catheters *(94)*, serve as further evidence that antibiotic use shapes the character of healthcare-associated UTIs.

In the report from the NNIS system with data from 1992 to 1997 for healthcare-associated infections in medical ICUs, fungi accounted for almost 40% of urinary isolates *(34)*. *Candida albicans* alone accounted for 21% and was the single most frequent microorganism cultured. This was a marked change from a previous report with results from 1986 to 1989 that included all types of ICUs in which all fungi constituted 22.1% and *C. albicans* 12.8%. Extensive use of broad-spectrum antibiotics and antifungal drugs may have contributed to this increase, especially for the increasing prevalence of non-albicans *Candida*.

Epidemics of Healthcare-Associated UTIs Epidemics of healthcare-associated UTIs have garnered national attention when the causative microorganisms displayed unusually high levels of antibiotic resistance. In seven large epidemics investigated by the CDC between 1970 and 1975, asymptomatic catheter-associated UTIs were reservoirs of the epidemic microorganisms *(95)*. The most frequently observed risk factor in these epidemics was prior exposure to broad-spectrum antibiotic therapy.

Only three microorganisms caused the seven outbreaks: *K. pneumoniae, Serratia marcescens,* and *Proteus rettgeri*. Gastrointestinal carriage was especially prominent in outbreaks caused by *K. pneumoniae*, but the epidemic microorganism was thought to be transmitted from patient to patient on the hands of healthcare workers in all seven outbreaks. Healthcare-associated UTIs were also sources for other healthcare-associated infections as the epidemic microorganism was isolated repeatedly from nonurinary sites in five of the outbreaks.

Indwelling urinary catheters and other types of urologic instrumentation have contributed to the emergence of healthcare-associated pathogens highly resistant to antimicrobial agents. The urinary drainage bag is a potential site for extraintestinal transfer of resistance plasmids in Enterobacteriaceae as well as an environmental reservoir for cross-infection *(96)*. For instance, interhospital spread of multiply resistant *S. marcescens* occurred among patients with indwelling catheters in four geographically separate hospitals in one city *(97)*. Hand carriage by personnel rotating among hospitals was the apparent mode of transmission. Indirect contact transmission of highly resistant *P. rettgeri* appeared to be important in two reported outbreaks of healthcare-associated UTIs *(98,99)*.

Contaminated equipment and inadequate disinfectants have also been responsible for epidemics of UTIs. An outbreak of gentamicin-resistant *P. rettgeri* and *Providencia stuartii* UTIs in patients with chronic indwelling catheters in a rehabilitation unit was caused by contaminated urinary leg bags *(100)*. In another hospital, a contaminated drainage pan in a cystoscopy room caused a common-source outbreak of 105 cases of multiple antibiotic-resistant *S. marcescens* UTIs following cystoscopy, and cross-infection of 29 patients on nursing units amplified the magnitude of the epidemic *(101)*. At yet another hospital, inadequate disinfection of urologic instruments with reuse of 2% glutaraldehyde led to a 12-month-long epidemic of antibiotic-resistant *S. marcescens* UTIs after a variety of urologic procedures *(102)*. The use of chlorhexidine for hand washing caused an outbreak due to multiply antibiotic-resistant and chlorhexidine-resistant *S. marcescens* UTIs that lasted over 19 months *(103)*, and use of hexachlorophene solution in preparing patients and cleaning instruments for cystoscopy and transurethral resection of the prostate was associated with *Pseudomonas aeruginosa* UTIs *(104)*. Contaminated urine measuring containers and urometers were the reservoir for *P. aeruginosa* that caused 66 catheter-associated UTIs *(105)*. Clearly, rigorous application of existing infection control principles can prevent such epidemics.

Many of these and other reported epidemics had well-defined sources. Others occurred from previously unsuspected environmental reservoirs. For example, uninfected patients with condom catheters who had contaminated urine drainage bags served as a reservoir for infection of patients with indwelling catheters on the same hospital unit *(106)*. Contaminated drainage bags may also mislead surveillance personnel, as false diagnoses of UTIs made from urine specimens obtained from drainage bags can skew surveillance data. Such errors at one hospital led to a pseudoepidemic of *Trichosporon beigelii* UTIs that, if not recognized, could have subjected patients to the risks of antifungal treatment *(107)* (see also Chapter 9).

ETIOLOGIC AGENTS

The microorganisms usually responsible for catheter-associated UTIs are derived from the fecal flora native to the patient or that originate in the hospital environment. According to 1990–1992 data from the NNIS system, these include *E. coli* (25%); *Enterococcus* species (16%); *P. aeruginosa* (11%); *C. albicans* (8%); *K. pneumoniae* (7%); *Enterobacter* species and *Proteus mirabilis* (5% each); coagulase-negative staphylococci (CoNS) (4%); other fungi (3%); *Citrobacter* species, group D streptococci, other *Candida* species, and *S. aureus* (2% each); *Acinetobacter* species, *S. marcescens*, group B streptococci, other *Klebsiella* species, other streptococcal species, and other Enterobacteriaceae (1% each) *(108)*.

Although anaerobic bacteria have been isolated from catheter urine of patients with long-term catheters, and most secondary suppurative genitourinary infections commonly involve anaerobic bacteria, anaerobic UTIs

are rarely reported *(109,110)*. *S. aureus* is an occasional cause of catheter-associated UTI, with a high rate of secondary bacteremia, but is also frequently found in urine cultures secondary to *S. aureus* bacteremia *(81,111–113)*. In addition, some microorganisms, such as CoNS, have received increased attention in recent years, although their role as uropathogens is still unsettled *(114)*.

A single infecting species is responsible for about 80% of UTIs in patients with short-term catheters, but most patients with long-term catheters have polymicrobial infections with spontaneous turnover of individual species *(115)*. The microbial species causing healthcare-associated UTIs have always differed from those causing community-acquired UTIs. *E. coli,* for example, causes 80% or more of the cases in outpatients *(116)* versus <50% of the healthcare-associated ones. As with other complicated UTIs, recognized virulence factors of *E. coli* are not prevalent among the strains causing catheter-associated UTI *(117,118)*. The frequencies of the various pathogens also differ in chronically catheterized patients who have, for example, a particularly high risk of infection with *P. stuartii (119)*.

The frequency of individual pathogens causing healthcare-associated UTIs has changed markedly in the last two decades. The single most important factor influencing the distribution of infecting species in the hospital is the use of antimicrobial agents. Although reduced rates of healthcare-associated UTIs have been associated with antibiotic use in patients who have indwelling catheters for brief periods, this possible benefit has been offset by increased acquisition of resistant species such as enterococci, *Klebsiella, Pseudomonas, Proteus, Enterobacter*, and yeast (28,*34*).

At Salt Lake City's LDS Hospital, antibiotic use during the period of catheterization has steadily increased: 53% of 405 catheterized patients in 1972 received antibiotics, as compared to 80% of 1,309 in 1990 *(120)*. As a consequence, in 1990, *E. coli* accounted for only 10% to 20%, other gram-negative bacilli for 20% to 30%, enterococci for 20%, coagulase-negative staphylococci for 10%, and yeast for 20% to 30% of all isolates from urine cultures with microbial growth.

The incidence of healthcare-associated UTIs caused by *Candida* species and other yeasts has been increasing in recent years *(34,93)*. The risk for candiduria has been related to duration of catheterization, duration of hospitalization, and antibiotic use *(121)*. It is usually asymptomatic, but complications can include fungus balls in the bladder or renal pelvis, fever, renal and perirenal abscess, and disseminated candidiasis *(122–125)*.

Viral agents have not been systematically studied in patients with indwelling catheters. Cytomegalovirus can be isolated, often intermittently, from the urine of patients infected with this agent, but the risk of transmission to healthcare workers is probably negligible *(126–128)*. Human immunodeficiency virus type 1 (HIV-1), however, could not be detected in the urine of 48 seropositive individuals *(129)*, and no evidence suggests that HIV can be transmitted by urine. Nevertheless, because urine can become contaminated with blood, especially after catheterization, standard precautions should apply to the handling of urine as well as blood. The proper use of gloves, particularly changing gloves between tasks, not only can protect the healthcare worker but also can theoretically prevent transmission of UTIs.

PATHOGENESIS

Role of the Catheter

Microbial colonization of bladder urine precedes most invasive UTIs. Urine is an excellent growth medium for common urinary tract pathogens *(130,131)*. Nonetheless, the urinary tract above the distal urethra is normally free of bacteria, and micturition permits nearly complete cyclic emptying of the bladder, thereby rapidly eliminating the small numbers of microorganisms introduced through minor urethral trauma *(132)*. The indwelling transurethral catheter breaches this normal defense mechanism, distending the urethra, and blocking the ducts of the periurethral glands. The retention balloon prevents the complete emptying of the bladder and creates a small pool of residual urine in which microorganisms can multiply. The resulting increase in susceptibility to infection is shown by observations that low-level bacteriuria progresses very rapidly to levels exceeding 100,000 colony-forming units (CFUs)/mL when any microorganisms appear in the catheterized bladder (28,133).

Since the catheter is a continuously open channel, microorganisms can migrate upstream into the bladder through the lumen of the catheter. As long ago as 1957, Dutton and Ralston (134) showed that nonmotile bacteria could ascend sterile tubing against a flow of sterile urine. In addition, the external surface of the catheter stresses the urethral surface, creating a channel for bacterial colonization and entry outside the catheter *(24)*. It has been reemphasized in recent years that the urethra is not merely a passive conduit but has its own complex defense mechanism *(135)*. Exfoliation of urethral cells with bound uropathogens is one example of an overlooked defense mechanism, and differences in the rates of exfoliation of cells in menstruating women or those on hormone replacement as compared with postmenopausal individuals may account for the different rates of UTIs in these populations. The effect of a foreign body on the rate of exfoliation of urethral cells and its contribution to bacteriuria has not been well defined.

The foreign material of the catheter also may promote infection by a number of other mechanisms. For instance, by blunting the local inflammatory response as shown in other types of implanted foreign bodies *(136)*, the catheter may interfere with the removal of bacteria that gain entry to the bladder. In mouse models, Toll-like receptor 4 (TLR4) on both bladder epithelial cells and leukocytes protects against *E. coli* infection by recruiting inflammatory cells and upregulating chemokine expression needed for an innate immune response *(137,138)*. Although the effect of the urinary catheter on the local innate immune response has not been well studied, a dysfunctional TLR4 may hinder inflammation and bacterial clearance from the urinary tract *(138)*. The possibility that the innate immune response is blunted in catheter-associated UTIs is suggested by observations that, in humans, healthcare-associated UTIs are seldom symptomatic (139) and the sensitivity of detecting catheter-associated UTIs by screening for pyuria is only 37%

(140). Pyuria is also less frequently associated with yeast and gram-positive microorganisms than with gram-negative microorganisms colonizing the catheterized urinary tract.

Recently, the function of defensins, specifically human β-defensin 1, which is produced by renal epithelial cells, and their role in UTI and pyelonephritis have been studied more closely. β-Defensin 1 has activity against *E. coli*, although the concentration required is tenfold higher than is present in the urine. However, it is also possible that defensins could exist on epithelial cells to form an antimicrobial barrier, a process that may be affected by or compromised by the presence of a urinary catheter *(141)*. Studies have shown that the presence of a catheter may enhance the adherence of gram-negative bacteria to uroepithelial cells. For unknown reasons, 2 to 4 days before the onset of bacteriuria, epithelial cells harvested from the catheterized bladder show a transient increase in the adherence of gram-negative bacteria *(142)*.

Bacteria may also adhere to and migrate along the extraluminal surface of the catheter itself. The physical and chemical properties of the catheter material, therefore, are posited as important determinants of UTI *(143)*. In consequence, efforts have been made to develop an adhesion-resistant or colonization-resistant urinary catheter. An *in vitro* study found marked differences in the ability of various gram-positive and gram-negative bacteria to attach to red rubber catheters and those coated with either a hydrophilic substance, silicone, or tetrafluoroethylene (Teflon) *(144)*. Most bacteria are hydrophobic, and none of the tested bacteria adhered to the hydrophilic catheter. However, studies of hydrophilic catheters in patients have demonstrated no clinical benefit *(145–147)*. Regardless of their influence on bacterial adhesion, catheters made of Teflon-coated latex or silicone have been introduced for clinical use with the hope of improved biocompatibility, but in the absence of established infection there is little evidence of less irritation and inflammation in the urethra from these catheters than from those made of latex rubber *(148,149)*.

Bacteria that colonize both the external and the internal surfaces of urinary catheters grow in microcolonies within a biofilm that encases the bacterial cells. When urine cultures reveal a single species, the biofilm often contains a mixed community with up to four species. In recent years, there has been greater understanding of the biology of biofilms, with additional insight into the process by which planktonic or freely suspended microorganisms become surface-associated microorganisms or biofilms *(150–152)*. A biofilm is loosely defined as a collection of microbial cells that is stably associated with a surface and enclosed in a matrix of primary polysaccharide material. The microbial cells in a biofilm are also different from their freely suspended counterparts with respect to gene transcription and growth. The initial step in the process is the formation of a conditioning film by the urine on the catheter surface followed by attachment of the microbial cell to the surface of the urinary catheter or substratum. The surface properties of the catheter appear to play a role, with microorganisms more rapidly attaching to hydrophobic surfaces like Teflon and plastics than to hydrophilic substances like glass *(153)*. It is thought that hydrophobic interactions occur between the cell and the catheter surface and overcome local repulsive forces, thereby enabling attachment. *In vitro* studies have also shown that the nutrient content of the aqueous medium, in this case urine, also affects the number of bacterial cells that attach to the surface. In certain bacteria, differences in bacterial surface hydrophobicity and presence of fimbriae (pili) and flagella also influence the rate and amount of attachment.

The next step in the formation of a biofilm is a change in gene expression by attached cells upon initial adherence *(154)*. Most of these changes are needed for adaptation to living in a new environment and the change from a planktonic to a surface-associated form. After attachment, the bacterial cells produce extracellular polymeric substances (EPS), which will account for 50% to 90% of the total mass of the biofilm *(155)*. The EPS is composed mainly of polysaccharides and is highly hydrated. The overall charge and composition of the polysaccharides and the amount of EPS produced can vary between different microorganisms and may contribute to antimicrobial resistance by decreasing diffusion of antibiotics through the EPS *(156)*. Genetic variation in the pathways controlling polysaccharide biosynthesis has been shown to result in structural differences in biofilm produced by *P. aeruginosa (157)*.

An *in vitro* study has shown that certain cell-to-cell signals are needed for biofilm formation in a process called quorum sensing *(158)*. In a model using *P. aeruginosa*, mutants lacking two signaling genes were only able to produce a biofilm that was flat, undifferentiated, and phenotypically vastly different from the wild type and much less resistant to surfactant treatment. These signaling systems are also thought to play a role in dispersion of microorganisms from the biofilm, although the process is still not fully understood. The final architecture of the biofilm is a heterogeneous mixture of microcolonies of microbial cells surrounded by an EPS matrix with microbial colonies separated by water channels that play a role in transport of nutrients and possibly antimicrobial agents.

Several factors account for the fact that biofilm-associated infections are resistant to treatment without removal of the catheter. The rate of penetration of antimicrobial agents through the biofilm may be reduced to such an extent that they do not reach a sufficient concentration to be effective. Also, even small amounts of bacterial enzymes such as beta-lactamases might be sufficient to hydrolyze the reduced numbers of antimicrobial molecules that manage to reach the microbial cells. Another factor is the reduced metabolism and reproductive rate of the cells living within the biofilm, as some antimicrobial agents act only on rapidly dividing cells *(159,160)*.

These mechanisms, however, do not readily explain the resistance of biofilms to the activity of fluoroquinolones that readily equilibrate across biofilms and kill nongrowing planktonic cells of *P. aeruginosa*. Recently, it has been shown *in vitro* that increased concentrations of a quinolone did not result in further killing after an initial three- to four-log decrease in the bacterial population in biofilms *(161,162)*. This small fraction of persistent cells may account for high-level resistance of biofilm-associated bacteria. In support of this concept, it has been demonstrated that *E. coli* can use indole, produced by proliferating cells, as a diffusible signaling molecule to turn on drug efflux pumps among all bacteria within a population *(163)*. Thus, a few resistant cells in a colony may provide "umbrella" protection to

antibiotic-induced damage. Whether this mechanism is active in biofilms is not established.

Bacterial Factors

Bacterial *virulence factors* (VFs) have been sought to explain each stage of UTI pathogenesis: bacterial adherence to uroepithelial cells and to the catheter surface, intraluminal migration of bacteria within the drainage tubing against the direction of urine flow, ascending infection through the ureters to the upper urinary tract, invasion of the kidney to cause pyelonephritis, invasion of the bloodstream to cause bacteremia, and persistence of bacteriuria in long-term catheterized patients. The swarming motility of *Proteus mirabilis* has been postulated as a VF for ascending infection of the ureters *(164)*. Other virulence factors encoded by genes localized to chromosomal pathogenicity islands, including hemolysin, the siderophore aerobactin, and adhesive organelles (S pili, Dr family adhesins, P pili, and type 1 pili), have been identified in strains of uropathogenic *E. coli* (UPEC) causing urinary infection syndromes in noncatheterized patients *(165)*. In addition, uropathogenic *E. coli* have recently been shown to secrete mimics of the intracellular signaling domain of TLR—thereby blocking activation of the innate immune response and enhancing virulence *(166,167)*. However, *E. coli* is a less common cause of infection in catheterized patients, and many strains causing urosepsis in catheterized patients typically lack these VFs *(117,168)*. Catheterization enables otherwise avirulent microorganisms to persist and initiate infection *(169)*.

The diversity of microorganisms causing catheter-associated UTIs and the relatively greater importance of host compromise make it unlikely that recognition of common virulence properties will lead to strategies capable either of blocking attachment or of predicting strains most likely to cause bacteremia. Type 1 pili that are mannose sensitive and mediate adherence to epithelial cells and polymorphonuclear leukocytes, for example, have been found in 61% of *E. coli*, 55% of *Klebsiella* species, and 11% of *Proteus* species from catheterized patients *(170)*. Moreover, *E. coli* flora of the urethral meatus, when present, has been shown to change frequently from isolates expressing adhesins to those without this property, perhaps resulting from on-off phase variation in phenotype *(117)*.

In contrast, type 1 pili-mediated adherence has been correlated with persistence of *E. coli* in the long-term catheterized urinary tract *(171)*. In an animal model of cystitis, UPEC expressing type 1 pili were able to invade and persist within bladder cells and serve as a reservoir for recurrent infection *(172)*. This is a dynamic, cooperative interaction between the UPEC microorganism and the uroepethelial cells, dependent on actin cytoskeleton reorganization via a microtubule-dependent process *(173)*. Evidence for similar intracellular reservoirs, termed intracellular bacterial communities, has also been demonstrated in humans *(174)*. So-called type 3 pili [mannose-resistant, *Klebsiella*-like (MR/K) hemagglutination] found in *Providencia, Proteus,* and *Morganella* species also may play a role in long-term catheter-associated bacteriuria through adherence to the catheter material *(175)*, and numerous other adhesins continue to be discovered. Further evidence shows that *E. coli* strains lacking the more common virulence factors (P pili and hemolysin) often carry multiple antibiotic resistance and aerobactin plasmids and are associated with bacteremia in patients with urinary tract abnormalities *(176)*.

Urease, a VF of *Proteus* species, is undoubtedly important, since virtually all patients with *Proteus* bacteriuria develop upper tract infection. Urea splitting by microorganisms such as *Proteus* species and *Corynebacterium* group D2 causes alkalinization of the urine that damages the urothelium, and urease inhibitors such as acetohydroxamic acid can prevent invasion of kidney tissue *(177,178)*.

Pathways of Infection

Clinical studies have also contributed to our understanding of the pathogenesis of catheter-related urinary infections (15,28,29,*114,179–184*). Such studies have confirmed the importance of the extraluminal pathway of infection during closed drainage, and they have revealed other problems that complicate the prevention of UTIs. For example, in the hospital, indwelling catheterization may unmask community-acquired asymptomatic bacteriuria *(185)*. The incidence of asymptomatic bacteriuria is higher in hospitalized than in nonhospitalized populations and varies from 10% to 30% in women on medical wards to 70% in men on urology wards *(186)*.

Catheter insertion may also push microorganisms into the previously uninfected bladder, a mode of infection that has not been well studied but may account for a risk of at least 2% based on the incidence of bacteriuria after a straight in-and-out catheterization *(187,188)*. Urethral catheterization following use of an external condom catheter system may be associated with an even higher risk of infection that is due to the introduction of a large bacterial inoculum that results from the warm moist conditions inside the condom *(189)*. Finally, infection may be acquired, or become clinically manifest, after the catheter is removed, perhaps in association with straight catheterizations during bladder training. The relative importance of each of these patterns of infection, and, therefore, the effectiveness of prevention, depends on host factors, patient care practices, and environmental influences.

The use of sterile barriers and procedures in insertion of central venous catheters reduce the rates of healthcare-associated bacteremia, but the effectiveness of such maximal sterile procedures during urinary catheter insertion has not been conclusively demonstrated. Patients who had a urinary catheter inserted in an operating room had a lower incidence of early healthcare-associated UTIs *(190)*, but a separate small randomized study showed no difference between sterile and nonsterile urinary catheter insertion *(191)*. Nonetheless, catheter insertion under suboptimal conditions and with poor visualization of the urethral meatus may increase the risks of subsequent UTIs.

Closed systems are designed to block the intraluminal pathway of infection by preventing exogenous contamination from air, dust, and the environment. Modern systems for closed sterile urinary drainage consist of a plastic collection bag fused to the distal end of the collecting tube. But since the system is vented to the air and since the collection bag must be emptied frequently, the system is never truly closed. Improper emptying of the bag or nonsterile disconnection of the junction between the catheter and the collection tube may result in microbial contamination of the

system. Large populations of bacteria can grow in the collection bag and travel upstream against the flow of urine to infect the bladder within a day or two (15,28,134,*179,192*).

After the first week of indwelling catheterization, the extraluminal pathway of infection becomes increasingly important as fecal bacteria migrate and colonize the perineal and meatal-urethral surfaces. The first direct evidence for the existence of this external pathway came many years ago from experimental application of *S. marcescens* (which was then considered a nonpathogenic microorganism) to the periurethral area; the microorganism was then recovered from catheter urine 1 to 3 days later (193). Supporting evidence came from the finding that colonization of the perineum or fossa navicularis with pathogens usually preceded the development of bladder bacteriuria by several days in catheterized urology patients *(194,195)*. Indirect evidence indicated that more than 85% of patients had the onset of bacteriuria and colonization of the drainage bag on the same day, implying that the major pathway of infection during closed drainage is extraluminal (15,28,*196*).

Each pathway is accompanied, to some extent, by a characteristic pattern of infection by different species. In general, exogenous microorganisms more frequently enter through the intraluminal pathway, whereas endogenous microorganisms cause infection through the extraluminal route. Exogenous microorganisms such as *Citrobacter freundii, Pseudomonas* species, *Serratia* species, and nonfermenting gram-negative bacilli that are not part of the normal flora are commonly acquired from transient carriage on the hands of personnel or from collection containers and may be transmitted by cross-infection (197). In contrast, endogenous microorganisms that enter through the pericatheter space are generally part of the patient's normal fecal and perineal flora.

Exogenous microorganisms may become a part of the perineal flora as a consequence of hospitalization and especially of antibiotic use. Selden et al. *(198)* found that the gastrointestinal tract of hospitalized patients frequently became colonized with multidrug-resistant *Klebsiella,* and that the fecal reservoir then served as a source for endogenous infections, with the urinary tract being the commonest site. Finally, many microorganisms are associated with both exogenous and endogenous infection. Bacteriuria with CoNS has been linked to disconnections of the catheter-drainage tube junction and, perhaps, exogenous sources (29), as well as to endogenous meatal colonization *(114)*.

The effect of the duration of indwelling bladder catheterization and the relative importance of each of the possible mechanisms of bacterial entry were confirmed in a study documenting that 66% of healthcare-associated UTIs were acquired extraluminally and 18% were detected within the first 24 hours *(190)*. After this time, the extraluminal route was also more frequent. Gram-positive microorganisms and yeasts were far more likely to be extraluminally acquired, whereas gram-negative bacilli were associated with both routes equally.

Host Factors

The effective prevention of exogenous intraluminal infection by closed drainage systems has revealed differences in the risk of infection among different categories of patients (15,28). Risk factors that were identified in a study analyzed by a multivariable statistical technique include increasing duration of use, female gender, absence of systemic antibiotics, diabetes mellitus, and renal insufficiency (serum creatinine >2 mg/dL) *(184)*. Advanced age and severe underlying illness also have been identified as risk factors by univariate analysis (28). Thus, biologic differences in the nature of patient populations account for differing rates of catheter-related UTIs. Importantly, these patient variables can distort interhospital comparisons of infection rates.

Colonization of the urethral meatus appears to be a pathogenetic link between host factors and the risk of infection. In one study of 612 patients with meatal colonization by gram-negative bacilli or enterococci, 110 (18%) developed bacteriuria as compared to 28 (5%) of 601 patients not colonized ($p < .001$) (181). Meatal colonization was more frequent for each of the high-risk groups than for their lower-risk comparison groups. For example, 72% of female patients had meatal colonization as compared with 30% of male patients ($p < .0001$). Overall, the same species was isolated from prior meatal and later urine cultures in 94 (68%) of 138 patients with catheter-induced bacteriuria —further evidence that the extraluminal spread of bacteria within the periurethral space is the major route by which bacteria enter the bladder during closed drainage.

The increased risk of bacteriuria for catheterized women has been blamed in part on the short length of the female urethra, a conclusion that is not well founded. For instance, consider the pathogenesis of bacteriuria due to CoNS. The prevalence of meatal colonization with CoNS, according to one study, was similar in both sexes, as were the rates of bacteriuria with these microorganisms; in both sexes, the rates of CoNS bacteriuria were significantly higher in those with a prior meatal culture yielding CoNS (4.5% vs. 1.5%, $p < .05$) *(114)*. These data suggest that meatal colonization is the major risk factor and that urethral length is relatively unimportant in the catheterized patient.

Although the rates of bacteriuria due to gram-negative bacilli and enterococci are generally lower in men than in women, these differences correlated with differences in rates of meatal colonization with these microorganisms (181). For example, the rate of bacteriuria was only slightly higher in women whose meatal cultures showed negative results (12%) than in men whose meatal cultures showed positive results (8%); the extraluminal pathway predominated in both sexes. Therefore, either the intraluminal or the extraluminal pathway may predominate under given conditions, depending on the local environment, the quality of catheter care, and the nature of the catheterized population.

Unfortunately, factors influencing meatal and urethral colonization have not been studied extensively in catheterized patients. One study using serotyping of *E. coli* isolates causing urethral and rectal colonization observed that the same strains were later present in bladder urine. Systemic antibiotics were associated with a lower rate of bacteriuria while having little apparent effect on serial cultures of urethral colonization (183). In catheterized patients with spinal cord injuries or who had undergone renal transplantation, bacteria colonizing the urethral meatus were acquired after admission to the hospital *(182)*. The density of bacterial colonization increased during catheterization,

was associated with increased rates of bacteriuria, and was greater in patients on open wards than in those in reverse isolation.

By sampling the intraurethral flora using cultures of the external surface of catheters after removal, Kunin and Steele *(199)* documented gradually increasing colonization of the urethra with gram-negative bacilli and enterococci with extended durations of catheterization. They further found that predominantly gram-positive species could be grown from removed catheters of patients with sterile urine. Despite high concentrations of antibiotics in the urine, antibacterial activity could not be detected on the catheters, perhaps explaining the lack of effect of antibiotics on the urethral flora.

DIAGNOSIS

The differing needs of clinicians and epidemiologists are responsible for disagreements over terminology, particularly the definition of UTIs in asymptomatic catheterized patients *(200)*. A clinician uses a diagnosis to define an illness that requires treatment and to help form a prognosis. An epidemiologist selects a pragmatic case definition for surveillance that can be proficiently applied. An investigator demands objective data regardless of cost. These considerations lead to disparate criteria for diagnosis of healthcare-associated UTIs.

The term *bacteriuria,* or, in the case of yeasts, *candiduria,* is widely used by authors when there is no clinical, histologic, or immunologic evidence of infection. Bacteriuria literally means the presence of bacteria in urine and therefore is evidence of colonization and a precursor of infection. The only generally accepted criteria for infection of the urinary tract, therefore, require the presence of symptoms or other evidence of tissue invasion in addition to recovery of a pathogen from a source within the urinary tract.

The CDC has recently revised surveillance definitions, as part of the NHSN reporting system. Formulated as algorithms, these aim to distinguish healthcare-associated from community-acquired infections and infection from colonization *(201)*. These definitions exclude infections that are present or incubating at the time of hospital admission. Unavoidable incongruities occur in the use of these definitions, however. For example, unless a urine culture is performed at the time of hospital admission, preexisting asymptomatic bacteriuria may be falsely attributed to later catheterization. On the other hand, the NHSN criteria no longer include the classification of asymptomatic catheter-associated bacteriuria and introduce two new categories: symptomatic UTI and asymptomatic bacteremic UTI. Another important change is that symptomatic patients with bacteriuria of fewer than 100,000 colonies per milliliter will not be classified as UTI unless predefined criteria are demonstrated on urinalysis.

The common goal for diagnostic criteria is to provide a basis for predicting morbidity and mortality. Quantitative bacterial cultures of urine have proven satisfactory for this purpose. Except with very low colony counts (<100 colonies/mL), the problem of contamination and false-positive results is virtually nonexistent when urine is obtained by aseptic needle aspiration from the sampling port on the drainage tube. Evidence indicates that the diagnosis of infection associated with short-term indwelling catheterization is supported with colony counts as low as 100 microorganisms per milliliter *(202)*. Colony counts of this magnitude are reproducibly present in the same or higher numbers, usually more than 100,000 colonies per milliliter, within 1 or 2 days except for those patients receiving antibiotics or who have infection with fastidious slow-growing microorganisms (133).

The epidemiologist must be cautious when interpreting reported infection rates because of the influence of colony counts on comparative data. The infection rates found in clinical trials, for example, are actually rates of bacteriuria and may be markedly different from rates of clinical UTIs (29,*203*). Some investigators have restricted the definition of uropathogens to certain species of bacteria, which also affects the observed rate of bacteriuria. In addition, very low colony counts (100 or 1,000 colonies/mL) are commonly selected as a threshold to define bacteriuria in clinical trials, with the result that rates are higher than those from routine surveillance. This confers greater sensitivity and hence greater power to detect differences between study and control groups. Infection rates may also be higher in hospitals that use protocols for obtaining urine cultures from all patients regardless of symptoms.

From a clinical perspective, secondary bacteremia occasionally occurs in bacteriuric patients with colony counts of fewer than 100,000 microorganisms per milliliter, and some rapid tests for bacteriuria are insensitive to such low colony counts *(204,205)*. Colony counts may also be lower in urine aspirates from replacement catheters than in those from the original catheters, although the differences are seldom large enough to be detected by conventional urine cultures *(206)*. One proposed method of detecting infection, the culturing of the tip of a removed Foley catheter, has proven ineffective *(207)*.

Few studies have carefully examined the relation of bacteriuria to pyuria. Musher et al. *(208)* found that pyuria nearly always accompanied bacteriuria (>100,000 bacteria/mL) in catheterized male patients, but pyuria was also present in nearly 30% of urine specimens from catheterized male patients without bacteriuria. Therefore, the finding of pyuria did not help to discriminate infection from colonization. In a study of patients with spinal cord injury who underwent intermittent catheterization, bacteriuria with more than 100,000 gram-negative bacilli per milliliter, or colonization with yeast regardless of the colony count, resulted in pyuria *(209)*. In patients with long-term indwelling catheters who had chronic pyuria and bacteriuria, neither urinalysis nor urine culture was a reliable test for symptomatic UTI *(210)*. In contrast, in a study of patients with short-term indwelling urinary catheters, Tambyah and Maki (140) found that only 37% of patients with bacteriuria had pyuria, and similarly bacteriuria was present in 37% of patients with pyuria. The authors concluded that the differences between their results and the previous study done by Musher et al. were likely due to different patient populations.

The NHSN surveillance algorithm uses symptoms to define UTI if other supporting evidence is present, and no longer recognizes asymptomatic bacteriuria, even if the urine culture yields more than 100,000 colonies

per milliliter. However, the symptoms of UTI, such as dysuria, urgency, frequency, or suprapubic tenderness, are often obscured by the presence of the catheter and, except for fever, may become evident only when the catheter is removed. Urinary catheters contribute directly to healthcare-associated febrile illnesses *(211)*. However, fever may be absent in elderly, debilitated, or immunosuppressed patients who also may be unable to report other symptoms. In a companion study by Tambyah and Maki (139), more than 90% of patients with catheter-associated UTI were asymptomatic, but 52% were diagnosed by their physicians using the hospital laboratory. Interestingly, symptoms referable to the urinary tract had no predictive value for the diagnosis of infection. As a corollary, no study has demonstrated that symptoms referable to the urinary tract are a reliable indication of the risk of developing a complication from UTI. To the contrary, a study of *S. aureus* bacteriuria in elderly long-term care patients found that only half of those with subsequent bacteremia met criteria for symptomatic UTI *(81)*.

Objective, reproducible, and economical methods for surveillance are obviously needed. One proposal for the surveillance of healthcare-associated UTIs avoids time-consuming reviews of patient records by using concurrent review of microbiology laboratory reports *(212)*. Because evaluation of symptomatic patients usually includes a urine culture, the sensitivity of laboratory-based surveillance approaches 98% when healthcare-associated UTI is defined by positive urine culture on the third hospital day or later.

PREVENTION

Closed Sterile Drainage

An understanding of the major risk factors and pathways of infection should facilitate logical strategies for the prevention of healthcare-associated UTIs. The most successful infection control method, closed sterile drainage, reduces the risk of infection only through the exogenous pathway and requires little additional effort by healthcare workers. Nonetheless, irregularities in catheter care and resulting breaches of closed systems are pervasive problems and are therefore a target for prevention efforts (28,29). Improper hand hygiene—with a nondisinfectant soap, for example *(213)*—is also an important risk factor for exogenous infection. Proper technique depends on healthcare workers and is difficult to monitor and enforce *(214)*.

Infection Control and Surveillance Programs

The CDC's Study on the Efficacy of Nosocomial Infection Control (SENIC) remains today the major source of data regarding the preventability of healthcare-associated infections including UTIs *(215)*. Complicated methodology hindered the understanding and limited the impact of the SENIC study. The multiple factors influencing UTI rates, for example, could not be independently assessed. Nonetheless, the study suggested the yet-unfulfilled potential of existing methods for prevention and the role of surveillance itself as a control measure.

Beginning in 2008, the NHSN became available in the United States as a way for healthcare facilities to report HAI data, including those on healthcare-associated UTI. Although not yet fully implemented, it presents an opportunity for national, risk-adjusted estimates of infection rates. Like the SENIC study however, the success and value of the process will depend on minimizing complexity and burden on individual facility infection preventionists.

The SENIC report estimated that intensive infection surveillance and control programs—those with at least one infection control practitioner (infection preventionist in current terminology) per 250 beds—might have been able to reduce the UTI rate by 33%. Unfortunately, because relatively few hospitals had effective programs in the mid-1970s, only 2% of the number of healthcare-associated UTIs predicted in the absence of such programs were actually prevented. A follow-up survey in 1983 found that the proportion of hospitals with effective programs had increased from 7% to 24%, with potentially 6% of the UTIs prevented *(216)*.

Guidelines

Almost three decades ago, the CDC developed the first guideline for the prevention of catheter-associated UTIs *(217)*. It emphasized principles for maintaining closed sterile drainage but overlooked the role of surveillance *(218)*. These guidelines have recently been revised, based on a systematic review of the literature though 2007, emphasizing prevention measures for a wider variety of patients and specific surveillance recommendations (219).

Additional recent guidelines have been issued by the Infectious Diseases Society of America (IDSA) *(220)*, the Society for Healthcare Epidemiology of America (SHEA) *(221)*, the Association for Professionals in Infection Control and Epidemiology (APIC) *(222)*, and from the European and Asian urological societies *(223)*.

The extent of adherence to these guidelines remains unknown, although evidence points to marked variation among institutions. Catheter care violations, such as accidental junction disconnections, improper closure of the outflow spigot, and improper positioning of the collection bag, are common and are associated with increased rates of bacteriuria. Studies at the Salt Lake City LDS Hospital reported these errors in 11% of catheter-days and overall in 29% of catheterized patients with little change over time despite intensive education of healthcare workers (29). Modifications in the design of drainage systems, such as antireflux valves and seals of the catheter-drainage tubing junction, aimed at reducing the frequency of errors in catheter care by passive means, have proved disappointing.

Adjuncts to Closed Drainage

In the past few decades, many adjuncts to closed drainage have been introduced and aggressively marketed by device manufacturers, often without adequate clinical investigation and evidence of efficacy. These efforts have focused on more effectively preventing infection by both the intraluminal and the extraluminal pathways.

Randomized controlled trials (RCTs) have been useful in the evaluation of preventive measures for healthcare-associated UTIs. Many seemingly logical adjuncts to closed drainage have not been efficacious when evaluated in RCTs. For example, RCTs showed that a costly and once widely used procedure, daily meatal care, is not cost-effective

and, in fact, that meatal care with iodophors is deleterious (224,*225–227*). However, closed sterile urinary drainage has not been evaluated in RCTs, because its efficacy has been evident from nonrandomized studies *(228)*.

RCTs are expensive and susceptible to many limitations, including errors in design and analysis. Because of the varying importance of the different pathways for acquisition of catheter-associated UTIs in different settings and patient populations, the results of a single RCT may be valid only for the time and place a study was conducted. RCTs are also susceptible to exploitation by manufacturers. Accordingly, Kunin *(229)* has suggested that the efficacy of new devices for infection control should be supported with carefully controlled studies by at least three groups working independently.

RCTs relevant to healthcare-associated UTIs are instructive and may help identify productive areas for future investigation. The listing of 52 representative RCTs from 1962 to 2003 is shown in Table 20-1 intentionally omits some studies of prophylactic antibiotic use in surgery, urology, and gynecology in which catheter-related UTI was an outcome measure. It also omits comparative trials that were not randomized, and some of those included were not randomized at the individual patient level. Furthermore, 30 of the 52 RCTs were restricted to certain types of patient populations, and the results, therefore, may not be generally applicable to all catheterized patients.

Judgments of outcomes as positive (+) or negative (–) were based on the presence or absence, respectively, of statistically significant differences ($p < .05$) between the study and control groups. Some outcomes that were otherwise negative were judged to be equivocal (+/–) if a significant difference was found in at least one subset of the population or if the authors believed a trend favored the intervention.

The majority of these RCTs (35 of 53) had either negative or equivocal outcomes. The studies ranged in size from 31 patients to 27,878 patients. Study size was correlated to outcome: 15 positive outcomes occurred in 26 studies with fewer than 200 patients, as compared to only two positive outcomes in 13 studies with more than 500 patients. Smaller studies, therefore, may have erroneous outcomes.

The types of interventions studied in these RCTs can be grouped in four categories: (a) alternative methods of bladder drainage (intermittent straight and suprapubic catheters); (b) methods to prevent extraluminal infection (urethral lubrication, meatal disinfection, and catheters coated with hydrophilic polymers or antimicrobial compounds); (c) methods to prevent intraluminal infection (antireflux valves and vents, instillation of disinfectants into the bag, irrigation of the bladder with disinfectants or antimicrobials, and junction seals); and (d) combined approaches including systemic antibiotic prophylaxis.

With the exception of antibiotic prophylaxis, none of the individual interventions met criteria for efficacy in at least three RCTs. Systemic antibiotic prophylaxis, with six of seven trials having positive outcomes, and methods that included junction seals, with two positive and two equivocal outcomes among seven trials, appeared to be the most promising approaches. Yet only one of these positive outcomes—an RCT of antibiotic prophylaxis—occurred in a study of more than 500 patients. Junction seals are potentially effective, although they do not yet meet Kunin's criteria for efficacy. However, prevention of junction disconnections might reduce the incidence of bacteriuria by only about 10% (29).

An intriguing approach to antibiotic prophylaxis, evaluated in a single small trial, involved the use of ampicillin 1 hour before, at the time of, and 6 hours after catheter insertion *(230)*. This study found significant protection for up to 1 week after use of this regimen. The use of antimicrobials during catheterization, especially fluoroquinolones—effective in two RCTs—merits further investigation but cannot yet be recommended pending large-scale clinical trials.

Methods to prevent UTIs that are effective in one patient group, such as males undergoing prostatectomy, may not be suitable for general use. All of the RCTs of antibiotic prophylaxis were restricted to certain types of patients. All three positive trials of bladder irrigation with antimicrobials involved patients undergoing urologic or gynecologic procedures, and the control group for one trial received open drainage. Ideally, preventive methods should be evaluated in general hospital use among all patient services. The only RCT of antibiotic irrigation that met this criterion showed no benefit, although the authors believed that this failure was due to an increased rate of junction disconnections in the treatment group *(180)*.

Methods found to be efficacious in RCTs should then be evaluated for effectiveness and cost-benefit in routine clinical practice. For example, the routine use of preconnected catheters with junction seals has not been evaluated despite a strong rationale for an expected cost-benefit based on a single RCT *(231)*. In addition, the largest RCT of the use of catheters with presealed junctions showed only a small reduction in the frequency of disconnections *(232)*. A large RCT showed that tape seals applied after catheterization were not effective in reducing either the frequency of junction disconnections or the rate of bacteriuria *(233)*. Thus, the protective effect of the presealed catheter junctions on the rate of bacteriuria is difficult to interpret and may be related to effects of its use other than preventing disconnections or to the fact that factory preconnection may be important.

The results from recent RCTs and a meta-analysis *(234)* of RCTs of silver-coated catheters were inconclusive *(235,236)* or negative *(237)*. In a recent review of all studies of silver-coated catheters including controlled clinical trials, RCTs, systematic reviews, and meta-analyses, only seven studies satisfied the reviewers' selection criteria for adequate quality and only one had a high-quality score *(238)*. The authors concluded that current evidence is insufficient to recommend silver-coated catheters. In contrast, a recent Cochrane review found a benefit to the use of silver alloy and antibiotic-impregnated catheters for reducing asymptomatic bacteriuria during short-term use *(239)*. Moreover, several studies of possible cost-benefit by reducing infection rates with the more expensive silver-coated catheters have estimated cost savings per patient of only $4.09 *(234)* but annual hospital-wide savings from $12,563 to as much as $573,293 *(236,240)*. In another trial of an antibiotic-impregnated urinary catheter (using minocycline and rifampin), a small number of male patients undergoing radical prostatectomy showed a statistically significant reduction in gram-positive bacteriuria

TABLE 20-1

Randomized Controlled Clinical Trials for the Prevention of Catheter-Associated Urinary Tract Infections, 1962–2007

First Author (Reference)	*Year*	*No. of Patients Studied*	*Intervention Studied*	*Outcome of Trial*	*Comments*
Martin *(267)*	1962	40	Constant bladder irrigation with acetic acid or neomycin–polymyxin vs. open drainage	+	Gynecology patients
Butler *(268)*	1968	470	Polymyxin B vs. placebo lubricant	–	
Finkelberg *(269)*	1969	400	Eight different closed systems	–	
Kunin *(270)*	1971	314	Intraurethral lubricating catheter	+/–	
Brehmer *(194)*	1972	40	Polymyxin B–neomycin–bacitracin spray of perineum and meatus	+	Prostatectomies
Monson *(145)*	1974	287	Hydrophilic, polymer-coated catheter	–	
Garibaldi (28)	1974	405	Antireflux valves in drainage bags	–	
Little *(271)*	1974	747	Systemic antibiotic prophylaxis	+	Prostatectomies
Monson *(272)*	1977	506	Top-vented vs. nonvented drainage system	+/–	
Britt *(273)*	1977	196	Systemic antibiotic prophylaxis	+/–	Hysterectomies
Bastable *(274)*	1977	223	Continuous irrigation with chlorhexidine	–	Prostatectomies
Warren *(180)*	1978	187	Continuous irrigation with neomycin–polymyxin B	–	
Matthew *(275)*	1978	87	Nitrofurantoin prophylaxis	+	Prostatectomies
Keys *(276)*	1979	236	Top-vented vs. bag-vented system	–	
Kirk *(277)*	1979	125	Chlorhexidine instillation in bladder	+	Urology service
Maizels *(278)*	1980	31	Hydrogen peroxide instillation in bag	+	Spinal cord injury patients
Burke (224)	1981	846	Meatal care with green soap or povidone–iodine	–	
Burke *(225)*	1983	428	Meatal care with polyantibiotic ointment	+/–	
Platt *(231)*	1983	1,494	Preconnected catheters with sealed junction	+/–	
Gillespie *(279)*	1983	58	Chlorhexidine instillations in bag	–	Prostatectomies
Thompson *(196)*	1984	668	Hydrogen peroxide instillation in bag	–	
Sweet *(280)*	1985	134	Hydrogen peroxide instillation in bag	–	ICU patients
Mountokalakis *(230)*	1985	78	Ampicillin prophylaxis before catheterization	+	Neurology patients
Klarskov *(281)*	1986	40	Hydrophilic catheters with junction seals; povidone–iodine applications	+	Female GU or Gyn surgery patients
Davies *(282)*	1987	44	Chlorhexidine vs. saline bladder instillations	–	Geriatric patients
Sethia *(283)*	1987	66	Suprapubic vs. urethral catheters	+/–	Surgery patients
Charton *(284)*	1987	95	Preoperative netilmicin prophylaxis	+	Prostatectomies
Ball *(285)*	1987	89	Chlorhexidine bladder irrigations	+	Prostatectomies
Hozack *(286)*	1988	54	Straight catheterization post-op	–	Orthopedic patients
DeGroot-Kosolcharoen *(287)*	1988	202	Preconnected silicone vs. latex catheters	+/–	Male patients
Schaeffer *(288)*	1988	74	Silver-oxide/trichloroisocyanuric acid antimicrobial drainage system	+	Spinal cord injury patients
Michelson *(289)*	1988	96	Intermittent vs. indwelling catheters	–	Orthopedic patients
Verbrugh *(290)*	1988	105	Norfloxacin prophylaxis	+	Gynecology patients
Al-Juburi *(291)*	1989	109	Hydrophilic preconnected catheter with povidone–iodine instillations in bag	+	
Liedberg *(292)*	1990	120	Silver alloy–coated catheters	+	Postop patients
Johnson *(293)*	1990	482	Silver oxide–coated catheter	+/–	Selected services
Classen *(226)*	1991	747	Meatal care with polyantibiotic cream	+/–	
Classen *(147)*	1991	606	Preconnected hydrophilic catheter with povidone–iodine applied to catheter and bag	–	
Huth *(233)*	1992	1,740	Tape seals applied to catheter junction	–	
van der Wall *(294)*	1992	184	Ciprofloxacin prophylaxis	+	Surgery patients

(*Continued*)

TABLE 20-1

Randomized Controlled Clinical Trials for the Prevention of Catheter-Associated Urinary Tract Infections, 1962–2007 (*Continued*)

First Author (Reference)	*Year*	*No. of Patients Studied*	*Intervention Studied*	*Outcome of Trial*	*Comments*
Schneeberger *(295)*	1992	264	Povidone–iodine bladder irrigations	–	Urology patients
Skelly *(296)*	1992	67	Intermittent vs. indwelling catheters	–	Orthopedic patients
Huth *(227)*	1992	696	Meatal care with silver sulfadiazine cream	–	
Wille *(297)*	1993	181	Preconnected hydrophilic catheter with povidone–iodine instillations in bag	–	Selected units
Riley *(120)*	1995	1,309	Silver oxide–coated catheter	–	
Maki *(298)*	1998	852	Silver-hydrogel–impregnated catheter	+/–	
Maki *(299,300)*	1998	417	Nitrofurazone-coated catheter	+/–	
Darouiche *(241)*	1999	124	Minocycline- and rifampin-coated catheter	+	Prostatectomies
Thibon *(235)*	2000	199	Silver-hydrogel–coated catheter	–	Selected units
Karchmer *(236)*	2000	27,878	Silver alloy–coated catheter	+	Selected units
Keerasuntonpong *(301)*	2003	153	3-day urinary bag change	–	
Srinivasan *(237)*	2006	3,336	Silicon-based silver-impregnated catheter	–	
Stensballe *(242)*	2007	212	Nitrofurazone-impregnated silicone catheter	+	Adult trauma patients

but not gram-negative bacteriuria or candiduria *(241)*. More recently, an RCT of nitrofurazone-impregnated catheters used in adult trauma patients showed a significant reduction in the onset of bacteriuria and funguria up to 30 days, as compared to a silicone catheter *(242)*. Despite the conflicting evidence, current HICPAC guidelines (219) recommend institutions consider using antimicrobial- or antiseptic-impregnated catheters if the UTI rate is elevated and does not decrease after implementing a comprehensive approach to reduce infections.

Alternatives to Foley Catheters

Alternatives to the Foley catheter include the condom catheter for male patients and analogous external urine collection devices for female patients, the intraurethral stent, the conformable catheter, and older approaches such as adult diapers and biofeedback training *(243–245)*. None of these devices has been evaluated in RCTs. However, they are applicable to only certain types of patients (e.g., external devices for women with incontinence or intraurethral stent catheters for males with prostatic obstruction). The conformable catheter, a type of balloon catheter with a collapsible intraurethral segment that may cause less trauma to the urethra, has been tested only in women without urethral strictures and is not commercially available.

A newer method to reduce the use of indwelling catheters involves the use of a portable ultrasound device to scan the bladder before catheterization to accurately measure the volume of urine in the bladder. In a nonrandomized study, this device enabled reduced use of intermittent and indwelling urinary catheters with a reduction in the incidence of UTIs *(246)*. Another study using this method in postoperative patients reported that the rate of urinary catheterization decreased from 31% to 16% *(247)*. However, despite some promise as an objective, safe, and noninvasive technology for assessing the need for urinary catheterization, the use of bladder ultrasound remains underutilized.

Secondary Prevention

Secondary prevention of the complications of UTIs is desirable but has not been evaluated in RCTs. In 1968, Butler and Kunin *(248)* first proposed that routine monitoring of urine cultures from patients undergoing short-term catheterization could enable the use of specific antimicrobial therapy in order to reduce the number of patient-days at risk for gram-negative sepsis. Large-scale clinical trials to test this hypothesis have still not been done. Limited observational studies have been underpowered to detect clinical benefit from early treatment *(60,185)*. However, treatment of asymptomatic bacteriuria in long-term catheterized patients has shown no beneficial effects *(249)*.

Guidelines for the management of catheter-associated UTIs focus on decreasing antibiotic use for asymptomatic bacteriuria. The recommendations are, however, based on very few clinical data, despite the great frequency of this problem and the diverse approaches that have been used. There is also a dearth of well-controlled trials that could be a basis for specific recommendations. Many believe that treatment of asymptomatic bacteriuria while the catheter remains in place has little apparent benefit *(202)*. However, even a single dose of an aminoglycoside antibiotic, if combined with a catheter change, can eradicate bacteria from the urine of catheterized patients *(250)*. The efficacy of this approach has not been evaluated in large-scale trials, but one clinical trial found that daily treatment with a fluoroquinolone antibiotic failed more than half the time with or without a catheter change *(251)*. The high rate

of relapse and reinfection, as well as the adverse consequences of antibiotic use, has also discouraged the routine treatment of asymptomatic bacteriuria.

Wide variation by clinicians likely exists in the use of diagnostic urine cultures, in the indications for antimicrobial treatment, and in the duration of treatment. The practice of obtaining urine cultures only in symptomatic patients may prevent unnecessary treatment *(252)*, but it also prevents an aggressive approach to the detection and management of catheter-associated bacteriuria. A common recommendation is that urine cultures should be obtained at the times of insertion and upon removal of the catheter with an appropriate follow-up culture for those who have acquired bacteriuria *(253)*. Other clinicians recommend against routine cultures even at the time of catheter removal *(254)*. At present, there are few studies to assist in resolving these conflicting recommendations but the opinion is growing to discourage intensive monitoring by culture *(255)*, although the logic behind this approach has been questioned by some authorities *(256)*.

Whether to perform routine cultures to identify catheter-associated bacteriuria, especially in high-risk patients, is an important issue for healthcare epidemiologists. The effective use of closed drainage requires ongoing surveillance, or periodic culture monitoring as recommended by Kunin (7), to uncover epidemic rates, evidence of cross-infection, and possible environmental sources of exogenous infection. The prevention of mortality that is not associated with bacteremia or sepsis may also challenge current approaches to asymptomatic bacteriuria *(65)*. A recent report from France documented a 70% reduction of catheter-related UTI in an ICU setting over 10 years with the use of weekly screening and reflex cultures of all patients with indwelling urinary catheters for more than 2 days in the ICU *(257)*.

The generalization that asymptomatic catheter-associated UTIs should not be treated is already outmoded for certain patient populations. Immunocompromised patients and those undergoing a urologic operation or a surgical procedure involving prosthetic material may also be at high risk for complications of untreated asymptomatic bacteriuria. One study found that asymptomatic bacteriuria in women after short-term catheterization also warranted therapy, even though the bacteriuria resolved spontaneously in 36% of patients *(258)*. In addition, asymptomatic *S. marcescens* UTIs, known to cause a high rate of bacteremia with a prolonged lag time between the onset of bacteriuria and the development of bacteremia, may warrant treatment *(62)*. Therefore, as hospital populations change, with increasing numbers of critically ill and immunocompromised patients, treatment should be considered for many patients with asymptomatic bacteriuria.

Routine monitoring of catheter urine cultures could, in theory, promote more restrained and targeted antibiotic use in catheterized patients and could help eliminate environmental reservoirs of antibiotic-resistant microorganisms *(259)*. More than 80% of catheterized patients receive antibiotics for treatment or prophylaxis of nonurinary infections. Selection of resistance can occur when these antibiotics remain in the drainage bag for extended periods. Virtually no studies assess the contribution of UTIs to the overall problem of antibiotic resistance or means to eliminate these reservoirs of resistant microorganisms. Furthermore, concern has been expressed that the use of antimicrobial-coated catheters may select for resistant microorganisms.

Candiduria has emerged as a problem with a still unclear natural history and few controlled trials of the efficacy of treatment with antifungal agents. Catheter-associated candiduria may resolve in 35% to 40% of patients with catheter removal and in 20% with catheter change alone without antifungal therapy *(260,261)*. On the other hand, the clearance of candiduria by treatment with fluconazole was only temporary *(260)*, though largely in the setting of continued catheter use. Consensus guidelines developed by the Infectious Diseases Society of America for the treatment of urinary candidiasis recommend treatment for certain types of patients, including those with symptoms, neutropenia, or renal allografts, those undergoing urologic manipulation, and low birth weight infants *(262)*. Because use of fluconazole is a risk factor for *Candida glabrata* UTI *(263)* and because the benefits of treatment are still unclear, treatment of catheterized patients with this agent should be avoided if possible.

CONCLUSION

In recent years, a patient safety movement has gathered momentum throughout the world, generating broad public interest in and support for efforts to prevent medical mistakes and adverse clinical outcomes. Healthcare-associated infections are the most common complications affecting hospitalized patients *(264,265)*, and catheter-associated UTIs are the most frequent and perhaps most preventable type of healthcare-associated infection. Despite several decades of investigation by clinicians and epidemiologists, advances in the prevention of such infections are disappointing. Strategies for prevention have been evaluated in randomized controlled trials more frequently for infections associated with urinary catheters than for any other type of healthcare-associated infection. Often, these studies were necessary because of the aggressive marketing of newer modifications of closed drainage systems by their manufacturers. Most of the well-designed large trials found no significant benefits of the new devices and saved healthcare costs through avoidance of more costly equipment. However, other trials have reduced healthcare costs by identifying widely used preventive measures that were not cost-effective or were even harmful. This frustrating history now appears to be a recurring theme with the recent marketing of antimicrobial-coated catheters accompanied by enthusiastic initial reports, followed by disappointing large-scale trials.

Despite the research efforts of a small cadre of committed investigators, healthcare epidemiologists have neglected healthcare-associated UTIs because these infections are associated with relatively low mortality and costs. A reappraisal of the status of UTIs is overdue because of the important relation between antibiotic use in patients with urinary drainage systems and the emergence of multiply antibiotic-resistant hospital pathogens. Drug resistance is now a global problem with the threat of bacterial infections that cannot

be treated with any existing antibiotic and limited prospects for the development of more effective antibiotics. Therefore, we can no longer afford to neglect a category of infection that accounts for nearly half of the healthcare-associated infections; nor can we ignore a patient population—those with indwelling urinary catheter systems—in which antibiotic use is so prevalent.

Epidemiologists must more fully examine and assure the appropriate use of urinary drainage, not simply the problem of healthcare-associated UTIs. Kunin (266) has emphasized that the unnecessary and prolonged use of catheters, the most obvious cause of healthcare-associated UTIs, must be addressed rather than waiting for the perfect technology. Epidemiologists must employ the strengths of their own discipline and not rely only on technical advances from industry.

The agenda for hospital epidemiologists is clear: to eliminate unnecessary urethral catheterization, to promote noninvasive alternatives to the Foley catheter, to reduce the duration of catheterization, and to promote aseptic care of closed drainage systems. Quality improvement programs can successfully restrict the initial use and reduce the duration of catheterization *(42)*, and innovative methods such as the ultrasound bladder scan *(246,247)* can also reduce the use of indwelling urinary catheters in some clinical situations. Because marked variation is inherent in the management of urinary drainage, the techniques of quality management and continuous quality improvement may be especially suitable to identify and implement the best practices. These strategies depend on epidemiologists for the definition and measurement of important outcomes. In an era that touts outcomes research and patient safety, managing urinary drainage represents a model in which the outcomes are definable and important (see also Chapters 10–12).

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CHAPTER 21

Surgical Site Infections

Sarah Y. Won and Edward S. Wong

Despite advances in operative techniques, better understanding of the pathogenesis of surgical site infections (SSIs), and widespread use of prophylactic antibiotics, SSIs continue to be a major source of morbidity and mortality for patients undergoing operative procedures. It is estimated that SSIs develop in 2% to 5% of the 27 million patients undergoing surgical procedures each year, resulting in 300,000 to 500,000 infections *(1–3)*. They account for approximately 20% of all healthcare-associated infections (HAIs), making the surgical site the second most common site of HAIs, second only to infections of the urinary tract *(3)*. Compared to surgical patients without SSIs, patients with SSIs have a 2 to >12 times increased risk of death, with 77% of deaths in SSI patients related to the infection *(4–7)*. SSIs add, on average, 7.4 additional hospital days, but can add up to an additional 18 inpatient days, at a cost of between $3,000 and $60,000 per SSI (*1–2,4–10,* 11).

In addition, the rising incidence of methicillin-resistant *Stapylococcus aureus* (MRSA), which is responsible for 7.5% of all SSIs, adds considerable morbidity and mortality in the United States (12). MRSA SSIs may triple rates of death and add an additional $14,000 per infection, compared to patients with methicillin-sensitive *S. aureus* (MSSA) SSIs *(4)*. Total cost of SSIs, including indirect expenses related to SSIs, likely exceeds $10 billion annually in the United States *(5)*.

As a consequence of the significant morbidity, mortality, and cost of SSIs, prevention of SSIs has been receiving increased regulatory, third-party payer, and public attention. SSI prevention has become part of a major quality improvement initiative called Surgical Care Improvement Projects (SCIPs) (13). The Centers for Medicare and Medicaid Services (CMS), the primary payer for Medicare and Medicaid patients, are no longer paying additional reimbursements for certain SSIs, like mediastinitis and select orthopedic infections, and require reporting on two SSI prevention process measures advocated by SCIP *(14)* (see Table 21-1). Public reporting of SSI rates is mandated in an increasing number of states. As a result, understanding the epidemiology, implementing evidence-based prevention measures, and surveillance of SSIs have become all the more important for infection preventionists, surgical teams, and hospitals.

DEFINITION OF SURGICAL SITE INFECTIONS

Clinically, a surgical site can be considered infected when purulent drainage is present at the incision site. This may be associated with local swelling, erythema, tenderness, wound dehiscence, or abscess formation. However, local signs and symptoms may not always be present, nor are they necessarily due to infection when they are present. Therefore, the clinical definition of SSI that has been the most widely adopted is the simplest one—that of a surgical site draining a purulent exudate. Clinicians are encouraged to culture all purulent exudates, but neither culture nor a positive microbiologic result is required for diagnosis of an SSI.

However, the definition of an SSI that is to be used for surveillance and epidemiologic purposes must meet additional needs. Such a definition must be simple to use but also unambiguous so that hospitals with varying surveillance resources will be able to apply it and obtain consistent results so that comparisons between hospitals are meaningful. The Centers for Disease Control and Prevention (CDC) has developed and published definitions for the surveillance of SSIs—see below (15), and they are now widely adopted for surveillance and are the *de facto* national standard.

SSIs are classified as incisional or organ/space. Incisional SSIs are divided further into superficial incisional SSI (when they involve the skin and or subcutaneous tissue—see below) or deep superficial SSI (involvement of the fascia and/or muscle—see definitions below). An organ/space SSI involves structures or organs beneath the area of the incision (15). The anatomic location of each site is depicted in Figure 21-1.

Superficial incisional SSIs are the most common, accounting for more than 50% of all SSIs. However, while only one third of all SSIs are organ/space infections, these infections account for over 90% of deaths related to SSIs *(16)*.

Operative sites are followed for 30 days for the development of SSI, unless an implant is involved, in which case the period of surveillance is extended to a year (15).

TABLE 21-1

Six Performance Measures of the CMS' SCIP

1. Delivery of intravenous antimicrobial prophylaxis within 1 h before incision (2 h are allowed for administration of vancomycin or fluoroquinolones)
2. Use of antimicrobial prophylactic agents consistent with published guidelines
3. Discontinuation of use of prophylactic antibiotics within 24 h after surgery (48 h allowable for cardiothoracic procedures in adults)
4. Proper hair removal: no hair removal or hair removal with clippers or depilatory method. Use of razors is not appropriate
5. Controlling blood glucose during immediate postoperative period for patients undergoing cardiac surgery: controlled 6:00 AM blood glucose level (<200 mg/dL) on postoperative days 1 and 2, with procedure day postoperative day 0
6. Maintenance of perioperative normothermia for patients undergoing colorectal surgery

(From Bratzler DW, Hunt DR. The surgical infection prevention and surgical care improvement projects: national initiatives to improve outcomes for patients having surgery. *Clin Infect Dis* 2006;43:322–330 with permission from Oxford University Press.)

Superficial Incisional Surgical Site Infections: Superficial Incisional Primary/Superficial Incisional Secondary

Superficial incisional SSIs (superficial incisional primary [SIP] or superficial incisional secondary [SIS]) must occur within 30 days after the operative procedure *and* must involve only skin and/or subcutaneous tissue of the incision, *and* at least one of the following must be present:

1. Purulent drainage from the superficial incision
2. Microorganisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection—pain or tenderness, localized swelling, redness, or heat—*and* the superficial incision is deliberately opened by the surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician

There are two specific types of superficial incisional SSI:

- Superficial incisional primary (SIP): a superficial incisional SSI that is identified in the primary incision in a patient who has had an operation with one or more incisions (e.g., C-section incision or chest incision for coronary artery bypass graft [CAGB] with a donor site)
- Superficial incisional secondary (SIS): a superficial incisional SSI that is identified in the secondary incision in a patient who has had an operation with more than one incision (e.g., donor site [leg] incision for CABG)

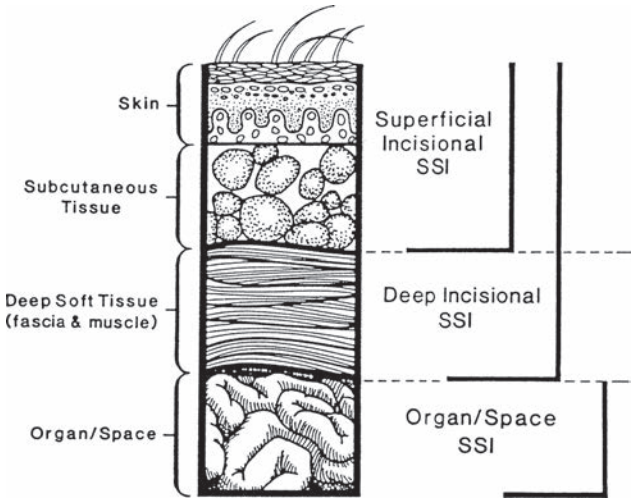

FIGURE 21-1 The anatomy of SSIs and their appropriate classifications.

The following should not be reported as superficial incisional SSIs: (a) stitch abscess (minimal inflammation and discharge confined to the points of suture penetration), (b) localized stab wound infection, (c) infection of a circumcision site in newborns, (d) infected burn wound, (e) incisional SSI that involves or extends into the fascial and muscle layers (should be reported as deep incisional SSI), and (f) involves both superficial and deep incision sites (report as deep incisional SSI).

Deep Incisional Surgical Site Infections: Deep Incisional Primary/Deep Incisional Secondary

Deep incisional SSIs (deep incisional primary [DIP] or deep incisional secondary [DIS]) must occur within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place; the infection must appear to be related to the operative procedure; *and* the infection must involve deep soft tissues (fascial and muscle layers) of the incision; *and* at least *one* of the following must be present:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision that spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured when the patient has at least *one* of the following signs or symptoms: fever (>38°C), or localized pain or tenderness. A culture-negative finding does not meet this criteria.
3. An abscess or other evidence of infection involving the deep incision that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

There are two specific types of deep incisional SSI:

- Deep incisional primary (DIP): a deep incisional SSI that is identified in the primary incision in a patient

who has had an operation with one or more incisions (e.g., C-section incision or chest incision for CAGB with a donor site)
- Deep incisional secondary (DIS): a deep incisional SSI that is identified in the secondary incision in a patient who has had an operation with more than one incision (e.g., donor site [leg] incision for CABG)

Infection that involves *both* superficial and deep incision sites should be classified as a deep incisional SSI.

Organ/Space Surgical Site Infections

Organ/space SSIs involve any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSIs to identify the location of the infection (e.g., intra-abdominal site).

Organ/space SSIs must occur within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears related to the operative procedure; *and* the infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure; *and* at least one of the following must be present:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space
2. Microorganisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician

Occasionally, an organ/space infection drains through the incision. Such infection generally does not involve reoperation and is considered a complication of the incision; therefore, it should be classified as a deep incisional SSI.

INCIDENCE OF SURGICAL SITE INFECTIONS

The true incidence of SSIs across the United States has traditionally been difficult to measure for several reasons: (a) much of the earlier incident data came from the CDC's National Nosocomial Infections Surveillance System (NNIS), which was a voluntary network of 200 larger acute care hospitals that reported HAIs to the CDC, and was not representative of all hospitals; (b) the increasing number of outpatient surgical procedures that were not included in SSI surveillance; (c) and with shorter inpatient stays, SSIs occurring postdischarge with unclear if any or how much postdischarge surveillance was performed.

Since 2005, the National Health Safety Network (NHSN) superseded the NNIS, and unlike the NNIS, the NHSN allows for surveillance of healthcare infections outside the intensive care units, and at other types of healthcare facilities, including ambulatory surgery centers *(14)*. In addition, the NHSN currently includes data from more than 2,000 hospitals across the United States due to two main reasons (a) 21 states' legislative mandates to report surveillance data through the NHSN, and (b) the opening of the NHSN to all hospitals, regardless of size *(16–19)*. Therefore, these SSI rates may be more representative of the true incidence of SSIs. In the most recent NHSN report 2006 to 2008, which includes data from 1,545 hospitals, SSI rates were reported by operative procedure and NNIS risk index (an index used to predict risk of SSIs; see further description below), with lowest risk of SSI designated by NNIS risk index = 0, and highest risk designated by NNIS risk index = 3. Between 2006 and 2008, the pooled mean number of SSI per 100 inpatient operations was as low as 0.2 for gallbladder surgery (NNIS risk index = 0, lowest SSI risk group) and as high as 26.7 for rectal surgery (risk index = 3, highest SSI risk group) *(17)*.

In general, the highest rates of infection occur after abdominal surgeries (reported per 100 surgeries): rectal (3.5–26.7), liver transplant (11.6–20.1), bile/liver/pancreas (8.1–13.7), colon (4.0–9.5), small bowel (3.4–6.8), and kidney transplant (3.7–6.6); however, rates for appendix (1.1–3.5), gallbladder (0.23–1.72), and exploratory abdominal surgery (1.7–2.8) were fairly low. Neck surgeries (NNIS risk index = 2 and 3) also had a high rate of 11.4 SSIs per 100 surgeries. Rates of other high-volume surgeries, therefore with a high absolute number of infections, include all coronary bypass surgery (0.4–8.5), cardiac surgery (1.1–1.8), hip prosthesis (0.7–2.4), knee prosthesis (0.6–1.6), laminectomies (0.7–2.3), spinal fusion (0.7–4.2), cesarean section (1.5–3.8), vaginal hysterectomy (0.7–1.2), and abdominal hysterectomy (1.1–4.0).

For eight outpatient procedures, the rates were between 0.0 and 1.31 per 100 surgeries, but again, it is unclear if any or how postdischarge surveillance was performed *(18)*.

In contrast to SSIs among adults, the rate of SSIs among children has not been studied as extensively. However, medical centers with large pediatric surgical services have published their infection rates. Among these centers, the rate of pediatric SSIs varied from 3.4 per 1,000 admissions at the Children's Hospital in Buffalo *(18)* to 5.5 per 1,000 admissions at the University of Virginia *(20)*. Horwitz reported a rate of 4.4% of all surgeries at three institutions *(21)*. Duque-Estrada reported an overall infection rate of 575 pediatric surgeries to be 6.7%, ranging from 2.7% of clean surgeries to 14.6% of dirty/infected surgeries *(20)*. Both the Horwitz and the Duque-Estrada studies showed increased risk due to the amount of contamination at surgery and duration of surgery, with no difference in risk due to patient-specific factors, length of prior hospitalization, location of operation, or other coexisting diseases, raising the concern that factors at operation, rather than overall physiologic status, contribute to SSIs in children. Another study examining risk factors for sternal wound infection in children undergoing cardiac surgery with sternotomy showed overall SSI rate of 2.7%, with 62% of the infections defined as superficial infections and 38% deep infections. Younger age, cyanotic heart disease, and central venous catheter dwell time increased risk *(22)*. According to CDC estimates based on NNIS, National Health Discharge Service (NHDS), and the American Hospital Association survey, the SSI rates from well-baby nurseries, high-risk nurseries, and intensive care units (both children and adults) were 0.003, 0.2, and 0.95 per 1,000 admission-days, respectively *(3)*.

MICROBIOLOGY

Table 21-2 depicts the most common SSI pathogens and their antibiotic resistance as reported to the NHSN from January 2006 to October 2007 *(14)*. Over the past several decades, the species of microorganisms, and their relative importance, in causing SSI still have not changed considerably. *S. aureus* and coagulase-negative staphylococci continue to be the two most common pathogens isolated largely from clean surgical procedures. When surgery involves entry of the respiratory, gastrointestinal, or gynecologic tracts, pathogens are often polymicrobic, involving aerobic and anaerobic microorganisms endogenous to the organ resected or entered.

In recent years, however, there has been noted in SSIs, as in other sites of HAIs, a shift toward infections with antibiotic-resistant strains of both gram-positive and gram-negative microorganisms. In the NHSN report, from 2006 to 2007, about half of *S. aureus* SSI isolates were methicillin resistant, and 20% of enterococcal infections were vancomycin resistant. Almost a quarter of all *E. coli* were resistant to quinolones, almost 15% of *K. pneumoniae* resistant to third-generation cephalasporins, more than 30% of *A. baumanii* were resistant to carbapenems, and 2% to 5% of *E. coli* and *K. pneumoniae* were carbapenem resistant (12). Infections involving fungi, especially *Candida albicans* and non-albicans *Candida* species, are becoming more common because of the increasing number of immunocompromised patients undergoing operative procedures and use of broad-spectrum antibiotics.

In addition, SSIs caused by unusual microorganisms are also increasingly being recognized; for example, SSIs caused by *Rhizopus rhizopodiformis* due to contaminated adhesive dressings *(23,24)*, multiple outbreaks of infections with rapid growing *Mycobacterium* species *(25–29)*, *Nocardia,* and *Rhodococcus bronchialis* after coronary artery bypass surgery have been reported *(30,31)*. Healthcare-associated SSIs and prosthetic valve endocarditis due to *Legionella pneumophila* after contamination by tap water have been described *(32–34)*. Clusters of infections by such unusual microorganisms clearly warrant investigation to rule out common source exposures.

PATHOPHYSIOLOGY AND RISK FACTORS OF SURGICAL SITE INFECTION

In 1965, Altemeier and Culbertson *(35)* stated that the risk of an infection varies (a) directly in proportion to the dose of bacterial contamination, (b) directly in proportion

TABLE 21-2

SSI Pathogens (NHSN) 2006–2007, *n* = 7,025

Pathogen, Antimicrobial	*% (No.) of Pathogenic Isolates Reported*	*% (No.) of Pathogenic Isolates Resistant*[a]
S. aureus	30.0 (2108)	
Oxacillin		49.2 (1,006)
Coagulase-negative staphylococci	13.7 (965)	Not reported
Enterococcus spp.	11.2 (788)	
Vancomycin		19.7 (136)
Ampicillin		23.8 (151)
Escherichia coli	9.6 (671)	
Ceftriaxone or ceftazidime		5.3 (26)
Fluoroquinolones		22.7 (143)
Carbapenem		2.5 (11)
Pseudomonas aeruginosa	(5.6) 390	
Fluoroquinolone		15.9 (60)
Piperacillin or piperacillin/tazobactam		7.9 (23)
Amikacin		2.0 (4)
Imipenem/meropenem		11.8 (33)
Ceftazidime		5.7 (15)
Enterobacter spp.		
Klebsiella pneumoniae	3.0 (213)	
Ceftriaxone or ceftazidime		8.1 (3)
Carbapenem		5.2 (8)
Candida spp.	2.0 (145)	
Klebsiella oxytoca	0.7 (40)	
Ceftriaxone or ceftazidime		8.1 (3)
Acinetobacter baumanii	0.6 (42)	
Carbapenem		30.16 (11)
Other	19.4 (1,363)	

[a]% (No.) of pathogenic isolates tested that were resistant.
(From Hidron AI, et al. NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* 2008;29(11):996–1011, with permission.)

to the virulence of the microorganism, and (c) inversely in proportion to the resistance of the host, that is, the patient's ability to control the microbial contamination.

The host's ability to control the inevitable bacterial contamination of a surgical wound is a complex interaction between overall host characteristics (i.e., age, immunosuppression, obesity, diabetes), appropriate antimicrobial prophylaxis, surgical site conditions during and at the end of the operation (i.e., blood flow, damaged or necrotic tissue, foreign material, including drains and sutures), and operative characteristics (i.e., use of razors for shaving, skill of surgeon, type of surgery). Practically, the surgical site condition may be influenced by perioperative homeostasis, which includes blood glucose levels, normovolemia, oxygenation, and temperature. The condition of the surgical site is also determined by the underlying disease process at the surgical site, that is, severity of trauma or prior radiation.

MICROBIAL RISK FACTORS

Surgical Site Classification

The risk of developing an SSI is affected by the degree of microbial contamination of the operative site. A widely accepted system of classifying operative site contamination was developed by the National Research Council for its cooperative study of the effects of ultraviolet irradiation of operating rooms on SSIs *(36)*, with the least contamination in clean sites and the most in dirty-infected sites. This classification scheme, in a modified form, is as follows:

Clean sites (wounds): These are surgical sites in which no inflammation is encountered and the respiratory, alimentary, genital, and urinary tracts are not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Surgical sites for operations that follow nonpenetrating (blunt) trauma should be included in this category if they meet these criteria.

Clean-contaminated sites (wounds): These are operative sites in which the respiratory, alimentary, genital, or urinary tract is entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

Contaminated sites (wounds): These include open, fresh accidental wounds or operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract. Surgical sites through which there is entry into the genitourinary tract with infected urine or biliary tract with infected bile, and surgical sites in which acute, nonpurulent inflammation is encountered, fall into this category.

Dirty and infected sites (wounds): These include old traumatic wounds with retained devitalized tissue, foreign bodies, or fecal contamination. Surgical sites where a perforated viscus or pus is encountered during the operation fall into this category.

Early studies showed that this surgical site (wound) classification scheme did predict the risk of subsequent SSIs. In Cruse and Foord's *(37)* study, surgery involving clean, clean-contaminated, contaminated, and dirty surgical sites had infection rates of 1.5%, 7.7%, 15.2%, and 40%, respectively. The SSI rates in the National Research Council cooperative study were 3.3% for refined clean sites, 7.4% for other clean sites, 16.4% for contaminated sites, and 28.6% for dirty sites *(36)*.

The correlation of site (wound) class to the risk of SSIs would suggest that intraoperative site contamination should also be linked to the risk of subsequent infections. However, conflicting results were obtained when the microbiology of intraoperative site contamination was examined and attempts were made to correlate microorganisms isolated intraoperatively with pathogens responsible for the SSIs. Barlett et al. *(38)* isolated bacteria from 43 of 91 (47%) intraoperative surgical site irrigation cultures. However, they found no significant difference in the rate of subsequent SSIs between those patients with and those without positive cultures. Further, there was no relationship between the concentration of bacteria in the sites and the subsequent development of infection. A more recent prospective study of neurosurgical patients found no association between total colony-forming unit (CFU) counts of skin flora, either before or after skin preparation, at the operative site and SSIs *(39)*. Therefore, it is clear that degree of microbial contamination is only one risk factor for development of SSIs.

Sources for Pathogens Causing Surgical Site Infections

Pathogens that cause SSIs are predominately acquired endogenously from the patient's own flora or potentially from exogenous contact with operating room personnel or the environment. It is believed that, within 24 hours of an operative procedure, most surgical sites are sufficiently sealed, unless the site was closed secondarily or involved drain placement, making the surgical site resistant to inoculation and infection. Thus, most pathogens, whether endogenously or exogenously acquired, are believed to be implanted at the time of surgery *(40)*. Theoretically, the operative site can be seeded postoperatively by the hematogenous or lymphatic route or by direct inoculation of the closed operative site, but such mechanisms of acquisition are thought to occur infrequently *(40)*. Ehrenkranz and Pfaff *(41)*, however, described a cluster of sternal infections occurring postoperatively that were preceded by infections caused by the same microorganisms at remote sites (pneumonias and bacteremias). In the outbreak of *Legionella* sternal infections reported by Lowry et al. *(34)*, patients were not exposed to contaminated tap water containing *Legionella* during bathing and dressing changes until well after cardiac surgery. Thus, there is evidence to suggest that inoculation (and infection) may occasionally occur postoperatively. Nonetheless, the period of greatest risk for infection remains the time between opening and closing the operative site.

Endogenous Sources of Pathogens The patient's own flora at or contiguous to the site of operation accounts for the majority of SSIs *(42)*. *S. aureus* and coagulase-negative staphylococci, the first and second most frequent causative microorganisms, are residents of skin and mucous membranes, and presumably they are directly inoculated

into the operative site during incision or subsequent manipulations. Between 2006 and 2007, 44% of all SSIs reported to the NHSN were either due to coagulase-negative *Staphylococcus* or *S. aureus*; over 56% of SSIs were due to gram-positive microorganisms and yeast, common skin commensals (12). Unsurprisingly, colonization of the nares and skin with *S. aureus* is a risk factor for developing SSI due to *S. aureus,* and may quadruple the odds of a *S. aureus* SSI compared to those who are not colonized (43). Recently, in a double-blind randomized trial, rapid identification of *S. aureus* colonization by PCR, and subsequent decolonization of the skin and nares of colonized individuals with chlorhexidine showed a 60% reduction in cardiac surgery SSIs due to *S. aureus* (44). However, in order to prevent one *S. aureus* SSI, the number needed to screen and treat was 250 and 23, respectively, making screening and decolonization not cost-effective.

Skin antisepsis during preparation of the operative site for surgery is routinely performed and reduces the surface population of all skin microorganisms, therefore reducing risk of SSIs. Darouiche et al. (45) recently published a prospective randomized study of patients undergoing clean-contaminated surgery (70% abdominal, 30% nonabdominal), which demonstrated a >40% reduction in total SSIs among patients randomized to preoperative chlorhexidine-alcohol skin preparation compared to providine-iodine scrub. This decrease was due to a significant decline in incidence of superficial and deep incision infections caused by gram-positive bacteria and *Candida,* demonstrating the importance of skin flora on incisional SSI pathogenesis, even among clean-contaminated surgeries.

However, if the skin became heavily colonized—for example, as a result of dermatitis—resident flora may persist and be carried into the operative site. In addition, even optimal skin antisepsis may not be able to eradicate all skin bacteria, as up to 20% of these bacteria live beneath the skin's surface along the hair follicles and sebaceous glands *(40)*.

During nonclean surgery, besides the significant role of skin flora that can contaminate the incision, normal flora of the gastrointestinal, respiratory, genital, and urinary tracts can directly contaminate the operative site when these tracts are opened or when injury has occurred to one of these tracts prior to surgery.

The patient's endogenous flora at distant sites may also be a source of SSI. Wiley and Ha'eri *(46)* noted that human albumin microspheres (HAMs) were like human skin squames and could be used as tracer particles. When they applied HAM to the patient's skin outside the area of the incision, they demonstrated that the tracer particles could be easily recovered from the operative site (in 40 of 40 orthopedic operations), suggesting that surface microflora can migrate from distant sites and gain entrance to the operative site despite distance and the use of cloth and adhesive drapes as barriers. Finally, microorganisms causing infections at remote sites may gain access to operative sites by hematogenous or lymphogenous seeding, which is most commonly associated with bacteremia after implantation of prosthetic material (47). Untreated urinary tract, skin, and respiratory tract infections have also been associated with an increase in the rate of SSIs *(48,49)*.

Exogenous Sources of Pathogens

Personnel The hands and nails of the operative team harbor microorganisms that can contaminate the surgical site by direct inoculation during the operative procedure *(50–52)*. This has led to the use of surgical gloves as a barrier to the transfer of microorganisms and to the surgical hand scrub to reduce the microbial population on the skin of the hands. Initially introduced as a way of protecting operating room personnel against dermatitis from Listerian antisepsis, surgical gloving has became a standard of practice as a method to prevent the passage of microorganisms from the surgeon's hands to the patient's surgical site. Whether surgical gloves are an effective barrier has been questioned, since studies have demonstrated that glove perforations occur frequently; this occurs in up to a third or more of operations *(37,52)*. Nonetheless, with appropriate preoperative scrubbing to reduce the burden of microorganisms on the surgeon's hands, there is no evidence that such perforations of surgical gloves are of any clinical significance. Dodds et al. *(53)* found no difference in the rate of SSIs among 100 hernia repairs that were or were not associated with glove perforations.

However, despite standard hand hygiene and gloving, outbreaks due to artificial nails have been reported, due to sequestered microorganisms trapped between the natural and artificial nail *(54)*.

In addition to the hands, other body sites in the operative team may be sources for exogenous contamination of the operative site. The hair and scalp of hospital staff (as well as of patients themselves), nares and oropharynges have been shown to harbor potentially pathogenic bacteria, including *S. aureus* and gram-negative bacteria *(55)*. Despite those observations, however, only a few outbreaks of SSIs have been traced to the hair/scalp or nasopharynx of the operative team *(50,56)*. However, outbreaks of group A *Streptococcus* SSI have been traced to anal or vaginal carriage by operating room personnel *(57–60)*.

Environment The microorganisms that are isolated from the operating room environment are usually considered nonpathogens or commensals that are rarely associated with infections (61). Atypical mycobacteria are ubiquitous and can be recovered from hospital dust but are rarely incriminated in SSIs. In the clusters of infections due to Mycobacterium fortuitum and M. chelonae that followed valve replacement surgery and augmentation mammoplasty (27–29), it was bone wax or gentian violet marking solution that was incriminated rather than the general operating room environment. Spores of Clostridium perfringens have been isolated from the ventilation system and floors of operating rooms (62), but when investigators looked for potential sources for these microorganisms that cause devastating SSIs, they concluded that *C. perfringens* was either endogenously acquired from the patient's own gastrointestinal flora (63) or acquired from contaminated surgical instruments that had been inadequately sterilized between cases (64).

In those rare instances when inanimate sources in the operating room have been incriminated, the sources have been contaminated solutions, antiseptics, or dressings. Contaminated elastic dressings have been implicated

in SSIs caused by *Rhizopus (24,25,65)* and *C. perfringens (66)*. Contaminated solutions have been the source for SSIs caused by *P. aeruginosa, P. multivorans,* and *Serratia marcescens (67–69)*.

It is currently standard practice to wet mop the floor of the operating room with a disinfectant between cases. Coupled with a more thorough wet vacuuming of the rooms and corridors at night, this routine is believed to provide a sufficiently clean environment that minimizes the risk of the operating room environmental surfaces and floors as a source of infection.

Air The role of the operating room air as a source of infection and the need for special ventilation systems in the operating room have long been subjects of debate. The largest source of airborne microbial contamination is the staff in the operating room (61,62). It is presumed that microorganisms become airborne as a result of conversation, which creates droplet nuclei from the respiratory tract, or as a result of shedding from hair or exposed skin. Tracer particle studies using HAMs suggest that airborne microorganisms from the respiratory tract or the head and neck area of operating room personnel can settle on the operative site (46,70,71). Despite this possibility, there is little evidence that the airborne route of transmission contributes significantly to SSIs. Evidence that SSI resulting from airborne contamination occurs at all is based on outbreaks of group A b-hemolytic streptococcal infections that have been reported in the literature (57–60). In these outbreaks, the evidence for airborne transmission was as follows. First, streptococci with the same serotype as the isolates from infected surgical sites were isolated from sites of colonization (anal, vaginal, or pharyngeal) in operating room personnel. Second, the sites of carriage (anal or vaginal) had no possibility of direct contact with the operative site. Moreover, some of these carriers were ancillary personnel who, while they were in the same room, did not work directly in the operative field. Finally, when settling plates were used during these investigations, the epidemic microorganism could be recovered from the air of a room during exercise by the carrier.

Additional evidence for the role of airborne transmission comes from studies on the use of laminar flow air systems and ultraviolet irradiation to provide ultraclean air. Early studies appeared to show a reduction in SSIs when special air-handling systems were used to reduce airborne microbial contamination *(72–75)*. However, many of these studies were flawed, because they were not comparative, had inadequate sample sizes, were not randomized or blinded, or included other interventions that could affect the rate of SSIs. A well-designed multicenter European study compared infection rates among total hip and knee replacement procedures that were performed in rooms with ultraclean air provided by special ventilation systems, antimicrobial prophylaxis alone, or ultraclean air plus antimicrobial prophylaxis (76). In rooms with ultraclean air, the frequency of SSIs decreased from 3.6% to 1.6%; however, when antimicrobial prophylaxis alone was used, the rates dropped from 3.4% to 0.8%. The combination of interventions decreased rates from 3.4% to 0.7%. These results helped demonstrate antimicrobial prophylaxis to be more beneficial in prevention of SSIs than ultraclean air, with no additional benefit of ultraclean air when antibiotics were used.

HOST RISK FACTORS

It is clear that degree of microbial contamination is only one of several variables that determine SSI outcome. Intuitively, host susceptibility, that is, the host's intrinsic ability to defend itself against microbial invasion, should be an important determinant of the risk of infection following surgery. Over the years, studies have demonstrated that such factors as age, obesity, current smoking, prior irradiation at the site of the procedure, malignancy, immunosuppressives, the presence of certain underlying diseases such as diabetes (and hyperglycemia), and *S. aureus* nasal colonization can all increase risk of SSI (*36*,43,*77–82*).

Age

Of these host factors, advanced age has consistently been found to be a risk factor for SSIs, likely due to increased comorbidities, decreased immune function, increasing frailty, and malnutrition (*36,37,77,83–85*). In contrast, others, like Garibaldi and Cushing *(86)*, did not find age to be a risk factor. In their study, it was suggested that age is a marker for increased comorbidities. In the national nosocomial infection study by Haley et al. *(87)*, the percentage of SSIs after 75 years decreased. Recently, Kaye, using a large cohort of over 70,000 procedures, demonstrated that the risk of SSI increased by 1.1% per year between ages of 17 and 65; however, at ≥65 years, the risk of SSI decreased by 1.2% per year *(88)*. Though unclear why rates of SSI should decrease after 65 years of age, lower rates may be a reflection of a surgical selection bias, that only healthier older patients are taken for surgery, or that very old patients are "hardy survivors," with better genetics that enable them to better handle the stressors of surgery. Nevertheless, other studies have shown that elderly patients with SSIs are at increased risk for death compared to younger patients with SSIs. For instance, elderly patients with *S. aureus* SSI were greater than three times more likely to die than younger patients with *S. aureus* SSIs *(89)*.

Diabetes and Hyperglycemia

One risk factor associated with SSIs is elevated blood glucose levels perioperatively or a history of diabetes. Pathophysiologically, diabetes impairs leukocyte adherence, phagocytosis, and overall ability to kill bacteria. In addition, the extracellular glycosylation of proteins due to high blood glucose levels impairs wound healing *(90)*. Cruse and Foord *(37)* reported higher rates of SSIs in their patients with diabetes, as did Nagachinta et al. (91) in their prospective study of 1,009 cardiac surgery patients. In the latter study's regression analysis, diabetes mellitus and obesity were the two host factors that remained independently associated with sternal or mediastinal SSIs. Since these early studies, diabetes has most consistently been associated with increased SSI, especially deep sternal wound infections, in cardiovascular patients (*90,92,93,*94), but has also been a documented risk factor in patients undergoing mastectomy and hepatobiliary-pancreatic cancer surgeries as well *(95,96)*.

More important than a history of diabetes may be the level of postoperative hyperglycemia. Latham et al. *(93)*

observed that in cardiac surgery patients, the risk of SSIs after cardiovascular surgery correlated with the level of postoperative hyperglycemia. The odds of developing an SSI was >2.5 when blood glucose was 200 or more within 48 hours after surgery, compared to those with levels <200 *(93)*. Other cohort studies *(90,94)* have also demonstrated improved deep sternal SSI rates with improving blood glucose levels to <200 in the 48 hours postoperatively, most effectively achieved with continuous insulin infusion.

However, it is unclear if more aggressive hyperglycemia management, below glucose levels of 200, is associated with decreases in cardiovascular SSI. The Diabetic Portland Project, which was an observational cohort study of diabetic cardiovascular surgery patients, demonstrated, over time, the progressive reduction in sternal wound infections, mortality, and length of stay with the use of progressive lowering of target blood glucose ranges by using continuous insulin pump protocols *(97)*. The lowest rates of deep sternal wound infections were found by targeting blood glucose levels of 100 to 150. However, a meta-analysis of five randomized controlled trials comparing conventional blood glucose control (blood glucose <200, which is the current recommendation by IDSA/CDC) versus strict glucose control did not show any SSI, mortality, or length of stay, benefits to strict glycemic control; however, the studies had multiple limitations of sample size and methodologic quality *(98)*.

In addition to postoperative hyperglycemia, long-term hyperglycemia may be a risk factor for SSIs as well. Dronge et al. *(99)* demonstrated in a retrospective study that patients with good long-term control of blood glucose (hemoglobin A1c <7%) had decreased infectious complications (SSIs, pneumonia, urinary tract infection, or sepsis) across a broad range of surgeries, specifically excluding cardiac cases. In Latham's study *(93)* of cardiac patients, patients with good long-term control of diabetes (hemoglobin A1C <8%) were at less risk of developing postoperative hyperglycemia.

Nutrition

The association between malnutrition and SSIs is not well proven. The National Research Council study showed that the crude rate of SSIs was 22% in severely malnourished patients compared to 7% in well-nourished patients *(36)*. However, subsequent studies have not demonstrated an increased risk of SSIs with malnutrition, after adjusting for other risk factors (91,*100*). Multiple trials have not demonstrated any benefit of preoperative total parenteral nutrition (TPN) or other "nutritional therapies" in prevention of SSIs (101).

On the contrary, studies have repeatedly demonstrated the increased risk of SSIs with obesity (*36*,91,*102,103*). This increased risk is likely multifactorial, including increased amount of tissue necrosis, compromised blood flow, but also may be due to inadequate dosing of prophylactic antibiotics *(104)*. Forse et al. *(104)* demonstrated a decrease in wound infections in morbidly obese patients undergoing gastroplasty surgery from 16.5% to 5.6% (2.5% in normal weight patients) by administration of 2 g of cefazolin, rather than 1 g normally administered perioperatively.

Smoking

Nicotine may increase rates of SSI by reducing blood flow, therefore delaying primary wound healing. Nagachinta et al. (91) demonstrated in a large prospective trial that patients who are current smokers have twice the increased odds of SSI compared to ex-smokers or nonsmokers. Other studies have supported these findings.

PROCEDURAL RISK FACTORS

Prolonged Preoperative Stay

Over the years, studies have consistently demonstrated an adverse effect of prolonged preoperative stay on the rate of SSIs. The National Research Council study found that the rate of SSI rose from 6% for a preoperative stay of 1 day to 14.7% when the preoperative stay was 21 or more days *(36)*. Cruse and Foord *(37)* reported that the overall infection rate was 1.1% for patients whose preoperative stay was 1 day versus 2.1% in patients who remained in the hospital for 1 week before their operation. These early studies might be criticized, because the influence of other risk factors was not specifically taken into account. Other studies, however, have used multivariate analysis methodology to adjust for potentially confounding variables (91,*105,106*). These studies continue to find prolonged preoperative stay to be an important independent risk factor for SSIs.

The mechanism(s) by which prolonged hospital stay brings about an increased risk of infection is unknown. A long preoperative stay may promote proliferation of endogenous microorganisms, which can then more heavily contaminate the surgical site, or such a stay may promote the acquisition of hospital-acquired multidrug-resistant pathogens. Prolonged preoperative stay also permits the performance of procedural interventions that allow microorganisms access into the body (portals of entry) or chemotherapeutic interventions that can adversely affect host resistance (e.g., steroids) or alter normal flora (e.g., through exposure to antibiotics). Researchers have found that patients who are hospitalized for cardiovascular surgery quickly become colonized with methicillin-resistant coagulase-negative staphylococci and that these microorganisms were responsible for surgical site complications including mediastinitis and prosthetic valve endocarditis *(106–109)*, though it is unclear whether these microorganisms were acquired during their admission or whether the perioperative antibiotics selected for drug-resistant strains.

Preoperative Shave

In 1971, Seropian and Reynolds *(110)* compared the SSI rate among 406 surgical patients randomized to hair removal by razor or by depilatory. The rate of infection after shaving was 5.6% compared with 0.6% when hair was removed by a depilatory or not removed at all ($p < .02$). In this study, the timing of hair removal also affected the infection rate. Among patients subjected to the razor, the infection rate was 3.1% when the shaving was done just before surgery versus 7.1% when the patient was shaved within 24 hours of surgery, and >20% when patients were shaved more than 24 hours before surgery. In the study by Cruse and Foord *(37)*, similar results were obtained. Patients who were shaved with a razor had the highest rate of infection at 2.5%, clipping decreased the infection rate to 1.7%, and shaving with an electric razor had a rate of 1.4%. Those who were

neither shaved nor clipped had the lowest infection rate of 0.9%. A recent meta-analysis that evaluated 11 randomized controlled trials concluded that there were no differences in SSI rates among those who had hair removal versus those who did not. If hair was removed by shaving versus clipping, the relative risk of SSI was two times higher (RR: 2.02, 95% confidence interval [CI]: 1.21–3.36) *(111)*.

When a scanning electron microscope was used to examine the skin after removal of hair with a razor, electric clipper, and a depilatory, photographs showed that the razor caused gross skin cuts, the clipper caused less injury, and the depilatory caused no injury *(112)*. Thus, the increase in SSIs may result from disruptions in the skin barrier caused by the razor, permitting an increase in colonization or actual invasion with either resident or exogenous microorganisms at the incision site.

Surgical Hand Antisepsis Surgical hand antisepsis is intended to reduce the number of microorganisms on the surgeon's hands and reduce contamination of the operative site through recognized or unrecognized breaks in surgical gloves. This is achieved through the use of an antiseptic hand scrub preparation or hand rub, which the U.S. Food and Drug Administration defines as "a nonirritating antimicrobial containing preparation that significantly reduces the number of microorganisms on intact skin" *(113)*. The only trial evaluating SSI rates found no difference in SSI rates between surgeons that underwent hand rubbing with alcohol solutions versus traditional surgical hand scrubbing. Five-minute hand rubbing with an alcohol solution, preceded by a 1-minute nonantiseptic hand wash before the surgeon's first procedure of the day or before any procedures if the hands were visibly dirty, was compared to at least 5 minutes of hand scrubbing with solutions containing 4% povidone iodine or 4% chlorhexidine gluconate. Not only were there no difference in rates of SSI, but hand-rubbing protocol was better tolerated and had increased rates of compliance (114). Other studies that evaluated CFU of bacteria as the outcome suggest that aqueous alcohol rubs are as effective, or more effective, in reducing CFUs *(115)*.

When comparing only aqueous scrubs, in a recent meta-analysis *(115)*, using microbiologic data as an end point, solutions containing chlorhexidine gluconate appear to be the most effective in reducing microbial hand flora compared with iodophors or hexachlorophene-containing products. No clinical data indicate that reduction of hand flora with hand scrubs will lead to a reduction in the rate of SSIs.

The wearing of long or artificial nails by operating room personnel may compromise the efficacy of the preoperative hand scrub. Several studies suggested that long or artificial nails enhance hand colonization with bacteria and fungi *(116,117)*. In several investigations, such enhanced colonization was linked to outbreaks of bloodstream infections by *P. aeruginosa* in a neonatal intensive care unit and SSIs with *S. marcescens* among cardiovascular surgery patients *(117,118)*. These reports have prompted the CDC in its latest guideline to recommend that operating room team members keep their nails short and that they not wear artificial nails (category IB) (101).

Preoperative Showers Preoperative bathing or showering with an antimicrobial product has been advocated as a preoperative measure with the goal of reducing skin colonization by bacteria that can contaminate the operative site. Cruse and Foord *(37)* reported that SSI rates for clean sites (wounds) were 2.3% for patients who did not shower, 2.1% for patients who showered with soap, and 1.3% for those who showered with hexachlorophene. Studies by Wihlborg *(119)* and Hayek et al. *(120)* seem to confirm the observations of Cruse and Foord. However, other trials have failed to demonstrate a significant difference in SSI rates when different methods of preoperative bathing were used. Garibaldi et al. *(121)* observed no significant difference in infection rates between surgical patients who showered with chlorhexidine and those who showered with povidone-iodine or bar soap. In a large prospective, randomized, double-blinded trial involving 1,400 patients who bathed preoperatively with or without chlorhexidine *(122)*, and a smaller, more recent study in 2009 *(123)* also were unable to find any significant difference in infection rates. In a recent meta-analysis (124), which included seven studies, there was no significant difference in infection rates between those who showered with chlorhexidine versus placebo or those who showered with chlorhexidine versus soap and water. However, one large study did show decreased SSI rates with chlorhexidine versus no shower *(125)*.

Barrier Devices Experimental studies using tracer particles suggest that microorganisms can be shed from hair, exposed skin, and mucous membranes of operating room personnel and that the patient's endogenous skin flora contiguous to or even distant from the operative site can gain access to the operative site through indirect contact *(46,70)*. The use of masks, hoods, and gowns by operating room personnel is intended to reduce shedding of microorganisms by operative personnel. Similarly, surgical drapes are used to cover the patient except for the operative site and to act as a barrier to contamination from endogenous skin flora by indirect contact. Despite the strong theoretical rationale based on these experimental studies, no clinical studies have proved that the use of the barrier devices discussed below has led to a reduction in the rates of SSI.

Masks A 1991 study found no difference in the numbers of SSIs among patients undergoing operations by surgeons who did or did not wear masks *(126)*. Similarly, Orr *(127)* observed no increase in the infection rate when masks were not worn for 6 months. These studies question the importance of surgical masks as an infection control measure. The most important role of the surgical mask is to prevent contamination of the mucous membranes of the operative team.

Caps Surgical caps are worn to prevent hair and skin squames, potentially laden with microorganisms, from falling into the operative field. As noted previously, with the exception of a few outbreaks traced to the hair as a source *(55,56)*, there is scant evidence that hair is an important source for surgical site contamination or that caps are effective in preventing such contamination.

Gowns and Drapes Overall, the use of gowns and drapes to prevent surgical site contamination and infection is logical, and their value is implied but not proven

in clinical studies *(128)*. One of the most important roles for surgical gowns is protection of the operative team from contamination by blood and body fluids.

In addition to drapes that simply cover the skin, adhesive plastic drapes are available that are applied to the skin at the operative site. The belief is that adherent coverage of skin up to the margin of the incision would more effectively prevent surgical site contamination from contiguous sites. Paradoxically, Cruse and Foord *(37)* noted a higher infection rate when plastic drapes were used. Other studies, including the findings of a recent meta-analysis, found no difference in infection rates when adhesive plastic drapes were compared to conventional drapes *(129–131)*.

Shoe Covers The use of shoe covers has been a standard practice in operating rooms. However, no studies demonstrate that their use affects SSIs. The American Hospital Association recommends shoe covers only when laundry facilities permit. The principal utility of shoe covers may be protection of the operative team's shoes from contamination by blood and other body fluids.

Preoperative Antibiotics Contamination of operative sites, even clean ones, is unavoidable despite the best preparation and operative technique. Studies by Culbertson et al. *(132)*, Howe and Marston *(133)*, and Burke *(134)* have shown that potentially pathogenic bacteria, including *S. aureus*, can be recovered from up to 90% of surgical sites just before closure. The goal of prophylactic antibiotics, therefore, is to eradicate or retard the growth of contaminant microorganisms such that SSI can be avoided. The practice began with Lister and his carbolic acid wound antisepsis. The advent of antibiotics saw their use as a means of preventing SSIs. Over the past 40 years, numerous animal and clinical trials have demonstrated the importance of appropriate perioperative antibiotics in preventing SSI. Based on these studies, CMS, the Joint Commission, and other organizations have created performance measures in the SCIP that emphasize the importance of using the appropriate antibiotics, appropriate timing of antibiotics, and prompt discontinuation of antibiotics in SSI prevention (13).

There are five main principles in the use of prophylactic antibiotics:

1. Use of antibiotics for appropriate procedures. The consensus among experts, including the CDC, is that antibiotic prophylaxis is appropriate when the operation is associated with a high risk of infection or when the consequences of an SSI are disastrous, even if the risk of infection may not be high—for example, in operations involving any prosthetic implant or cardiothoracic surgeries where mediastinal infections have catastrophic consequences (13,101,*135*). According to this principle, surgical prophylaxis is indicated for all clean-contaminated and contaminated operative procedures, and certain clean surgeries. Prophylactic antibiotics are not indicated for most clean surgery, which have low rates of infection and in which the risks of antibiotics may outweigh the benefits, or dirty/infected surgical sites for which the use of antibiotics are therapeutic and not prophylactic.
2. The antibiotic chosen should be effective against the most likely pathogen(s) encountered, taking into account their antibiotic susceptibilities, drug pharmacokinetics and concentrations, and patient allergies. All surgical procedures that require an incision through the skin are at risk for developing infections with staphylococcal species; therefore, all prophylactic antibiotics should have good staphylococcal coverage. Gastrointestinal, gynecological, and urologic procedures need additional gram-negative Enterobacteriaceae and anaerobic coverage. First (e.g., cefazolin)- and second-generation cephalosporins (e.g., cefoxitin) are the drugs of choice for most surgical procedures due to their activity against the most commonly isolated microorganisms, bactericidal activity, safety profile, and cost (101,*135*,136).

However, the rising incidences of methicillin-resistant *S. aureus* (MRSA), both community-associated and healthcare-associated, and methicillin-resistant *Staphylococcus epidermidis* challenge the empiric use of cephalosporins as prophylaxis. Currently, the CDC and most experts continue to recommend cephalosporins as empiric antibiotics of choice, unless the local prevalence of MRSA is high. However, "high" MRSA rates are not well defined. In addition, vancomycin use in place of cefazolin has not been shown to decrease overall rates of SSIs, as demonstrated in a randomized study of cardiac surgery patients. Those who received cefazolin for prophylaxis had higher rates of MRSA infections, while those who received vancomycin had higher rates of MSSA infections, with no difference in the overall rate of SSI *(137)*. In a meta-analysis of seven randomized trials that compared SSI in patients receiving glycopeptides prophylaxis (i.e., vancomycin) versus those who received β-lactams, neither agent was superior for the prevention of SSIs though glycopeptides were superior in the prevention of SSIs caused by methicillin-resistant gram-positive microorganisms (138). However, many of the studies included in the meta-analysis were performed over 10 years ago, when the incidence of MRSA was lower than present. In a more recent interrupted time series analysis (139), CABG patients were compared before and after an institutional switch from cefuroxime to vancomycin. The monthly SSI rates of CABG decreased by 2.1 cases per 100 surgeries when compared to control patients who had received vancomycin for valve replacement surgery during the entire time period. This study suggests that the decline in SSI rates in CABG patients was due to the change to vancomycin and decrease in infections caused by methicillin-resistant microorganisms, and not by other confounders (139).

Yet, the routine use of vancomycin in prophylaxis raises concerns of increasing the rates of vancomycin-resistant staphylococcal and enterococcal species *(140)*. In addition, vancomycin has a narrow spectrum of activity (no gram-negative coverage) compared to cephalosporins, slower bactericidal killing, long infusion times, and poorer tissue and bone penetration. Thus, routine use of vancomycin in place of cefazolin raises concerns for decreased efficacy against methicillin-susceptible microorganisms, poor drug levels in tissues, increased risk of vancomycin-resistant microorganisms, and a rise in gram-negative microorganisms as causes of SSI or other postsurgical infections (138,*140*).

Currently, the Society of Thoracic Surgeons recommends both vancomycin and cefazolin to be administered perioperatively in cardiac surgery patients if (a) in the setting of either a presumed or a known staphylococcal

colonization, (b) high incidence of MRSA, (c) patients susceptible to colonization (hospitalized >3 days, transfer from another inpatient facility, already receiving antibiotics), (d) or an operation for a patient receiving a prosthetic valve or a vascular graft insertion *(141)*. Certainly, surgical patients who need prophylaxis, and have been identified as MRSA carriers either by preoperative screening or during other healthcare exposures, should receive vancomycin in place of, or perhaps, in addition to a cephalosporin.

3. The timing of antibiotic administration should be such that there are adequate concentrations of the antibiotic in the tissue at the time contamination is likely to occur (as soon as the incision is made).

The classic work of Burke *(142)* in 1961 provided the experimental basis for the scientific study of antibiotic prophylaxis. He showed how critically important timing was in the administration of the antibiotic. Burke administered penicillin at various times before and after intradermal inoculation of *S. aureus* into the skin of guinea pigs and found that, when the antibiotic was administered before or shortly after the inoculation, there was a marked reduction in the severity of inflammation and infection. If administration of the antibiotic was delayed for more than 3 or 4 hours after inoculation, there was no appreciable difference in the size of the dermal lesion or infection compared with animals who received no prophylaxis. The clinical importance of the timing of preoperative antibiotics was reaffirmed by Classen et al. (143). These authors prospectively monitored the effect of the timing of administration of prophylactic antibiotics on the occurrence of SSIs in 2,847 elective clean and clean-contaminated procedures. When prophylactic antibiotics were administered during the 2 hours before incision, the SSI rate was the lowest, at 0.6%, with the rate more than doubling to 1.4% when given during the 3 hours after the incision. The highest rates of infection occurred when antibiotics were administered either early (2–24 hours before incision) at 3.8% or postoperatively (3–24 hours after incision) at 3.3%.

While guidelines differ on the exact ideal timing of antibiotics, ranging from 30 minutes up to 120 minutes prior to incision, the CMS and The Joint Commission have advocated infusion of antibiotics within 60 minutes prior to incision for antibiotics, except for vancomycin and fluoroquinolones that can be infused up to 2 hours prior to incision due to their long infusion times and risk for reactions (13). Currently, the timing of antibiotics within 60 minutes has become a national standard performance measure that is being collected and increasingly publically reported.

Since these early landmark studies, the recently published Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) (144), which prospectively collected data from 29 hospitals and 4,472 randomly selected cardiac, hip/knee arthroplasty, and hysterectomy cases, demonstrated that the risk of SSIs was lowest in patients who received prophylaxis 0 minutes to 30 minutes (for cephalasporins) prior to incision (or within 1 hour for vancomycin or a fluoroquinolone). When vancomycin and fluoroquinolones were excluded, the risk of infection was 1.6% when antibiotics were administered 0 to 30 minutes before incision, compared to 2.4% when the antibiotics were administered 31 to 60 minutes prior incision, with a conditional OR 1.74 (95% CI: 0.98–3.08). The risk of infection increased as the time before antibiotic administration and incision increased or if the antibiotic was infused after the incision (144). Nevertheless, their data do not warrant changing the guidelines from 60 minutes to 30 minutes prior to incision, as the differences in infection rates may be due to chance. Certainly, though, there is no risk and likely benefit in giving short-infusing antibiotics, like cephalosporins, within 0 to 30 minutes of incision.

4. It is important to maintain therapeutic levels of the drug in tissue and blood throughout the entire procedure, which may require redosing of antibiotics during longer procedures and/or higher dosages of antibiotics in obese patients. During prolonged procedures, the open wound is at ongoing risk for bacterial inoculation, and so, adequate concentrations of antibiotics should be maintained for the entire surgical procedure. Therefore, for procedures that are prolonged and have received antibiotics with short-half lives (most cephalosporins), redosing of antibiotics is recommended (11,101,*145*). The TRAPE study observed that the intraoperative lack of redosing with cephalosporins increased the odds of infection (OR: 3.08, 95% CI: 0.74–12.9) in procedures lasting more than 4 hours, as long as the initial dose of antibiotic was timed correctly (144).

In obese patients, traditional dosing of antibiotics may not be adequate to achieve therapeutic levels above the mean inhibitory concentration (MIC) of most microorganisms. In one study of morbidly obese individuals, a 2-g dose of cefazolin rather than 1-g dose was needed to have cefazolin levels greater than the MIC for most bacteria; in addition, this study showed that the use of the 2-g dose dramatically decreased rates of SSI from 26.5% to 5.6% *(104)*. However, in another study, authors found that, even after a 2-g perioperative dose of cefazolin, therapeutic tissue levels were achieved in only 48% of patients with a body mass index (BMI) between 40 and 49, and were achieved only in 10% of patients with a BMI ≥ 60 *(146)*, raising the issue of whether continuous cefazolin infusions are preferable in the morbidly obese.

5. Antibiotics should be discontinued to prevent rise of resistant microorganisms and *Clostridium difficile*. A review of 28 randomized trials comparing one dose versus multiple doses of perioperative antibiotics has not shown any difference in the rates of SSIs across multiple surgical procedures, as antibiotic prophylaxis is limited in efficacy once the wound is closed *(147)*. Even in cardiovascular surgery patients with drains left in place, studies have documented no improvement in SSI rates with antibiotics longer than 48 hours *(148)*. In addition, the prolonged courses of antibiotics have been associated with increased rates of antibiotic-resistant microorganisms and *C. difficile* infections *(148)*. Therefore, most guidelines, including SCIP, recommend discontinuation of prophylactic antibiotics within 24 hours, and within 48 hours after cardiac surgery (11,101,*149*).

The surgical procedures for which antibiotic prophylaxis is currently recommended are shown in Table 21-3.

Intraoperative Measures

Preparation of the Incisional Site

Since SSIs are primarily caused by the skin flora of patients undergoing surgeries, optimal skin antisepsis prior to incision is an important part of SSI prevention. Traditionally,

TABLE 21-3

Antibiotic Prophylaxis for Surgical Procedures to Prevent SSI

Procedure	*Expected Pathogens*	*Antibiotic of Choice*[a]
Cardiac (coronary artery bypass, valve replacement, pacemaker insertion)	*S. aureus, S. epidermidis*, GNB[b]	Cefazolin, cefuroxime, or vancomycin[c]
Vascular surgery	*S. aureus, S. epidermidis*, GNB	Cefazolin or vancomycin[b]
Neurosurgery		
CSF shunt procedures	*S. aureus, S. epidermidis*	Cefazolin or vancomycin[b]
Craniotomy	*S. aureus, S. epidermidis*	Cefazolin or vancomycin[b]
Thoracic (lung resection)	*S. aureus*	Cefazolin
Ophthalmic (lens extraction)	*S. aureus, S. epidermidis,* streptococci, GNB	Topical gentamicin, or tobramycin or neomycin-gramicidin-polymyxin B or subconjunctival cefazolin
Orthopedic		
Joint replacement	*S. aureus, S. epidermidis*	Cefazolin, or vancomycin[b]
Amputation of lower limb	*S. aureus*, GNB	Cefoxitin
General surgery		
Gastric resection	GNB	Cefazolin
Cholecystectomy	GNB, enterococci, clostridia	Cefazolin
Colon surgery	GNB, anaerobes	Oral neomycin and erythromycin base or cefoxitin
Appendectomy	GNB, anaerobes	Cefoxitin or cefotetan
Penetrating abdominal trauma	GNB, anaerobes, enterococci	Cefoxitin or cefotetan
Head and neck		
Procedures with incision through oral or pharyngeal mucosa	*S. aureus*, streptococci, anaerobes	Cefazolin or clindamycin
Gynecologic		
Hysterectomy	GNB, anaerobes, streptococci, enterococci	Cefazolin
Cesarean section	GNB, anaerobes, streptococci, enterococci	Cefazolin[c]
Abortion	GNB, anaerobes, streptococci, enterococci	Cefazolin[d]

[a]Unless indicated, route of administration is intravenous.
[b]To be used when methicillin-resistant *S. aureus* or *S. epidermidis* may be encountered or if patient is allergic to β-lactam antibiotics.
[c]Not to be used in uncomplicated elective procedures.
[d]To be used in uncomplicated abortions unless patient has history of previous pelvic inflammatory disease.
GNB, gram-negative bacilli.

the operative site is prepared first by cleaning to remove superficial bacteria and organic debris and then by application of an antimicrobial solution to reduce the deeply resident skin flora. The most commonly used preoperative skin preparation agents include iodine, chlorhexidine and iodine, or chlorhexidine-containing compounds. Both chlorhexidine and iodophors have a broad spectrum of activity and are effective in reducing the number of microorganisms on intact skin *(150–152)*. Chlorhexidine has a broad spectrum of activity and a substantive action after a single application; unlike the iodophors, it is not inactivated by blood and serum proteins. Chlorhexidine-alcohol has been recommended as the antiseptic of choice to prevent catheter-associated blood stream infections *(153)*.

Darouiche et al. (45) recently published the first multicentered prospective randomized study comparing efficacy of chlorhexidine-alcohol versus povidone-iodine in preventing SSIs in patients undergoing clean-contaminated surgery (70% abdominal, 30% nonabdominal). Patients were randomly assigned to have the operative skin site scrubbed with either 2% chlorhexidine gluconate and 70% isopropyl alcohol or preoperatively scrubbed and then painted with 10% povidone-iodine. Among the total 849 patients in this study, the chlorhexidine-alcohol group had a 41% reduction in risk of all SSIs (RR: 0.51, 95% CI: 0.41–0.85, $p = .0.004$), a 52% reduction in superficial SSIs (RR: 0.48, 95% CI: 0.28–0.84), and a 67% reduction in deep SSIs (RR: 0.33, 95% CI: 0.11–1.01, $p = .05$) compared to the povidone-iodine group. There was no significant difference in organ-space infections between the two groups. Seventeen patients were needed to be treated with chlorhexidine-alcohol versus povidone-iodine to prevent one SSI (45).

While the CDC has not recommended chlorhexidine-alcohol as the antiseptic of choice, this study strongly advocates for the routine use of chlorhexidine-alcohol over povidone-iodine for surgical site preparation (11).

Reduction of Airborne Contamination in the Operating Room Traffic and activity of operating room personnel, including talking and movement, are responsible for increasing the bacterial count in the air (70,71). These airborne microorganisms are usually attached to

dust particles, squames shed by operating room personnel from uncovered skin areas, or respiratory secretions generated by conversation. Attached to particles, these microorganisms settle quickly but can contaminate operative sites located a short distance from the source of the microorganisms. Because of the relationship between the number of operating room personnel and bacterial air count, one method of reducing airborne contamination would be to control the number of people allowed in the operating room and their activity ("traffic control"). Traditionally, this included restricting the number of people allowed in the operating room, closing the doors to the operating room to prevent in and out traffic, and limiting unnecessary movement and talking once in the operating room. The use of proper operating room attire should also serve to decrease the amount of airborne contamination by decreasing the amount of shedding from exposed body areas.

Airborne contamination may be further reduced through dilution by high-volume exchanges with clean, filtered air and introduction of outside air. The standard set by the Public Health Service for the minimum number of air exchanges for the operating room is 15 air changes per hour with three exchanges of outside air *(154)*. However, the value of such a standard requiring high air exchanges is unproven *(155)*. Maki et al. *(156)* compared the results of microbiologic sampling in the operating room and SSI rates in an old and a new hospital. The mean number of microorganisms was lower in the new hospital with 25 air exchanges per hour, compared with 16 air exchanges per hour in the old building. However, they observed no difference in the SSI rates.

Laminar flow ventilation systems and ultraviolet irradiation further decrease airborne contamination to very low levels (ultraclean air). As noted, such ultraclean air would only be expected to lower the SSI rate for clean surgery; specifically, ultraclean air might be of benefit in orthopedic surgery involving the insertion of prosthetic devices, but not for procedures in the other surgical site classes (*36*,76). Even then, the same benefits may be achieved through the use of prophylactic antibiotics. Indeed, a follow-up study by the British National Health Service suggested that, for total joint replacement surgery, antimicrobial prophylaxis was more cost effective than an ultraclean air system *(157)*. Modern rates of organ/space (deep) SSIs following total hip arthroplasty using conventional air-handling systems, standard barrier techniques, and prophylactic antibiotics are comparable with rates reported with ultraclean air-handling systems *(158,159)*.

Length of Operation

The length of surgery has long been established as an important risk factor for SSI. Cruse and Foord *(37)* found a direct relationship between duration of surgery and the infection rate. Among clean wounds, the infection rates for operations lasting 1, 2, and 3 hours were 1.3%, 2.7%, and 3.6%, respectively. The SENIC study found that having an operation lasting more than 2 hours was one of four risk factors for SSI that remained significant when logistic regression techniques were applied to the SENIC database *(160)*. In refining the SENIC risk index for NNIS, Culver et al. *(161)* noted that the 75th percentile of the distributions of duration of surgery for each procedure was a better predictor of infection than the common cut point of 2 hours used for all procedures in the SENIC index. Garibaldi and Cushing *(86)* applied stepwise logistic regression to the analysis of 1,852 procedures and found that the duration of surgery >2 hours was associated with a relative risk of 3 (CI: 1.6–3.6) for SSIs.

Exactly how lengthening duration of surgery increases the risk for SSI remains speculative. Cruse and Foord *(37)* listed four possible explanations: (a) an increase in the contamination of the wound with longer operations; (b) an increase in tissue damage from drying, prolonged retraction, and manipulations; (c) an increase in the amount of suture and electrocoagulation, which may reduce the local resistance of the wound; and (d) greater suppression of host defenses from blood loss and shock. Garibaldi and Cushing *(86)* added that the duration of surgery may be a marker for factors that are difficult to incorporate in multivariate modeling such as the skill of the surgeon and complexity of surgery. Shapiro et al. *(162)* suggested that increased infections after prolonged hysterectomy may be the result of decreasing effects of antibiotic prophylaxis with lengthy procedures. This is the rationale for repeat dosing of antibiotics in operations lasting for more than 2 to 3 hours.

Surgical Technique

The skill of the surgeon has a central role in SSIs. Technique directly affects the degree of contamination of the surgical site through breaks in technique or inadvertent entry into a viscus. The skill of the surgeon also affects the condition of the surgical site and therefore its resistance to infection. The risk of infection is minimized by control of bleeding, gentle traction and handling of tissue, removal of necrotic tissue, and eradication of dead space. Finally, the skilled surgeon can reduce the duration of surgery, which affects the risk of SSI (see above).

The quality of a surgeon's operative technique cannot be easily assessed without direct observation, and thus the impact of a surgeon's technical skill on SSIs has not been evaluated except indirectly. Farber et al. *(163)* used a statewide surveillance program to examine the relationship between surgical volume and the incidence of SSIs. They noted a highly significant relationship between a lower number of procedures performed by surgeons and a higher rate of infection for appendectomies, herniorrhaphies, cholecystectomies, colon resections, and abdominal hysterectomies. One explanation put forth was that higher volume meant more experience, and surgeons with more experience generally acquire better technique. In a follow-up study by the same group, Miller et al. *(164)* examined the relationship of the level of physician training and incidence of endometritis after cesarean section. Among 15 variables examined by stepwise logistic regression analysis, only the presence of a resident as the lead surgeon was associated with a higher risk for endometritis. Surgical residents presumably would have less experience and skill than attending physicians.

Presence of Remote Infections

The presence of a remote infection at the time of surgery has been shown to affect the rate of SSIs. In the National Research Council study, the presence of a remote infection

increased the rate of SSI 2.7 times (18.4% vs. 6.7%) *(37)*. Edwards (*48*) observed that, among 383 patients who had cultures taken from SSIs and remote sites, 55% of the wound infections were preceded by infections of the urinary tract or lower respiratory tract with the same microorganisms. In the study by Garibaldi and Cushing *(86)*, the presence of a remote infection was significantly associated with an increased rate of infection on univariate analysis (odds ratio: 2.8; CI: 1.5–5.3). However, when the authors used logistic regression analysis to adjust for the influence of other variables, the presence of remote infection was no longer significantly associated with SSI.

Foreign Material

Early observational studies suggested that surgical drains contributed to the development of SSIs *(36,37,78)*. Experimental studies seemed to support these clinical observations. Nora et al. *(165)* were able to produce wound infections in dogs with drains placed before abdominal closure but not in dogs without drains. In the clinical phase of this study, the investigators observed that 17 of 50 patients with abdominal drains placed had *S. aureus* and *S. epidermidis* cultured from the interior surfaces of their drains and suggested that these microorganisms may migrate retrograde from overlying skin flora. The work of Magee et al. *(166)* suggested that the drains may also potentiate the risk of infection by acting as a foreign body and suppressing local tissue defenses.

Subsequent studies on the effect of drains on the risk of SSIs have produced conflicting results. Several prospective, randomized trials have also been published *(85,167–169)*. Three studies found no difference in infection rates when drains were used *(85,167,168)*. In the fourth study, Monson et al. *(169)* noted that patients randomized to receive high-pressure suction drainage after cholecystectomy had a significantly higher rate of SSI (15 of 239 with drains vs. 5 of 240 without, $p < .05$). A task force of experts from the Society for Hospital Epidemiology of America (SHEA), the Association of Practitioners in Infection Control, the CDC, and the Surgical Infection Society concluded, after review of the evidence, that the use of drains was only a possible contributor to SSIs. This was the weakest of three categories of risk factors, which included definitive and likely risk factors *(170)*.

In addition to drains, any foreign material, including sutures and prosthetic material, decreases the microbial burden necessary to induce infection. Elek and Conen *(171)* demonstrated that while 10^6 microorganisms of *Staphylococcus* per gram of tissue was required to cause an SSI in healthy normal tissue, if silk suture was introduced, only 10^2 microorganisms were required. Similarly, animal models have shown that the median infective dose (ID_{50}) to establish a wound infection was as low as one CFU in the presence of dextran microbeads *(172)*.

Perioperative Hypothermia

Perioperative hypothermia, which is <37°C, is a serious but common complication during surgery. Normally, body temperature is tightly regulated to within 0.2°C by thermoregulatory mechanisms. However, within 1 hour of administration of regional or general anesthesia, core body temperature rapidly declines between 1.0°C and 1.5°C, due to drug-induced vasodilation and redistribution of blood from the core to the periphery. Over the next several hours, body temperature more slowly continues to decline due to imbalance of heat generation and loss of heat into the cold surgical room environment. Once core body temperature reaches about 35°C, the body temperature begins to plateau with the reemergence of vasoconstriction *(173)*.

Multiple studies have documented the severe consequences of hypothermia, which include increased myocardial infarctions, increased risk of perioperative bleeding, and increased risk of SSI. Frank et al. *(174)*, in a randomized controlled study, documented a tripled risk of myocardial events with a decrease in core body temperature of 1.5°C. Schmied et al. *(175)*, in another randomized prospective clinical trial, demonstrated a 500 mL increased loss of blood in patients undergoing hip arthoplasties in patients with a decrease in body temperature of 1.5°C.

Perioperative hypothermia is thought to increase rates of SSIs by triggering vasoconstriction at the surgical site, during the critical first few hours after bacterial contamination. However, this thermoregulatory vasoconstriction due to hypothermia decreases concentration of oxygen into the tissues, causing tissue hypoxemia. Oxygen is critical for effective neutrophil killing of microorganisms at the surgical site *(176)*. Thus, hypothermia impairs optimal neutrophil function and allows establishment of bacterial infection. In addition, vasoconstriction may impair wound healing since scar formation is also oxygen dependent *(176)*. Kurz et al. (177), in a randomized, double-blind, prospective trial of patients undergoing colorectal surgery, demonstrated that patients who had a decrease of 1.9°C in core body temperature had triple the risk of SSIs, compared to those whose body temperature was maintained at about 37°C; and those infected remained hospitalized for an additional week compared to those who were not infected. Even among those who were not infected, hypothermic patients had a 20% increased duration of hospitalization, thought to be due to impaired healing.

Supplemental Oxygen

The use of a high inspired oxygen faction (FiO_2) during surgery has been advocated as one way to decrease SSIs. As stated above, optimizing the oxygen concentration at the surgical site in the first hours after bacterial contamination is critical in preventing SSIs, as oxygen is necessary to optimize wound healing and in eradication of bacteria by neutrophils. However, wound oxygen concentration is decreased in surgical wounds due to a combination of vasoconstriction caused by hypothermia, hypovolemia, and pain, or due to injury, inflammation, or coagulation *(178)*.

Therefore, in addition to decreasing hypothermia, ensuring adequate hydration and minimizing tissue injury are important in maintaining adequate blood flow and oxygen to the surgical tissues. In theory, increasing the inspired oxygen fraction should also increase wound oxygen, and, as a result, decrease SSIs. However, the randomized studies of increasing inspired oxygen from 30% to 80% have had contradictory results. Two trials by Grief (179) and Belda *(180)* demonstrated a 40% to 50% decrease in SSIs rates when 80% FiO_2 was administered, compared to 30% FiO_2, during surgery and the first hours postoperatively. However, two trials found no difference in rates of SSI, including the most recent PROXI trial (*181*,182). In contrast, Pryor in a smaller study found that the high FiO_2 group had double the rate of SSIs compared to the normal FiO_2 group *(183)*.

The editorial *(178)* accompanying the PROXI trial notes key differences in the trial designs, which may account for different effects of increasing FIO_2. In the trials by Grief and Belda (179,*180*), liberal fluid management and maintenance of euthermia were mandatory. However, in the PROXI trial (182), fluid management and euthermia were not standardized, with PROXI patients receiving less fluid and being more hypothermic compared to the trials by Grief and Belda. Pryor et al.'s study *(183)*, (the study that showed an increase in rates of SSI with increasing FiO_2), has been criticized for small sample size, nonhomogeneous groups, and failure to control for fluids and antibiotics. Overall, these findings suggest that inspired FiO_2 can increase wound oxygen and may prevent SSIs when vasoconstriction is minimized by minimizing hypothermia and by ensuring adequate fluid hydration.

Currently, it is still unclear whether the routine use of high FiO_2 prevents SSIs. Therefore, other measures to prevent SSIs as listed above should be rigorously followed.

GUIDELINES FOR THE PREVENTION OF SURGICAL SITE INFECTIONS

The CDC has published guidelines for prevention of SSIs *(184)*. In 1999, the Hospital Infection Control Practices Advisory Committee (HICPAC) of the CDC published revised guidelines (101). The guidelines contain 72 recommendations, and as in previous CDC guidelines, each recommendation is ranked by a revised scheme that takes into consideration the strength of the recommendation's scientific backing, the opinion of experts in the field, and the practicality and cost of implementation (Table 21-4). In the revised scheme, category IA and IB measures are strongly recommended for adoption by all hospitals. Category IA measures are supported by well-designed experimental or epidemiologic studies; category IB measures are not supported by definitive scientific studies, but they are backed by highly suggestive studies and are viewed as effective by experts in the field and by consensus of HICPAC. Category II recommendations are suggested for implementation by many but not necessarily all hospitals. These recommendations are backed by a strong theoretical rationale or suggestive clinical or epidemiologic studies. In the 1999 guideline, practices for which there is insufficient supportive evidence or for which no consensus could be reached are identified as unresolved issues for which no recommendations could be made.

More recently, SHEA has published guidelines that highlight practical recommendations for acute care hospitals (11).

ISSUES IN SSI PREVENTION

Surgical Infection Prevention Collaborative/ Surgical Care Improvement Project

In 2002, the CMS together with the CDC created the Surgical Infection Prevention Collaborative to prevent SSIs, by targeting three performance measures associated with antibiotic prophylaxis:

1. Delivery of intravenous antimicrobial prophylaxis within 1 hour before incision (within 2 hours for vancomycin or fluoroquinolones)
2. Use of a prophylactic antimicrobial consistent with published guidelines
3. Discontinuation of prophylactic antibiotic within 24 hours after surgery (discontinuation within 48 hours allowable for cardiothoracic procedures in adults) *(185)*

The first two, timing and selection, were selected as measures, because they have been well documented to decrease rates of SSI (see section above on antibiotic prophylaxis); the third was chosen to prevent excessive use of antibiotics, which drive antimicrobial resistance with no benefit on SSI rates *(185)*. However, despite the evidence supporting these practices, in a 2001 national survey of Medicare patients undergoing five major surgeries (cardiac, vascular, general abdominal colorectal, hip/knee total arthroplasty, and hysterectomies), antibiotics were given within 1 hour in only 55.7% of cases, appropriate antibiotics were given in 92.6% of cases, and antibiotics were discontinued within 24 hours after surgery in only 40.7% of cases *(186)*.

A national collaborative (56 hospitals and 43 Medicare Quality Improvement Organizations) instituted a 1-year study in order to study the effectiveness of a multidisciplinary systems-based approach to decrease rates of SSIs by specifically targeting these three performance measures *(187)*. This study reported improvement with these antimicrobial prophylaxis measures: antibiotics within 1 hour (median 72% at baseline to 92% at the end of the study), appropriate antibiotics (90% to 95%), and discontinuation with 24 hours (67% to 95%). They also noted improvement with other SSI-reducing performance measures, including normothermia in the operative room, use of supplemental oxygen, avoidance of shaving surgical site with razors, and glucose control. Combined, this collaborative demonstrated a median 27% reduction in SSI rates *(187)*.

In 2003, the SCIP, an extension of the Surgical Infection Prevention Collaborative, was created as a multiagency national quality partnership of over 40 organizations, steered by 10 organizations which includes CMS, CDC, the Veterans Association, American College of Surgeons, American Society of Anesthesiologists, the Agency for Healthcare Research and Quality, the American Hospital Association, and the Institute for Healthcare Improvement (15). The goal of SCIP was to reduce preventable surgical morbidity and mortality by 25% by 2010. Specifically, SCIP wanted to reduce postoperative complications, which includes preventing SSIs, venous thromboembolism, cardiac events, respiratory complications, and monitor global measures (risk-adjusted patient mortality and readmission) (15).

In the realm of SSI prevention, SCIP added three process measures beyond the three Surgical Infection Prevention antibiotic prophylaxis measures, which are:

1. Control blood glucose postoperatively in cardiac surgery patients (6:00 AM blood glucose level <200 mg/dL on postoperative days 1 and 2)
2. Proper hair removal (no hair removal or removal with clippers or depilatory method; razors not appropriate)
3. Maintenance of perioperative normothermia in patients undergoing colorectal surgery

While participation in SCIP is voluntary, in order to comply with the Deficit Reduction Act of 2005, hospitals

TABLE 21-4

Centers for Disease Control and Prevention (CDC) Guideline for the Prevention of SSI, 1999: Part II—Recommendations for the Prevention of SSI

1. Preoperative preparation of the patient
   a. Adequately control serum blood glucose level in all diabetic patients before elective operation and maintain blood glucose level <200 mg/dL during the operation and in the immediate postoperative period (48 h). Category IB.
   b. Always encourage tobacco cessation. At minimum, instruct patients to abstain for at least 30 d before elective operation from smoking cigarettes, cigars, pipes, or any other form of tobacco consumption (e.g., chewing/dipping). Category IB.
   c. No recommendation to taper or discontinue steroid use (when medically permissible) before elective operation. Unresolved issue.
   d. Consider delaying an elective operation in a severely malnourished patient. A good predictor of nutritional status is serum albumin. Category II.
   e. Attempt weight reduction in obese patients before elective operation. Category II.
   f. Identify and treat all infections remote to the surgical site before elective operation. Do not perform elective operations in patients with remote site infections. Category IA.
   g. Keep preoperative hospital stay as short as possible. Category IA.
   h. Prescribe preoperative showers/baths with an antiseptic agent the night before and the morning of the operation. Category IB.
   i. Do not remove hair preoperatively unless the hair at or around the incision site will interfere with the operation. Category IA.
   j. If hair is removed, it should be removed immediately before the operation using electric clippers rather than razors or depilatories. Category IA.
   k. Thoroughly wash and clean at and around the incision site to remove gross contamination before performing antiseptic skin preparation. Category IB.
   l. Use an acceptable antiseptic agent for skin preparation, such as alcohol (usually 70%–92%), chlorhexidine (4%, 2%, or 0.5% in alcohol base), or iodine/iodophors (usually 10% aqueous with 1% iodine or formulation with 7.5%). Category IB.
   m. Apply preoperative antiseptic skin preparation in concentric circles moving out toward the periphery. The prepped area must be large enough to extend the incision or create new incisions or drain sites, if necessary. Category IB.
2. Preoperative hand/forearm antisepsis

All members of the surgical team:
   a. Keep nails short and do not wear artificial nails. Category IB.
   b. No recommendations on wearing nail polish. Unresolved issue.
   c. Do not wear hand/arm jewelry. Category II.
   d. Perform a preoperative surgical scrub that includes hands and forearms up to the elbows before the sterile field, sterile instruments, or the patient's prepped skin is touched. Category IB.
   e. Clean underneath each fingernail prior to performing the surgical scrub. Category IB.
   f. Perform the surgical scrub for a duration of 3–5 min with an appropriate antiseptic. Category IB.
   g. After performing the surgical scrub, keep hands up and away from the body (elbows in flexed position) so that water runs from the tips of the fingers toward the elbows. Dry hands with a sterile towel and don a sterile gown and gloves. Category IB.
3. Antimicrobial prophylaxis
   a. Select a prophylactic antimicrobial agent based on its efficacy against the most common pathogens causing SSI for a specific operation. Category IA.
   b. Administer the antimicrobial prophylactic agent by the intravenous route except for colorectal operations. In colorectal operations, the antimicrobial agent is administered orally or a combination of oral and intravenous route is used. Category IA.
   c. Administer the antimicrobial agent before the operation starts to assure adequate microbial tissue levels before the skin incision is made. Ideally, antimicrobial prophylaxis should be administered within 30 min before, but not longer than 2 h before the initial incision. Category IA.
   d. For cesarean section, administer prophylaxis immediately after the umbilical cord is clamped. Category IA.[a]
   e. Administer prophylactic antimicrobial agent as close as possible to the time of induction of anesthesia. Category II.
   f. Do not extend prophylaxis postoperatively. Category IB.
   g. Consider additional intraoperative doses under the following circumstances: (a) operations whose duration exceeds the estimated serum half-life of the agent, (b) operations with major intraoperative blood loss, and (c) operations on morbidly obese patients. Category IB.
   h. Do not routinely use vancomycin for prophylaxis. Category IB.
4. Intraoperative issues

   4.1. Operating room environment

   A. Ventilation
   a. Maintain positive-pressure ventilation in the operating room with respect to the corridors and adjacent areas. Category IB.
   b. Maintain a minimum of 15 air changes per hour, of which at least three should be fresh air. Category IB.
   c. Filter all air, recirculated and fresh, through the appropriate filters per the American Institute of Architects recommendations. Category IB.
   d. Introduce all air at the ceiling and exhaust near the floor. Category IB.

(*Continued*)

TABLE 21-4

Centers for Disease Control and Prevention (CDC) Guideline for the Prevention of SSI, 1999: Part II—Recommendations for the Prevention of SSI (*Continued*)

e. No recommendation for the use of laminar flow ventilation or ultraviolet lights in the operating room to prevent SSI. Unresolved issue.
f. Keep operating room doors closed except as needed for passage of equipment, personnel, and the patient. Category IB.
g. Limit the number of personnel entering the operating room to necessary personnel. Category IB.

B. Cleaning and disinfection of environmental surfaces
a. No recommendation on disinfecting operating rooms between operations in the absence of visible soiling of surfaces or equipment. Unresolved issue.
b. When visible soiling or contamination, with blood or other body fluids, of surfaces or equipment occurs during an operation, use an EPA-approved hospital disinfectant to clean the affected areas before the next operation. Category IB.[b]
c. Wet vacuum the operating room floor after the last operation of the day or night with an EPA-approved hospital disinfectant. Category IB.
d. Do not perform special cleaning or disinfection of operating rooms after contaminated or dirty operations. Category IA.
e. Do not use tacky mats at the entrance to the operating room suite for infection control; this is not proven to decrease SSI risk. Category IA.

C. Microbiologic sampling
Do not perform routine environmental sampling of the operating room. Perform microbiologic sampling of operating room environmental surfaces or air only as part of an epidemiologic investigation. Category IB.

D. Sterilization of surgical instruments
a. Sterilize all surgical instruments according to published guidelines. Category IB.
b. Perform flash sterilization only in emergency situations. Category IB.
c. Do not use flash sterilization for routine reprocessing of surgical instruments. Category IB.

4.2. Surgical attire and drapes
a. No recommendations on how or where to launder scrub suits, or on restricting use of scrub suits to the operating suite or for covering scrub suits when out of the operating suite. Unresolved issue.
b. Change scrub suits when visibly soiled, contaminated, and/or penetrated by blood or other potentially infectious materials. Category IB.
c. Wear a surgical mask that fully covers the mouth and nose when entering the operating room if sterile instruments are exposed, or if an operation is about to begin or already under way. Wear the mask throughout the entire operation. Category IB.[b]
d. Wear a cap or hood to fully cover hair on the head and face when entering the operating room suite. Category IB.[b]
e. Do not wear shoe covers for the prevention of SSI. Category IA.
f. Wear shoe covers when gross contamination can reasonably be anticipated. Category II.[b]
g. The surgical team must wear sterile gloves, which are put on after donning a sterile gown. Category IB.[b]
h. Use materials for surgical gowns and drapes that are effective barriers when wet. Category IB.

4.3. Practice of anesthesiology
Anesthesia team members must adhere to recommended infection control practices during operations. Category IA.

4.4. Surgical technique
a. Handle tissue gently, maintain effective hemostasis, minimize devitalized tissue and foreign bodies (e.g., sutures, charred tissues, necrotic debris), and eradicate dead space at the surgical site. Category IB.
b. Use delayed primary closure or leave incision open to close by secondary intention, if the surgical site is heavily contaminated (e.g., class III and class IV). Category IB.
c. If drainage is deemed necessary, use a closed suction drain. Place the drain through a separate incision, rather than the main surgical incision. Remove the drain as soon as possible. Category IB.

5. Postoperative surgical incision care
a. Protect an incision closed primarily with a sterile dressing for 24–48 h postoperatively. Also ensure that the dressing remains dry and that it is not removed during bathing. Category IA.
b. No recommendation on whether or not to cover an incision closed primarily beyond 48 h, or on the appropriate time to shower/bathe with an uncovered incision. Unresolved issue.
c. Wash hands with an antiseptic agent before and after dressing changes, or any contact with the surgical site. Category IA.
d. For incisions left open postoperatively, no recommendation for dressing changes using a sterile technique vs. clean technique. Unresolved issue.
e. Educate the patient and family using a coordinated team approach on how to perform proper incision care, identify signs and symptoms of infection, and where to report any signs and symptoms of infection. Category II.

6. Surveillance
a. Use CDC definitions of SSI without modifications for identifying SSI among surgical inpatients and outpatients. Category IB.
b. For inpatient case finding, use direct prospective observation, indirect prospective detection, or a combination of both direct and indirect methods for the duration of the patient's hospitalization, and include a method of postdischarge surveillance that accommodates available resources and data needs. Category IB.

(*Continued*)

TABLE 21-4

Centers for Disease Control and Prevention (CDC) Guideline for the Prevention of SSI, 1999: Part II—Recommendations for the Prevention of SSI (*Continued*)

c. For outpatient case finding, use a method that accommodates available resources and data needs. Category IB.
d. For each patient undergoing an operation chosen for surveillance, record those variables shown to be associated with increased SSI risk (e.g., surgical wound class, ASA class, and duration or operation). Category IB.
e. Upon completion of the operation, a surgical team member assigns the surgical wound classification. Category IB.
f. Periodically calculate operation-specific SSI rates stratified by variables shown to be predictive of SSI risk. Category IB.
g. Report appropriately stratified, operation-specific SSI rates to surgical team members. The optimum frequency and format for such rate computations will be determined by stratified case-load sizes and the objectives of local, continuous, quality improvement initiatives. Category IB.
h. No recommendations to make available to the infection control committee coded surgeon-specific data. Uresolved issue.

[a]The Committee on Obstetric Practice of the American College of Obstetricians and Gynecologists now recommends that antimicrobial prophylaxis for cesarean deliveries be administered within 60 minutes of the start of the cesarean delivery unless the patient is already receiving appropriate antibiotics (e.g., for chorioamnionitis). *Obstet Gynecol* 2010;116:791–792.
[b]Federal regulation of the Occupational Safety and Health Administration.
ASA, American Society of Anesthesiologists; EPA, Environmental Protection Agency.

that provide acute inpatient care to Medicare patients must submit information on required quality measures to the CMS, in order to receive their full annual payment update. These measures are now posted on the U.S. Health and Human Services Web site, http://www.hospitalcompare.hhs.gov. Two SCIP measures—antimicrobial prophylaxis within 1 hour and discontinuation within 24 hours after surgery—are part of the required quality measures. In the near future, CMS may require the additional four SCIP SSI prevention measures as well (13,*188*).

Since October 2008, beyond mandating reporting of quality measurements, CMS is no longer paying additional reimbursements for certain conditions acquired during the hospitalization stay, which includes the following SSIs *(189)*:

1. CABG—mediastinitis
2. Bariatric surgery laparoscopic
   - Gastric bypass gastroenterostomy
   - Laparoscopic gastric restrictive surgery
3. Orthopedic procedures
   - Spine
   - Neck
   - Shoulder
   - Elbow

Risk Adjustment

As clinical outcomes have been increasingly emphasized as one way to measure and improve quality of care, an important obstacle to the use of SSIs as a quality assurance outcome indicator has been failure to adjust for differences in types of patients undergoing operations by different surgeons or admitted by different hospitals (differences in case mix of patients). The surgical site classification scheme of the National Research Council attempted to capture the risk of subsequent infection brought on by the degree of microbial contamination of the operative site *(57)*. However, as mentioned previously, this scheme fails to account for the patient's susceptibility to infection that is the result of underlying host conditions (the patient's intrinsic risk to infection).

The CDC developed, as part of its SENIC project, a risk index system that was an improvement over the traditional surgical site classification system *(158)*. By subjecting multiple variables to analysis by regression modeling, it found four risk factors that predicted 90% of SSIs among the SENIC database: (a) an operation that involved the abdomen, (b) an operation lasting longer than 2 hours, (c) an operation classified as either contaminated or dirty infected, and (d) a patient having three or more diagnoses at discharge. The last factor, having multiple diagnoses, was, in effect, a proxy variable for a patient's intrinsic risk to infection. When tested, the SENIC index predicted SSI risk for all surgical patients twice as well as traditional surgical site classifications.

Despite the improved performance over the traditional surgical site (wound) classification scheme, limitations in the SENIC index were noted. First, the SENIC index stratified the length of operation in a dichotomous fashion—that is, either <2 hours or 2 hours or greater. Intuitively, since the technical difficulty of operative procedures varies—for example, a coronary artery bypass procedure would take more operating time than a simple hernia repair—the appropriate cut point for what would be deemed an excessive length of operation should also vary to reflect the complexity of surgery. Second, the SENIC index required the number of discharge diagnoses, information that could only be gotten retrospectively after the patient has been discharged. Its use would thus seem problematic in infection control programs conducting ongoing, prospective surgical site surveillance.

To overcome these limitations, the NNIS system modified the SENIC patient risk index so that it was based on data easily obtainable at the time of surgery *(159)*. In the NNIS risk index, each operation is scored by the presence or absence of three risk factors: (a) a patient having an American Society of Anesthesiologists (ASA) preoperative assessment score of 3, 4, or 5; (b) an operation classified as either contaminated or dirty infected; and (c) an operation with duration of surgery more than *T* hours, where *T* depends on the operative procedure being performed. In the NNIS index, the ASA score becomes the

proxy variable for the patient's intrinsic risk and is more easily obtainable than the discharge diagnoses used for the SENIC index. The *T* cut point for each surgical procedure was derived from the NNIS database and was chosen to be the 75th percentile of the distribution of durations of surgery for that procedure. Unlike the SENIC risk index, where the risk factor of duration of operation is fixed at >2 hours, NNIS's cutoff for excessive length of operation is variable and indexed to a specific operative procedure. The NNIS risk index ranges from 0 (low-risk procedure) to 3 (high-risk procedure).

In validation studies, the basic NNIS risk index generally has performed well in predicting the risk of SSIs *(190)*. For the majority of operative procedures (30 of 40 procedures), a higher NNIS risk index score predicted a higher infection rate. For example, among the 35,293 cardiac surgeries reported to NNIS between 1992 and 2001, the SSI rate was 0.66% for risk index category 0, 1.63% for risk index 1, and 2.54% for risk index categories 2 and 3. Notable, however, was that in 10 procedures, the NNIS risk index performed poorly, as the infection rate was the same whether patients had a risk index of 0, 1, 2, or 3.

The basic NNIS index assumes that the risk index variables of wound class, ASA score, and operative duration account for the majority of operative risk for infection from various influences and that each variable should have equal importance or weight. It is clear from the poor performance of the basic NNIS risk index among certain operative procedures that these assumptions are not necessarily valid. Analysis of SSIs among cholecystectomies, colon surgery, appendectomies, and gastric surgery suggested that the rates of infections were lower when a laparoscope was used. The finding that use of a laparoscope had a protective effect for these four procedures had prompted the CDC to modify its basic NNIS index by allowing subtraction by 1 to a lower risk category when a laparoscope was used for those four procedures *(190)*. However, from the November 2008 NHSN publication, the CDC has found insufficient evidence to continue to adjust for laparoscopic procedures, and has therefore returned to the basic NNIS index with minor differences—the cut point for the duration of procedure is shown in minutes and is the exact 75th percentile of the distribution, rather than rounding to the nearest whole number of hours *(191)*.

Other modifications to the basic NNIS risk index may be necessary, and indeed the optimal approach may be to develop a specific risk index for each surgical procedure based on multivariate analyses of procedure-related risk factors.

Issues in SSI Prevention

***Staphylococcus* Decolonization** *S. aureus* is the most common pathogen isolated from SSIs, accounting for 20% to 30% of all SSIs (12). This pathogen is thought to be acquired largely from the patient's own flora (endogenous acquisition). Up to 30% of healthy humans are colonized in the nares with this microorganism, and up to 50% of healthcare workers may carry this microorganism (*192*,193). Nasal carriage of *S. aureus* has been shown to be a risk factor for hemodialysis catheter infections and for bacteremias in patients undergoing central venous catheterizations (*193*,194–197). Nasal carriage with *S. aureus* is also a risk factor for SSIs, with about four to nine times increased odds or risk of SSI (193,*198–200*). These findings prompted Klutyman's group to attempt to eradicate nasal colonization as a method to prevent SSIs among cardiothoracic surgery patients *(201)*. The nonrandomized trial using historical controls demonstrated a decrease in deep and incisional rates of SSI among treated versus untreated historical controls.

However, the first two placebo-controlled randomized trials using intranasal mupirocin failed to show a reduction in SSI rates in general surgery and orthopedic surgeries. In the first, Perl et al. (43) enrolled 4,030 patients about to undergo general, gynecologic, neurologic, or cardiothoracic surgery. Patients were randomized to receive mupirocin intranasally or placebo twice a day for up to 5 days before surgery. At the end of the study, mupirocin treatment was found to have no effect in reducing the SSI rate caused by *S. aureus*, though when the analysis was restricted to only those patients with nasal carriage of *S. aureus* before surgery, treatment with mupirocin was effective in preventing HAIs due to *S. aureus*. In the second, Kalmeijer et al. *(202)* randomized orthopedic surgery patients undergoing prosthetic implants. Despite effective nasal eradication of S. *aureus,* mupirocin nasal ointment did not decrease rates of SSI.

In a recent meta-analysis, it was suggested that intranasal mupirocin used in *S. aureus* carriers could reduce the rates of SSI due to *S. aureus* by 45%. However, they recommended further randomized studies to be performed *(203)*.

Two main hypotheses have been proposed to explain the failure of mupirocin in preventing SSIs: First, identification of *S. aureus* carriers by traditional culture methods and then decolonization may be too late in preventing SSIs as infections may already be established; second, *S. aureus* also colonizes the skin, not only the nares. In the most recent multicentered randomized placebo-controlled trial (44), Bode and colleagues conducted a study that allowed for rapid identification of *S. aureus* nasal carriers upon admission or during the week prior to admission, by utilizing a PCR assay. Patients expected to remain in the hospital for at least 4 days in internal medicine, or surgery services (cardiothoracic, vascular, orthopedic, gastrointestinal, or general) were included in the study. Once carriers were identified, carriers were randomized to placebo or to decolonization. The decolonization group was decolonized with application of mupirocin ointment to the nares twice a day for 5 days and daily chlorhexidine gluconate soap to the skin. Overall, 6,771 patients were screened, 1,251 patients identified as carriers. Of the 918 randomized patients, the mupirocin-chlorhexadine group had a highly significant 60% reduction in risk of SSIs due to *S. aureus* (RR: 0.42; 95% CI: 0.23–0.75) compared to the placebo group. However, 250 need to be screened by a rapid method and 23 carriers needed to be treated in order to prevent one hospital-acquired *S. aureus* infection, respectively.

In the editorial following the Bode article *(204)*, if the use of chlorhexadine surgical scrub becomes universal (which decreases rates of all SSIs, not just due to *S. aureus*), Wenzel notes the unclear additional benefit of rapid screening and identification for *S. aureus*. However, for procedures associated with high risk of poor outcomes if *S. aureus* SSI infection develops, like cardiothoracic or in procedures where prosthetic material is implanted, rapid screening and decolonization should be considered.

SURGICAL SITE SURVEILLANCE AS AN INFECTION CONTROL MEASURE

Cruse and Foord *(37)* noted that the rate of SSIs among clean procedures was reduced when the information on rates was reported back to practicing surgeons. In a 5-year prospective study, Condon et al. *(205)* similarly observed a decline in the clean SSI rate from 3% to 1% after the institution of their surgical site surveillance program with direct reporting of the results to surgeons. In the CDC study, Haley et al. *(160)* showed that establishment of a strong infection surveillance program and the feedback of SSI rates to surgeons lowered the overall SSI rate by 35%, and the reduction occurred among contaminated or dirty cases as well as in clean or clean-contaminated cases.

How such feedback brings about changes in surgeons' behavior is not known. The effect may be achieved through an improved general awareness of the problem of SSIs that feedback brings about, through a learning process that surgeons undergo when they review cases of infections and identify probable errors in technique, or because of an anxiety factor as surgeons become aware that their patients' outcomes are being monitored.

These studies, among others, form the basis for the CDC's recommendation that hospitals routinely perform surveillance for SSIs and report the information back to the surgeons (11,101).

SURVEILLANCE METHODOLOGY

For valid comparisons of rates of SSIs among hospitals, the surveillance methods for case finding in these hospitals must be similar. Multiple case-finding methods are currently available, including (a) direct method, through daily observation of the surgical site by infection control personnel or other surveyors and (b) indirect methods such as review of microbiology reports, patient medical records, fever charts, antibiotic use, surgeon or patient surveys, screening for hospital readmissions, operative reports, and/or coded diagnoses.

Direct, prospective observation of all postoperative patients for SSIs by trained personnel is generally viewed as the best method to identify SSIs (*2*,11,*37*). However, direct prospective observation is often not practical or feasible. Therefore, indirect methods are often used, and have demonstrated sensitivity of 84% to 89%, and specificity of 99.8%, compared to direct observation *(206,207)*.

Alternative Methods of Surveillance: Use of Automated Databases

Traditional surveillance for SSIs that rely on review of culture results, fever charts, Kardexes, medical records, or postdischarge telephone or written surveys requires significant expenditure of time and effort from infection control personnel. Hence, hospitals with limited resources are often forced to choose among not performing such surveillance, limiting their surveillance to a certain time periods, for example, 3 months out of a year (sampling), or rotating surveillance among different surgical procedural types. In the past decade, the growth and use of computers in the healthcare industry have resulted in the automated capture of healthcare data, some of which could be useful in the surveillance for SSIs. Computerized medical record systems found in today's hospitals, physicians' offices, and health maintenance organizations (HMOs) vary in their sophistication. These databases all capture administrative and demographic information, such as age, sex, underlying diagnoses, and length of hospitalization. More sophisticated databases often capture microbiology and pharmacy data, including the use of antibiotics. The most sophisticated medical record systems are usually found in tertiary referral hospitals or large HMOs. They often contain more specific operative data such as ASA score, duration of surgery, and codes for procedures like incision and drainage that more directly indicate an infection.

The use of automated healthcare databases holds promise as an alternative method of performing surveillance for SSIs, one that would require less effort than traditional methods. However, investigators continue to refine and improve their methodology. Studies have shown that the addition of certain International Classification of Diseases (ICD-9) codes and procedural codes, such as incision and drainage, to the algorithm improves on the specificity of quantitative antibiotic exposure while maintaining a high sensitivity *(208,209)*. More recently, investigators have explored the use of third-party claims data for measuring institutions' SSI rates. Use of insurers' claims data has several advantages over individual hospital data. Claims are made even when patients are hospitalized at institutions other than the ones that perform the surgical procedures. They are made when patients are seen in clinics, private offices, or emergency rooms. Sands et al. *(210)* found that an automated surveillance system based on health plan administrative and pharmacy data was more sensitive in detecting SSIs following CABG procedures than hospital-based surveillance (72% vs. 50%). This study was based on claims data from the Harvard Pilgrim Health Care providing coverage for patients for five hospitals. However, this approach needs to be validated using claims data from different insurers. In addition, the investigators also point out that variations in SSI indicators are affected by patient case mix and differences in case mix between hospitals may not be adequately captured in the claims data *(211)*.

The availability of such automated databases provides an opportunity to use such data in novel ways to identify SSIs, with increased sensitivity, and that requires less time and personnel.

NEED FOR POSTDISCHARGE SURVEILLANCE

Studies estimate that between 19% and 77% of SSIs do not become manifest until after patients are discharged from the hospital *(212–217)*; thus, a surveillance system based solely on inpatients would greatly underestimate the rate of SSIs. With decreasing postoperative stays and the continuing shift toward same-day procedures or outpatient procedures, the likelihood of missing SSIs will only increase unless postdischarge surveillance is performed.

Although the need for postdischarge surveillance may be clear, the best method to accomplish this remains

unknown. Polk et al. *(212)* surveyed patients by letter at 6 weeks and confirmed the diagnoses of infection with their surgeons. They found that 19% of SSIs had occurred after discharge. Rosendorf et al. *(214)* surveyed surgeons and patients at their follow-up clinic appointments and detected an additional 44% of infections by this method. Reimer et al. *(216)* used a telephone survey to contact patients at 30 days after discharge and found that 77% of their SSIs occurred after discharge. However, use of questionnaires or telephone surveys of patients is still insensitive, as one study demonstrated that patient-derived information underestimated the true number of SSIs occurring after discharge *(218)*.

Another issue is the appropriate length of postdischarge surveillance. The CDC recommends that surveillance for SSIs be performed for 30 days after discharge for procedures that do not involve implanted prosthetic materials *(219)*. This has become the *de facto* standard as most published studies have chosen this length of follow-up time. Weigelt et al. *(217)* found that 65% of SSIs occurred by the day of discharge, 82% were noted by the 7th day after discharge, 93% by the 14th day after discharge, and 97% by the 21st day after discharge. The results of this study support the choice of 30 days after discharge as the appropriate period of follow-up, since virtually 100% of the SSIs were detected within this period.

Currently, there are no standardized or reliable methods established for accurate detection of postdischarge SSIs. Because of this, the Surgical Wound Task Force on Surveillance of SSIs recommended that each institution develop and use a method that works based on considerations of its own resources, circumstances, and locale *(170)*. The National Healthcare Safety Network (NHSN) System of the CDC recommends postdischarge surveillance, using any combination of direct and indirect methods, as long as CDC definitions of SSI are used *(220)*. Nonetheless, the Joint Commission as part of their National Patient Safety Goals for preventing SSIs, mandated that institutions "measure SSI rates for the first 30 days following procedures that do not involve inserting implantable devices and for the first year following procedures involving implantable devices" *(221)*.The caveat is that hospitals may chose their own "measurement strategies" and target only those surgical procedures that carry a high risk based on their institution's own risk assessment.

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CHAPTER 22

Healthcare-Associated Pneumonia

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The substantial clinical and financial impact of healthcare-associated pneumonia makes this an important topic for healthcare epidemiologists. According to surveillance data from the National Nosocomial Infections Surveillance system of the Centers for Disease Control and Prevention (CDC), pneumonia is the second most common healthcare-associated infection overall (*1*) and the most common infection in intensive care units (ICUs) (*2*). Additionally, pneumonia is associated with significant mortality and considerable costs of care (*3*). The widespread use of tracheal intubation and mechanical ventilation (MV) to support the critically ill has defined an expanding group of patients who are at particularly high risk for developing healthcare-associated pneumonia. In this group of patients, the infection is usually called ventilator-associated pneumonia (VAP). Unfortunately, both the diagnosis and the prevention of VAP have proven to be difficult (*4*).

HISTORICAL ASPECTS

During the last four decades, much has been learned about the epidemiology of healthcare-associated pneumonia. In the 1960s Pierce, Sanford, and others investigated the relationship of epidemic necrotizing gram-negative pneumonia to contaminated reservoir nebulizers in respiratory therapy devices and described effective disinfection measures (*5–7*). During the 1970s and early 1980s, additional work described the continuing association of healthcare-associated pneumonia with respiratory therapy equipment (*8*), risk factors for postoperative pneumonia (*9*), and the relationship of healthcare-associated pneumonia with oropharyngeal (10) and gastric (*11*) gram-negative bacillary colonization. During the 1980s and 1990s, several preventive strategies were designed and tested with varying success, such as the use of sucralfate for stress ulcer prophylaxis (*12*), selective decontamination of the digestive tract (SDD) (*13*), and continuous subglottic aspiration (*14*). Moreover, controversies developed over the relevance of gastric colonization in the pathogenesis of VAP (*4,15,16*), the usefulness of SDD (*17,18*), and the necessity of bronchoscopic techniques for diagnosing VAP (*19,20*). In the most recent years, more general approaches for patient management, not only directed to VAP, have been applied in ICUs, such as strict control of blood glucose levels, noninvasive ventilation, sedation strategies to reduce duration of ventilation, and bundles of care. This chapter summarizes current knowledge of diagnosis, epidemiology, and prevention of healthcare-associated pneumonia.

DIAGNOSIS

Pneumonia refers to inflammation of the distal lung caused by infection with microorganisms and is characterized histologically by the accumulation of neutrophils in the distal bronchioles, alveoli, and interstitium. Three types of healthcare-associated pneumonia can be distinguished: hospital-acquired pneumonia, early-onset VAP, and late-onset VAP. Pneumonia is defined as VAP when diagnosed in an intubated, mechanically ventilated patient after more than 48 hours of ventilation; early-onset VAP occurs within the first 4 days of MV, and late-onset VAP occurs thereafter (*21*). The relevance of a rapid and accurate diagnosis of healthcare-associated pneumonia is obvious. The goals are to prescribe the optimal antibiotic therapy to only those patients with infection of the lungs. Using a technique with a low sensitivity, patients will remain untreated and may suffer significant morbidity and increased risk for mortality. In contrast, a technique with high sensitivity but low specificity will lead to unnecessary use of antibiotics, resulting in unnecessary exposure of patients to toxicity, a potential delay in diagnosing the real etiology of infection, increased hospital costs, and, most importantly, unnecessary selection and induction of resistant pathogenic microorganisms.

Clinical and Radiographic Findings

Traditionally, clinical and radiographic criteria have been used to identify cases of healthcare-associated pneumonia among patients who are not mechanically ventilated. Patients with healthcare-associated pneumonia are likely to have fever, purulent sputum, signs of pulmonary consolidation, and new or progressive radiographic infiltrates. Although they may complain of dyspnea, cough, and pleuritic chest pain, many patients with healthcare-associated pneumonia are unable to give a helpful history because of neurologic impairment or severity of illness. The CDC definitions of healthcare-associated pneumonia have been widely used for infection control surveillance and rely predominantly

on clinical and radiographic criteria, although the results of other diagnostic tests may also be used (*22*).

Diagnosing VAP is even more problematic than diagnosing healthcare-associated pneumonia in nonventilated patients (*23*). For scientific purposes, VAP is usually diagnosed using a modified version of the CDC's definitions (*24*). These criteria are a new or progressive radiographic infiltrate that has persisted for at least 48 hours plus at least three of the following: a temperature above 38.5°C or below 35.0°C, a leukocyte count of >10,000/mm^3 or <5,000/mm^3, purulent sputum, or isolation of pathogenic bacteria from an endotracheal aspirate. An alternative for the modified CDC criteria is the Clinical Pulmonary Infection Score (CPIS) as defined by Pugin et al. (*25*) (Table 22-1). This scoring system, basically, uses the same criteria as in the modified CDC criteria. The range of the score is from 0 to 12, with VAP defined by a score of 7 or more.

TABLE 22-1

CPIS Used for the Diagnosis of Ventilator-Associated Pneumonia

	Number of Points
1. Temperature (°C)	
≥36.5 and ≤38.4	0
≥38.5 and ≤38.9	1
≥39.0 and ≤36.0	2
2. Blood leukocytes (mm^3)	
≥4,000 and ≤11,000	0
<4,000 or >11,000	1
<4,000 or >11,000 and band forms ≥500	2
3. Tracheal secretions[a]	
<14+ of tracheal secretions	0
≥14+ of tracheal secretions	1
≥14+ of tracheal secretions and purulent secretions	2
4. Oxygenation: PaO_2/FlO_2 (mm Hg)	
>240 or ARDS	0
≤240 and no evidence of ARDS	2
5. Pulmonary radiography	
No infiltrate	0
Diffuse (or patchy) infiltrate	1
Localized infiltrate	2
6. Culture of tracheal aspirate (semiquantitative: 0, 1, 2, or 3+)	
Pathogenic bacteria cultured ≤1+ or no growth	0
Pathogenic bacteria cultured >1+	1
Pathogenic bacteria cultured >1+ and same pathogenic bacteria seen on the Gram stain >1+	2

[a]Quantity of tracheal aspirates per day (for each endotracheal aspiration, the quantity of secretions was estimated from 0 to 4+; estimation of the volume of total secretions per day was calculated by adding all the + values recorded over 24 h together).
Total points = CPIS (varies from 0 to 12 points).
ARDS, adult respiratory distress syndrome.
(Adapted from Pugin J, Auckenthaler R, Mili N, et al. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis* 1991;143:1121–1129.)

Although each of these criteria may have a reasonable sensitivity for VAP, specificity is poor. Radiographic infiltrates are sensitive indicators of VAP; however, more specific radiographic findings such as single air bronchograms, fissure abutment, or rapid progress to cavitation are infrequently present (*26*). Unfortunately, even the combination of clinical and radiographic criteria (as in the modified CDC criteria and the CPIS) has been unable to reliably diagnose cases of healthcare-associated pneumonia diagnosed by autopsy (*26,27*), histopathology (*28*), or other stringent criteria (*29–32*). In an autopsy study of ventilated patients, no radiographic sign predicted pneumonia more than 68% of the time, and no radiographic signs predicted pneumonia in the subgroup of patients with the adult respiratory distress syndrome (ARDS); when clinical and sputum culture results were added to the model, the diagnostic efficiency rose only to 72% (*26*). Two other reports have documented that fever and pulmonary infiltrates in mechanically ventilated patients were caused by processes other than pneumonia in 49% to 69% of cases (*29,30*). A variety of other conditions (such as drug reactions, atelectasis, chemical aspiration, congestive heart failure), alone or in combination, can mimic the clinical and radiographic presentation of healthcare-associated pneumonia (*33*); these conditions are not uncommon in patients with significant underlying medical illness. Furthermore, cultures of sputum and tracheal aspirate do not reliably identify pathogens causing healthcare-associated pneumonia (*33–36*) although surveillance cultures of sputum seem indicative for the pathogen eventually causing VAP and are superior in terms of choice of empiric antibiotic therapy compared to guidelines (*37*).

Interpretation of the usefulness of diagnostic techniques is seriously hampered, because populations studied varied widely, and the use of antibiotics, which strongly influences the yield of bacteriologic procedures, was not always taken into account. The largest problem, however, is the gold standard used to verify the value of diagnostic procedures. Histologic and bacteriologic examination of lung tissue remains the optimal standard to establish the diagnosis of pneumonia. However, these techniques require an open-lung biopsy or autopsy. Although histology and bacteriology of lung tissue, usually at autopsy, have been used as the gold standard in several studies, one should realize that patients who died form a subgroup of all patients with pneumonia. In addition, in several studies, autopsy findings are compared to diagnostic procedures performed several days earlier. In such circumstances, the physiologic host response to infection, usually in combination with antibiotic therapy, may have influenced the ultimate findings. These considerations also account for the evaluation of newer diagnostic techniques.

Quantitative Bronchoscopic Techniques

Diagnostic techniques have been improved by utilizing quantitative cultures of lower airway samples to more accurately diagnose healthcare-associated pneumonia and identify causative pathogens (*28,35,38–41*). The rationale of bronchoscopy is to avoid contamination of culture samples with material from the upper respiratory tract. Three bronchoscopic techniques have been used to diagnose VAP: protected specimen brush (PSB), bronchoalveolar lavage (BAL), and protected bronchoalveolar lavage (PBAL).

The PSB technique uses a double-lumen bronchoscopic catheter with a telescoping cannula and distal plug (*38*). A bacterial burden of $<10^4$ colony-forming units (CFU)/g in lung tissue has been associated with histologic pneumonia (*42*). Since the sample size with PSB is ±0.001 mL, a quantitative culture of 10^3 CFU/mL reflects about 10^6 CFU/mL at the site of infection and is generally used as a cutoff point for VAP. Quantitative cultures of PSB specimens have been shown to accurately identify pneumonia and its causative pathogens in mechanically ventilated patients undergoing open lung biopsy (*28*) and in mechanically ventilated baboons with diffuse lung injury (*35*). Studies in normal hosts (*43*), patients with chronic bronchitis (*44*), and mechanically ventilated patients with suspected pneumonia (*28,29,36*) indicate that quantitative PSB cultures are considerably more specific than clinical and radiographic criteria for diagnosing healthcare-associated pneumonia. Based on the pooled results of published studies (*28,29,35,45*), one review (*33*) reported PSB to have a sensitivity of 83% and a specificity of 91%. False-negative results have been attributed to sampling error and to antibiotic use (*36,41,45*). In several studies, PSB results were compared to histologic and microbiologic evaluation of lung tissue, with sensitivities ranging from 36% to 100% and specificities ranging from 50% to 95% (*28,46–49*).

Some investigators have also used quantitative cultures of BAL specimens to sample a larger portion of the lung, including alveoli (*39,40,50*). BAL entails sampling of an area of 10^6 alveoli. The tip of the bronchoscope is wedged, under visual control, into a third- or fourth-generation midsize bronchus, according to chest radiograph appearance. Lavage is carried out using at least 120 mL of sterile isotonic saline in several aliquot portions. The dilution of alveolar secretions in the lavage fluid is 10- to 100-fold, so a colony count of 10^4 CFU/mL in lavage fluid represents 10^5 to 10^6 bacteria per milliliter of alveolar secretion (*51*). In mechanically ventilated baboons, this method appears to be sensitive and provides the best correlation with culture of lung tissue (*50*). Like PSB, quantitative culture of BAL specimens appears to be more accurate than clinical and radiographic criteria for diagnosing healthcare-associated pneumonia (*39,40,52*); however, most studies evaluating quantitative BAL have not used rigorous criteria for determining whether pneumonia was actually present. BAL samples can become contaminated with bacterial flora from the upper respiratory tract, and reduced specificity may result (*39*). As with PSB, antibiotic use may diminish the sensitivity of BAL (*40,50*). In studies using histology and microbiologic examination of lung tissue as the gold standard, sensitivities of BAL ranged from 47% to 91%, and specificities ranged from 45% to 100% (*46–49*).

To reduce upper airway contamination while still obtaining a representative sample of affected alveoli, Meduri et al. (*41*) developed a technique to obtain PBAL specimens using a balloon-tipped telescoping catheter. In a study of 46 patients, including 25 with suspected VAP, quantitative PBAL culture proved to have a sensitivity of 92% and a specificity of 97% for diagnosing bacterial pneumonia (*41*). Castella and associates (*53*) applied a similar PBAL technique and found that PBAL displayed improved sensitivity (85%) compared with PSB (62%) and improved specificity (83%) compared with BAL (44%). PBAL appears to be somewhat more demanding and time-consuming than unprotected BAL, and has been studied less frequently than PSB and BAL.

After several years of experience with these bronchoscopic techniques, a consensus conference proposed a new definition for diagnosing VAP, which became known as the Memphis Ventilator-Associated Pneumonia Consensus Conference criteria (Table 22-2) (*42*). Definite VAP is only present with radiographic evidence of abscess and a positive needle aspirate, or if there is histologic proof of pneumonia at biopsy or autopsy. Probable VAP requires either positive quantitative or semiquantitative cultures from PSB or BAL, or blood or pleural fluid cultures of a microorganism found within 48 hours of isolation in the sputum, or abscess formation or consolidation with polymorphonuclear-cell infiltration at histologic examination.

Several technical and safety considerations pertaining to these bronchoscopic techniques warrant comment. The technique of the bronchoscopist may influence the results. The passage of the bronchoscope through the upper airway results in bacterial contamination of the suction channel, and the injection of topical anesthetic agents through the bronchoscope carries contaminants into the distal airways (*38*). Therefore, it is prudent to avoid suctioning or the injection of topical anesthetics prior to obtaining bronchoscopic samples. Other operator-dependent variables may also affect quantitative culture results. Elevated temperature, hypoxemia, increased radiographic infiltrates, bleeding, arrhythmias, and pneumothorax may be related to these bronchoscopic procedures, but serious or lasting complications appear to be rare (*19,20*). The use of a high FiO_2, careful monitoring of exhaled volumes and oxygen saturation, and prebronchoscopy assessment of risk should help prevent serious complications.

The most important question remains whether these bronchoscopic techniques influence (preferably improve) patient care in the ICU. Several studies have suggested that quantitative bronchoscopic sampling of the distal airways by PSB, BAL, or PBAL substantially improves the accuracy of diagnosing healthcare-associated pneumonia when compared to clinical and radiographic criteria. In this way, these techniques may help to distinguish between patients who do and patients who do not need antibiotic therapy. In one study, VAP was simultaneously diagnosed according to the modified CDC criteria, CPIS, and quantitative bronchoscopic sampling (*54*). Incidences of VAP were 22% using the modified CDC criteria, 20% using CPIS, 9% using the Memphis criteria for probable VAP, and 0.4% using the Memphis criteria for definite VAP. In another study, only 50% of all patients fulfilling the modified CDC criteria for VAP met the definition of probable VAP with the Memphis criteria (*55*).

Six studies determined the effects of withholding or withdrawing empiric antibiotic therapy if a clinical suspicion was not confirmed by a diagnostic test. In three Spanish studies and a large Canadian study, patients with a clinical suspicion of VAP were randomized to an invasive or noninvasive strategy (*56–59*). Because empirical therapy was not discontinued in any patient, regardless whether the suspicion was microbiologically confirmed or not, these studies cannot answer the question whether addition of these techniques to the diagnostic workup changes patient outcome, and have, therefore, not been included here.

TABLE 22-2

Recommended Definitions for VAP from the Memphis Ventilator-Associated Pneumonia Consensus Conference

Definite pneumonia. The patient meets the clinical criteria for suspicion of VAP of new (progressive) or persistent infiltrate and purulent tracheal secretions and demonstrates one of the following:

1. There is radiographic evidence, preferably CT evidence, of pulmonary abscess and positive needle aspirate culture from the abscess.
2. There is pathologic evidence of pneumonia on histologic examination of lung tissue obtained by open-lung biopsy or at a postmortem examination immediately after death that demonstrates abscess formation of an area of consolidation with intense polymorphonuclear leukocyte accumulation plus a positive quantitative culture of lung parenchyma (>10^4 microorganisms per gram of lung tissue). When used to confirm the diagnosis of pneumonia made by bronchoscopy, the lung tissue for histologic examination and culture must have been obtained within 3 d of the bronchoscopic procedure.

Probable pneumonia. In the absence of any of the above criteria for pneumonia, the patient meets the clinical criteria for suspicion of VAP of new (progressive) or persistent infiltrate and purulent tracheal secretions and demonstrates one of the following:

1. The presence of positive quantitative culture of a sample of secretions from the lower respiratory tract obtained by a technique that minimizes contamination with upper respiratory tract flora (PSB, BAL, PBAL).
2. The presence of positive blood culture unrelated to another source and obtained within 48 h before or after respiratory sampling. The microorganism(s) recovered should be identical to the microorganism recovered from a culture of lower respiratory tract secretions.
3. The presence of a positive pleural fluid culture in the absence of previous pleural instrumentation. The microorganism(s) recovered should be identical to the microorganism recovered from a culture of lower respiratory tract secretions.
4. The presence of pathologic evidence of pneumonia on histologic examination of lung tissue obtained by open-lung biopsy or at a postmortem examination immediately after death that demonstrates abscess formation of an area of consolidation with intense polymorphonuclear leukocyte accumulation plus a negative quantitative culture of lung parenchyma (<10^4 microorganisms per gram of lung tissue). When used to support the diagnosis of pneumonia made by bronchoscopy, the lung tissue for histologic examination and culture must have been obtained within 3 d of the bronchoscopic procedure.

Definitive absence of pneumonia. In patients not meeting the criteria for definite pneumonia, the absence of pneumonia is definitive if one of the following criteria are met:

1. Postmortem exam within 3 d of the suspicion of pneumonia showing no histologic sign of lung infection.
2. Definitive alternative etiology with no bacterial growth on a reliable respiratory specimen.
3. Cytologic identification of a process other than pneumonia (e.g., lung cancer) without significant bacterial growth on a reliable respiratory specimen.

Probable absence of pneumonia. Indicated by the lack of significant growth on a reliable respiratory specimen with one of the following:

1. Resolution without antibiotic therapy of one of the following: fever, radiographic infiltrate, or radiographic infiltrate and a definitive alternative diagnosis.
2. Persistent fever and radiographic infiltrate, with a definite alternative diagnosis established.

BAL, bronchoalveolar lavage; PBAL, protected BAL; PSB, protected specimen brush.
(Adapted from Pingleton SK, Fagon JY, Leeper KV Jr. Patient selection for clinical investigation of ventilator-associated pneumonia: criteria for evaluating diagnostic techniques. *Chest* 1992;102:553S–556S.)

In a landmark study, Fagon and collaborators randomized 413 mechanically ventilated patients with a clinical suspicion of VAP to a diagnostic strategy based on semiquantitative cultures of endotracheal aspirates (n = 209) or an invasive strategy (n = 204) (60). The invasive strategy consisted of bronchoscopy with direct microscopic examination of specimens (see above) and quantitative cultures. Quantitative cultures (PSB cutoff point ≥10^3 CFU/mL, BAL cutoff point ≥10^4 CFU/mL) were used to adjust or withdraw empirical treatment. In 117 of 204 patients, direct examinations yielded no bacteria. However, 20 of these patients had signs of severe sepsis and received antibiotics, although the suspicion of VAP was not confirmed. Of the remaining 97 patients, seven had significant quantitative cultures and antibiotics were started when culture results were available. So in all, the clinical suspicion of VAP was not confirmed in 90 patients. When comparing antibiotic use between patients randomized to either of the two invasive strategies, patients undergoing bronchoscopy had more antibiotic free days. Twenty-nine patients did not receive antibiotics up to day 28 (compared to four in the clinical management group), and patient survival was better among those randomized to the invasive strategy as well.

A different approach was used by Singh et al. (*61*). They determined CPIS scores of patients with a clinical suspicion of VAP and randomized those with a CPIS score ≤ six to different therapeutic strategies; antibiotics for 10 to 21 days (n = 42) or ciprofloxacin for 3 days (n = 39), which could be compared with withdrawing empirical therapy. Patients randomized to a short course had less antibiotic use, lower antibiotic costs, fewer superinfections with

antibiotic resistant pathogens, and no increase in length of stay or mortality. So, it seems safe to withdraw antibiotics after 3 days in patients with CPIS scores ≤6. However, the question is whether patients with such a low CPIS score should receive antimicrobial treatment in the first place.

Investigational Methods

A number of adjunctive or alternative methods for diagnosing healthcare-associated pneumonia have been proposed. Several reports have evaluated nonbronchoscopic techniques for sampling distal airway secretions, including brush (*36*), BAL (*25,49,62,63*), and endotracheal aspirates (*45*). Although such techniques might reduce costs, they have not been adequately validated or standardized, and sampling error can occur. In one study, however, good diagnostic agreement was demonstrated between quantitative cultures from PSB and mini-BAL done by respiratory therapists in patients with suspected VAP (*64*). And in another study, using postmortem analysis as the gold standard, blind bronchial sampling had a higher sensitivity for VAP than PSB (*49*).

The identification of intracellular microorganisms (ICOs) by Giemsa stain of BAL specimens has been reported to be highly predictive of healthcare-associated pneumonia (*25,41,65*). This technique has been compared to histologic and microbiologic examination of lung tissue at autopsy in two studies, with contradictory results. Specificities were high in both studies, 100% and 89% (*46,47*). However, sensitivity was 91% in one study when >5% of leukocytes containing intracellular bacteria was considered positive for VAP (*46*). In the other study, sensitivity was only 37%, when any leukocyte with intracellular bacteria was considered as a threshold for diagnosis of VAP (*47*). Since the presence of ICOs is indicative for the cellular response of the lung to invading microorganisms, it must have discriminatory value differentiating between infection and colonization. Determination of ICOs as an additional, early, indicator of VAP is being used increasingly, the cutoff value of 2% of cells with ICOs is used most frequently as diagnostic for VAP. An additional advantage of the determination of ICOs is that it is not influenced by recent antibiotic use (60,*66,67*).

Measurement of cytokines or inflammatory mediators may be adjunctive tools for diagnosing VAP in the future. Although blood levels of inflammatory mediators poorly correlated with quantitative results from bronchoscopic samples (*68,69*), elevated concentrations of endotoxin (>5 endotoxin units/mL) in BAL fluid had a sensitivity of 100% and specificity of 75% for diagnosing VAP (*70*). Soluble Triggering Receptor Expressed on Myeloid cells-1 (sTREM-1) has proven to be a biomarker for sepsis; however, for the diagnosis of VAP, the determination of sTREM-1 in BAL fluid showed high sensitivity and specificity in the first study (*71*). Unfortunately, this could not be repeated in several later studies (*72*). Procalcitonin is secreted as part of an inflammatory response but only when triggered by infection as shown in severe sepsis. The value of procalcitonin in pulmonary infection remains unclear and studies aiming to establish a diagnostic cutoff value of procalcitonin in case of VAP show contradictory results; sequential measurements might be more useful (*73*).

Other methods that cannot presently be recommended but that may merit further investigation include the detection of elastin fibers (*25,74*) and antibody-coated bacteria (*75*) in respiratory secretions and high-resolution computed tomography (CT) (*76*).

DESCRIPTIVE EPIDEMIOLOGY

Incidence

Incidence rates of VAP among ICU patients depend on the type of ICU, the severity of illness of patients studied, and the criteria for diagnosis. The overall incidence of pneumonia decreases when the definition of pneumonia becomes more strict. Therefore, whether investigators used bronchoscopic techniques in their diagnosis of VAP or just clinical and radiographic parameters is important with regard to incidence rates of VAP. In a number of studies aiming to ascertain incidences of VAP, or to evaluate modalities to diagnose VAP, or studies in which risk factors for VAP were assessed, the cumulative incidences of VAP range from 8.6% to 64.7%. Moreover, in studies on the effect of preventive measures on the occurrence of VAP, incidences of up to 78% have been reported in the control groups (*77*). In the Extended Prevalence of Infection in Intensive Care study (EPIC II), 13,796 patients in 1,265 ICUs were studied on a single day, 51% of the patients were considered infected, and 64% of them had pneumonia (*78*).

The cumulative risk for developing VAP during ICU stay increases until day 5. In one study, the calculated rates for VAP were 3% per day in the first week, 2% per day in the second week, and 1% per day thereafter (*79*). Two other studies suggest that there is a relatively constant 1% to 3% risk per day for developing VAP while MV continues for medical and surgical ICU patients (equivalent to 10 to 30 cases per 10,000 patient-ventilator-days) (*80,81*).

A number of studies have reported incidence rates for healthcare-associated pneumonia in other patient groups, such as the elderly, trauma patients, or cancer patients. However, these studies have relied primarily on clinical diagnostic criteria (10,*11,80–85*).

RISK FACTORS

The strongest risk factor for healthcare-associated pneumonia appears to be tracheal intubation and MV, which results in a 3- to 21-fold increase in the risk of developing healthcare-associated pneumonia (*8,81,85–88*). Because other pathogenetic factors may be different, it is useful to consider nonventilated and ventilated patients (Table 22-3) separately when discussing risk factors.

When nonventilated or broad hospital populations are considered, factors found by multivariate analysis to significantly increase the risk of healthcare-associated pneumonia include chronic lung disease (*85,119*), severity of illness (*119*), upper abdominal or thoracic surgery (*85,119,120*), duration of surgery (*119*), age (*85*), poor nutritional state (*120,121*), immunosuppressive therapy (*120,122*), depressed level of consciousness (*85,123*), large volume of aspiration (*85*), impaired airway reflexes or difficulty handling secretions (*123*), nasoenteric intubation

TABLE 22-3

Risk Factors for ICU-Acquired and Ventilator-Associated Pneumonia

ICU-Acquired Pneumonia	*Ventilator-Associated Pneumonia*
Identified risk factors with no or only limited possibilities for prevention	
Naso/orotracheal intubation (*85,89*)	Emergent intubation (*90*)
Duration of MV (*85,89,91–93*)	Duration of MV (*94–97*)
Severity of illness (*91,93,98*)	Severity of illness (*90,99*)
History of COPD (*85*)	History of COPD (*94,96,100*)
Reason for admission	Reason for admission
Trauma (*85,91,92*)	Trauma/head trauma/blunt trauma (*79,84,90,101*)
Neurologic disease (*89,98*)	Hypotension (*90*)
Thoraco/abdominal surgery (*85,102*)	Coma (*103*)
Coma (*91,104*)	Neurosurgery (*97,101*)
Age (*85,92*)	Acute respiratory distress syndrome (*101,105,106*)
	Burns (*79*)
	Neurologic disease (*79*)
	Cardiac disease (*79*)
	Age (*99*)
Identified risk factors that offer possibilities for prevention	
Antacids (*98*)	Antacids or H_2-antagonists (*84,107,108*)
Large-volume aspiration (*85*)	Large-volume aspiration (*79,96,101*)
Presence of nasogastric tube (*102*)	Enteral nutrition (*97,103*)
Impaired airway reflexes (*89,91*)	Contaminated ventilator circuits (*84,109*)
Depressed consciousness (*85*)	Reintubation (*96,103,108,110,111*)
	Previous antibiotic use (*94,95,99,100,107,112–114*)
	Absence of previous antibiotic use (*79,114*)
	Nonelevated head position (*99*)
	Paralytic agents (*79*)
Risk factors identified incidentally or needing further investigation to assess their influence on infection and possibilities for prevention	
Male gender (*98*)	Male gender (*110*)
Recent bronchoscopy (*102*)	Fall-winter season (*84*)
Thoracic drainage (*98*)	Failure of continuous aspiration of subglottic secretions (*112*)
Coagulation products (*98*)	Inadequate intracuff pressure (*112*)
	Administration of aerosols (*110*)
	Presence of a tracheostomy (*108,110*)
	Transport out of the ICU (*110*)
	Sinusitis (*115,116*)
	Multiple central venous line insertions (*108*)
	Positive end expiratory pressure (*2*)
	Corticosteroid therapy (*97*)
	Dental plaque colonization (*117*)
	Accidental extubation (*118*)

MV, mechanical ventilation; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

(*123*), neuromuscular disease (*121*), and male gender (*119*). Additional risk factors suggested by univariate analysis include duration of hospitalization (*6,9*), oropharyngeal colonization with gram-negative bacilli (10), obesity (*9*), antibiotic therapy (*6*), reflux esophagitis (*124*), and previous pneumonia (*124*).

The risk factors associated with the development of VAP have been determined in studies using multivariate analysis techniques, Cox regression techniques, and case–control designs, or have been suggested on the basis of reviews. Determination of risk factors for VAP has several clinical implications. They offer prognostic information about the probability of developing VAP, they help to reveal the pathogenesis of VAP, and they may provide possible targets for preventive strategies. By risk stratification, one can determine which patients may benefit most

from pneumonia prophylaxis (*125*). Risk factor analyses for ICU-acquired pneumonia (i.e., pneumonia diagnosed in ICU patients with or without MV) have clearly identified MV to be the most important risk factor (*85,89,91–93*). In general, the risk factors that have been identified can be divided into three groups: (a) risk factors that are well known (intubation, duration of MV, etc.) but very difficult to modify and that offer no or only limited possibilities for prevention, (b) risk factors that seem to play a role in the pathogenesis of VAP and have stimulated the development of a number of preventive strategies, and (c) risk factors that have been identified only incidentally or need further investigations to assess their significance and the possibility for prevention. Several risk factor analyses identified previous antibiotic use to be significantly associated with the development of VAP (*94,95,99,100,107,112*). In contrast, antibiotics conferred protection for VAP in a risk factor analysis (*79*), and the absence of prior antibiotic treatment was a risk factor for VAP caused by *Haemophilus influenzae* (*113*). Lately, attention has been drawn to the association between the mode of MV, ventilator-induced lung injury, and inflammation or infection (*126,127*).

Mortality

Published crude mortality rates for healthcare-associated pneumonia range widely from 20% to 71% for hospital-wide, ICU, and ventilated patient groups with a median of 41.5% (*8,21,80–85,96,99,121,128–131*); within the wide reported range, it is not possible to distinguish between these groups. Several factors have been associated with a greater risk of mortality, most prominently *Pseudomonas aeruginosa* as a pathogen, severity of underlying illness, inappropriate antibiotic therapy, and age (*80,82,85,96,99,102,132–134*).

With regard to mortality and VAP, the existing controversy is whether patients die from or die with VAP. In a number of studies, VAP was not independently associated with mortality (*68,84,96,108,*135,*136,137*). A recent systematic review of all observational studies on VAP and mortality demonstrated extensive heterogeneity in outcome, precluding the possibility to quantify the association between VAP and mortality. Only in two subgroups, patients with trauma or ARDS, heterogeneity allowed any conclusions, and in both subgroups VAP was not associated with increased mortality (*138*).

Morbidity and Cost

Healthcare-associated pneumonia is associated with substantial morbidity. Reported rates of secondary bacteremia have ranged from 4% to 38% (*68,80,82,84,85,96,108,131*), and empyema developed in 5% to 8% of patients with healthcare-associated pneumonia (*68,139,140*).

The excess costs associated with healthcare-associated pneumonia are remarkable. According to estimates published by the CDC, an average of 5.9 days of increased length of stay and $5,683 in extra hospital charges result from each episode of healthcare-associated pneumonia (*141*). More recently, Warren et al. found the attributable costs of VAP, after adjustment for underlying severity of illness, to be approximately $11,897 (*3*). Published estimates of excess duration of hospitalization attributed to healthcare-associated pneumonia have ranged from 4 to 22 days (*3,82,128,133,134,137,142–146*), and total hospital costs and hospital length of stay are linearly related (147). A cost-effectiveness analysis of patients receiving oropharyngeal decontamination as a preventive strategy for healthcare-associated pneumonia showed an estimated cost saving of $13,430 for every episode of VAP prevented (*148*).

PATHOGENS

A variety of pathogens appear to be important as causes of healthcare-associated pneumonia. The National Healthcare Safety Network (NHSN) system provides the largest database describing microorganisms isolated from both ventilated and nonventilated patients with healthcare-associated pneumonia. According to NHSN system data from 2006 to 2007, the most frequently isolated pathogen is *Staphylococcus aureus* (24%), followed by *P. aeruginosa* (16%), *Enterobacter* spp. (8%), *Acinetobacter baumanni* (8%), and *Escherichia coli* (5%) (*149*). Problematic resistant pathogens account for a minority of infections (24%). *P. aeruginosa* and *Acinetobacter* spp. are more commonly reported in VAP than in non-VAP. Compared with data from 1997, the proportion of Enterobacteriaceae has decreased, and the proportions of *A. baumannii* and *S. aureus* have increased (*149*).

Besides the difference in duration of MV at time of diagnosis, early-onset and late-onset VAP also have a different etiologic spectrum. Early-onset VAP is mainly caused by *Streptococcus pneumoniae, S. aureus,* and *H. influenzae,* pathogens that presumably already colonize the respiratory tract at the time of intubation. Late-onset VAP is caused by healthcare-associated pathogens such as Enterobacteriaceae, *S. aureus,* and *P. aeruginosa*. Because these healthcare-associated pathogens are known to cause serious infections under certain circumstances, they are usually grouped and labeled as potentially pathogenic microorganisms (PPMO). In many studies, colonization and infection with PPMO is analyzed instead of the separate species. Although PPMO are regarded as a single group, it should be kept in mind that each species has its own characteristics with regard to preferred site of colonization, routes and vectors of transmission, and clinical spectrum.

Studies using quantitative cultures of BAL and/or PSB demonstrate that approximately 60% of all cases of VAP are associated with gram-negative bacteria, mainly *P. aeruginosa* (20%), and 35% with gram-positive bacteria (*80,131,150,151*). *S. aureus* is the most frequent gram-positive pathogen causing VAP (20%). In comatose multiple trauma patients, incidences of *S. aureus* VAP as high as 56% have been reported (*104,152–154*). VAP is often polymicrobial with incidences ranging from 20% to 60% of all episodes of VAP (*12,150,155*). The proportional distribution of the species causing VAP within the etiologic spectrum, as well as their antibiotic susceptibility, may vary considerably between hospital settings, patient populations, and countries.

The importance of anaerobic bacteria in the pathogenesis of VAP has not been studied extensively. Isolation of anaerobic bacteria requires specific transport conditions and culture media, which usually are not systematically achieved during bacteriologic investigation of respiratory tract samples. The incidence of VAP in which anaerobic bacteria are involved, therefore, is probably underestimated. In a prospective study of 130 episodes

of VAP, aerobic and anaerobic bacteria were isolated from PSB (≥10^3 CFU/mL) in 26 (20%) patients, and anaerobic bacteria only were isolated in four (3%) patients (*151*). In another prospective study, no anaerobic microorganisms were isolated in a group of 143 patients, of whom 63 were diagnosed with VAP, despite painstaking microbiological efforts (*156*). Moreover, only one nonpathogenic anaerobic microorganism was isolated in 25 patients with suspected aspiration pneumonia receiving MV of which 12 met the criteria of pneumonia (*156*).

Though less common, other pathogens may also be problematic. Additional work is needed to clarify the roles of influenza and other respiratory viruses, *Mycoplasma pneumoniae,* and *Chlamydia pneumoniae;* however, several reports suggest that these pathogens may account for a modest proportion of cases (*157–164*). More recently, reports on herpes simplex virus, human metapneumovirus, cytomegalovirus, and Epstein Barr virus infections in immunocompetent mechanically ventilated ICU patients have been presented, either as a primary cause of pneumonia or as part of a polymicrobial episode. The clinical relevance of these viral microorganisms, however, remains to be determined (*165,166*). *Legionella* can be an important cause of healthcare-associated pneumonia, particularly when there is colonization of the hospital hot water system (*167–171*). *Aspergillus* and cytomegalovirus are important pathogens in bone marrow transplant recipients (*172*) and other immunocompromised patients. The risk of *Aspergillus* infection may be increased by adjacent construction activity or by a faulty ventilation system (*172–174*). Healthcare-associated infections due to respiratory viruses, *Legionella, Aspergillus,* cytomegalovirus, and *Mycobacterium tuberculosis* are discussed at greater length in other chapters (*36,38,41,42*).

PATHOGENESIS

Colonization of the upper respiratory tract precedes the development of healthcare-associated pneumonia (*114*,135,*175*). For upper respiratory tract colonization and pneumonia to develop, pathogenic microorganisms must reach the distal lung and then multiply, overcoming host defenses at each step. Host defenses include filtration and humidification of air in the upper airways, epiglottic and cough reflexes, ciliary transport by respiratory epithelium, phagocytes and opsonins in the distal lung, and systemic cell-mediated and humoral immunity (*176,177*).

The predominant mode of inoculation is aspiration; however, inhalation (particularly *Aspergillus* and other fungal molds), seeding via the bloodstream, and reactivation of latent infection (*M. tuberculosis,* cytomegalovirus in immunocompromised patients) account for some pneumonias that develop in hospitalized patients. Translocation from the gastrointestinal tract has also been hypothesized as a mode of inoculation (*178*), but this has not been confirmed.

Colonization

The relationship between colonization of the upper respiratory tract and the development of VAP was established by Johanson and coworkers (10) in 1972. Healthcare-associated respiratory infections developed in 23% of ICU patients with upper respiratory tract colonization but in only 3% of noncolonized patients (10). Moreover, upper respiratory tract colonization increased with severity of illness. Repeated oropharyngeal cultures obtained from 33 normal subjects revealed gram-negative bacteria in 6% of subjects, while these pathogens were cultured from 35% of moderately ill hospitalized patients and 73% of moribund patients (179). Since then, many variables have been determined that enhance colonization and infection of the respiratory tract in ICU patients (*180*). Although increased exposure to pathogens may play a role, this cannot exclusively explain increased colonization rates. Nursing and medical staff have similar colonization rates as normal subjects not working in a hospital setting (179). A reduced capacity to clear pathogens and/or increased adherence of microorganisms are more likely mechanisms to account for the higher colonization rates in critically ill patients. The latter mechanisms can be the result of decreased host immunologic function, destruction of epithelial surfaces (*181,182*), impaired mucociliary clearance, proinflammatory enzymes, and fibronectin-reducing proteases (*183*). Furthermore, during ICU stay, approximately 60% of patients receive systemic antibiotics. Antibiotic therapy can rapidly change the commensal oropharyngeal flora, resulting in an increase in oropharyngeal and upper respiratory tract colonization with aerobic gram-negative or gram-positive bacilli and yeasts, possibly due to loss of the normal bacterial flora (*180,184*) and to selection of pathogens that are resistant to the antibiotics used (*185–189*).

Routes of Colonization Microorganisms reach the lungs after aspiration of colonized oropharyngeal fluid. Microaspiration occurs frequently, both in healthy people and in critically ill patients (*190,191*). Pathogens colonizing the respiratory tract and causing VAP are derived from either endogenous or exogenous sources. The stomach and intestine are the most important endogenous sources. In addition, pathogens colonizing the upper respiratory tract (oropharynx, sinus cavities, the nares, and dental plaque) may be aspirated. Contaminated environment (sinks, faucets, sheets, etc.), contaminated equipment (MV devices, ventilator circuits, radiographic equipment, etc.), contaminated enteral feeding, and other colonized patients in ICU are potential exogenous sources.

Several routes of colonization by which pathogens are transported from their endogenous or exogenous sources to the upper respiratory tract of the patient are possible. In the gastropulmonary route of colonization (*192,193*), endogenous bacteria reach the upper respiratory tract via the stomach and subsequently colonize the oropharynx and trachea, after which the bacteria are aspirated in the lower respiratory tract. This route of colonization has been propagated as important in the pathogenesis of VAP for many years. The rectopulmonary route of colonization has attracted less attention. In this route, intestinal microorganisms spread from the rectal area via the patient's skin or the hands of healthcare personnel to the upper respiratory tract. Finally, transfer of pathogens from exogenous sources most probably occurs via

hands of nursing and medical staff, which enables direct inoculation of microorganisms into the tracheobronchial tree during manipulation of ventilator circuits or tubes (*194–196*). This is called the exogenous route of colonization or cross-colonization when another patient is the exogenous source.

Essential Conditions to Study the Pathogenesis of VAP Since colonization is not always followed by infection, infection rates with a certain pathogen form only the tip of the iceberg of the complete epidemiology (*175,195*). When studying the epidemiology of microorganisms in ICU, surveillance of colonization is indispensable. In clinical practice, surveillance is advised only for high-risk patients in specific clinical settings (*197*). However, when determining the epidemiology of ICU pathogens in detail, surveillance should include all patients within the ICU, as well as equipment and environmental surfaces for certain pathogens. Surveillance cultures from patients should be taken on admission and subsequently with a frequency high enough to study sequences of colonization from initial body sites to other body sites. Moreover, patients may be colonized or infected with multiple genotypes of the same species, both at one particular body site and at different body sites (*194*). Therefore, analysis of a single isolate may not accurately represent the bacterial flora. Analysis of several isolates and determination of similarity of isolates is crucial (*198*).

Comparison of bacterial phenotypes, such as antibiotic susceptibility patterns, serotypes, phage types, and outer membrane protein types, is relatively easy to perform, but lacks specificity (*198,199*). Genomic DNA fingerprinting techniques, such as pulsed-field gel electrophoresis, random amplification of polymorphic DNA, arbitrarily primed polymerase chain reaction, and multiple loci variable-number tandem repeats analysis (MLVA), have a higher specificity and discriminatory power while maintaining epidemiologic linkage. These techniques, therefore, are considered the methods of choice to determine identity of bacterial isolates in the epidemiology of healthcare-associated outbreaks (*200–202*). However, the techniques are often cumbersome and expensive, and therefore not always feasible in routine practice.

In summary, the optimal study design to study routes of colonization that may lead to VAP includes (a) determination of the incidence of VAP, preferably diagnosed by bronchoscopic techniques; (b) performance of surveillance cultures of all patients present in ICU, and possibly environment and equipment; (c) culturing several body sites on admission and with a sufficient frequency thereafter; (d) analyzing several isolates of each species, cultured from each site; and (e) determination of similarity of isolates of a certain pathogen by genotyping techniques.

Endogenous Routes

Gastric Colonization and the Gastropulmonary Route In critically ill patients, gastric acidity may be decreased (i.e., pH value higher) due to decreased acid production, because of the application of enteral feeding or stress-ulcer prophylaxis (antacids, H_2-antagonists, H^+K^+–adenosine triphosphatase [ATPase] inhibitors). If the gastric environment favors bacterial growth, bacteria may multiply; hence, colonization with gram-negative bacteria occurs frequently at this site (*12,192,193*). Because of the simultaneous occurrence of gastric colonization and the development of VAP, a causal relationship has been assumed. In the so-called gastropulmonary route of colonization, bacteria presumably reach the upper respiratory tract by retrograde movement from the colonized stomach, and bacteria are aspirated into the lower respiratory tract. Based on studies reporting correlations between development of VAP and concurrent or preceding gastric colonization with the same species, a central role in the pathogenesis of VAP was assigned to gastric colonization (*11,192,203*). The importance of gastric colonization was investigated in several studies (*11,12,204–211*), and percentages of patients in whom the stomach served as a source of colonization or infection of the respiratory tract ranged from 4% to 24% for colonization and from 0% to 15% for the development of VAP (*4*). Thus, the role of the stomach and gastropulmonary route of colonization remains a subject of debate (*15*). Nevertheless, based on the alleged importance of gastric colonization, modulation of colonization at this site is still being used as a measure to prevent VAP.

Oropharyngeal Colonization The results of studies performed by Johanson and coworkers (10,179) in the early 1970s pointed toward an association between colonization of the upper respiratory tract and the development of VAP. However, at that time, VAP could not be diagnosed with bronchoscopy and the diagnosis relied on relatively nonspecific clinical, radiographic, and microbiologic criteria. Moreover, only antibiotic susceptibility patterns and serotyping were employed to determine the similarity of isolates, because molecular genotyping techniques were not yet available. Remarkably, in the following years, research on the pathogenesis of VAP almost exclusively focused on the role of gastric colonization and the gastropulmonary route of colonization. Approximately 20 years later, new studies on sequences of colonization in patients who developed VAP provided additional evidence in support of Johanson et al.'s earlier findings (*192,207*). In a number of other studies, serial cultures of multiple body sites were obtained to determine sequences of colonization leading to VAP, all supporting a more important role of oropharyngeal than gastric colonization in the pathogenesis of VAP (*12,204–206,208,212*).

In conclusion, the evidence at hand strongly suggests an important role for the oropharynx in the pathogenesis of VAP that offers a potential target for preventive strategies.

Intestinal Colonization and the Rectopulmonary Route The intestines are a large endogenous source of gram-negative bacteria, which may spread to the upper respiratory tract via the patients' skin or hands of healthcare personnel. This so-called rectopulmonary route of colonization, in reality, is an exogenous route for endogenous microorganisms. Still, due to decreased intestinal peristalsis and gastric emptying in critically ill patients, bacteria can colonize the proximal small intestine and subsequently migrate to the stomach via duodenogastric reflux (*211,213*). The rectopulmonary route of colonization has attracted little attention, especially when compared with other routes

of colonization. To our knowledge, only four studies have been performed with special attention to the rectopulmonary route (*194,214–216*), and the available data suggest that rectal colonization with *Enterobacter* spp. and *P. aeruginosa* frequently occurs in critically ill patients, but secondary colonization of the upper respiratory tract seems infrequent. The relevance of rectal colonization and the rectopulmonary route of colonization in the pathogenesis of VAP remains largely undetermined.

Exogenous Routes Data on the role of exogenous sources in colonization and infection of ICU patients are derived mainly from case reports and descriptions of outbreaks. Sinks (*217–219*), distilled water systems (*220*), faucets (*221*), tube-feeding formulas (*222,223*), and ventilator circuits (*224*) have been reported as exogenous sources of PPMO, causing outbreaks of healthcare-associated infections. Especially *P. aeruginosa* possesses the ability to proliferate in aqueous sources throughout the hospital. In addition, patients themselves are major reservoirs of healthcare-associated pathogens (*225*). It is unlikely that airborne transmission contributes to the spread of staphylococci and gram-negative bacilli (*225*). Therefore, transfer of these pathogens most probably occurs via hands of nursing and medical staff or equipment (stethoscopes, blood pressure cuffs, etc.) (*194–196*). Direct inoculation of pathogens into the tracheobronchial tree from contaminated hands is possible during manipulation of ventilator circuits or tubes. If the tracheobronchial epithelium is able to bind pathogens, colonization and subsequent pneumonia may occur. This hypothesis is supported by studies reporting lower incidences of healthcare-associated infections after increasing hand-washing frequency or use of gloves or antiseptic hand-washing products (*226–228*). The importance of cross-colonization in nonepidemic situations has rarely been studied (*195,219,229–233*).

In summary, multiple data have shown that cross-colonization, mainly from patient to patient via hands of healthcare workers or equipment may be an important route of colonization. However, endogenous colonization, usually driven by selective pressure, may be equally or even more important, even in settings with high levels of endemic prevalence.

PREVENTION

Guidelines for the prevention of hospital-acquired or healthcare-associated pneumonia have been formulated by the American Thoracic Society (ATS)/Infectious Disease Society of America (234) and the CDC, with the consensus recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC) (235). Both guidelines, updated in 2004 and 2003, respectively, incorporate general recommendations regarding infection control practices that decrease the incidence of many infections, sometimes including VAP, such as pneumococcal and influenza vaccination of at-risk populations, hand-washing protocols, isolation of patients with multiply resistant respiratory tract pathogens, staff education, maintaining adequate staffing levels, and surveillance for bacterial pneumonia in high-risk ICU patients (234,235). Furthermore, an extensive list of recommendations regarding interruption of transmission of microorganisms from human or inanimate sources to patients is described. These recommendations include sterilization, disinfection, maintenance instructions for ventilator systems and circuits, hand washing, and barrier precautions (235). Moreover, a number of recommendations have been added in these updated guidelines that may reduce duration of MV and ICU stay and, thereby, reduce the incidence of VAP although these recommendations have no direct effect on the development of VAP. These measures include using a ventilator weaning and sedation protocol (*236*), a restricted red blood cell transfusion trigger policy (*237*), early goal-directed therapy in case of sepsis (*238*), and intensive insulin therapy (*239*). Finally, there are a number of preventive strategies considered effective in preventing VAP and recommended by the ATS guidelines with an evidence level I or II (234) or advised by the CDC/HICPAC guideline with a categorization of recommendation Category I or II (235), which are described in the following section.

Selective Decontamination of the Digestive Tract

In 1971, the concept of colonization resistance was proposed by van der Waaij et al. (*240*), who suggested a beneficial effect of the anaerobic flora in resisting colonization by aerobic gram-negative bacilli in the digestive tract. Many infections are caused by these enteric bacilli. SDD was developed to selectively eliminate the aerobic gram-negative bacilli and yeasts from the digestive tract, leaving the anaerobic flora unaffected. The first clinical studies with this technique were performed in granulocytopenic patients and showed favorable results (*241*). In the early 1980s, Stoutenbeek and coworkers (242) adapted the technique for ICU patients. The full concept of SDD aims to eradicate microorganisms from the intestine, the stomach, and the oropharynx by nonabsorbable antibiotics, which are combined with systemic antibiotic prophylaxis during the first days of ICU admission. In the SDD regimen, the combination of colistin and an aminoglycoside is generally used both of which are effective against gram-negative bacilli and *S. aureus*. Moreover, both agents are nonabsorbable and do not affect the anaerobic intestinal flora. Amphotericin B was added to prevent overgrowth with yeasts and systemic prophylaxis to prevent early infections. Since the introduction of this preventive strategy, dozens of studies in a variety of ICU populations (*77,185–187*,242,*243–273*,274,*275*) and many meta-analyses have been performed.

The full regimen of SDD (including oropharyngeal and intestinal decontamination and systemic prophylaxis) was studied in at least 17 trials (242,*244–256,269–271*) with VAP or respiratory tract infections as the end point. Only four of these had a double-blind placebo-controlled design (*247,251,269,270*). Twelve reported beneficial effects on incidence of VAP (*244,246,248,251,254,269,271*) or all respiratory tract infections (242,*245,249,256,270*), including only two of the four double-blind studies. The overall RRR of VAP in these 17 trials was 0.68 (95% CI: 0.61–0.73).

Several meta-analyses of SDD studies have been published, with more or less comparable results. They conclude that SDD decreases the incidence of VAP caused by aerobic gram-negative bacteria with RRRs ranging from

0.40 to 0.78, the reported outcomes regarding prevention of VAP, however, are related to the methodological quality of the individual studies (*276*).

As an alternative to SDD, investigators have evaluated the effects of selective oropharyngeal decontamination (SOD) alone (*77,266,267*). In a prospective randomized placebo-controlled double-blind study, 87 patients received topical antimicrobial prophylaxis in the oropharynx and 139 patients received placebo. The aim of the study was to prevent VAP by modulation of oropharyngeal colonization, without influencing gastric and intestinal colonization and without systemic prophylaxis. Oropharyngeal colonization present on admission was eradicated in 75% of the patients (4% among control patients), and only 10% of study patients acquired oropharyngeal colonization, as compared to 61% of control patients. There were no significant differences in gastric and intestinal colonization. This regimen resulted in an RRR for VAP of 0.62 (95% CI: 0.26–0.98) (274).

There is only one study in which SDD and SOD (using the same topical antibiotics in the oropharyngeal paste) were compared. This was a multicenter cluster-randomized crossover study in 13 ICUs in the Netherlands (277). During study periods of 6 months, all eligible patients (those receiving MV > 48 hours) received SDD, and the next 6 months all patients received either SOD or standard care (no SDD and no SOD), and the final regimen was used for all patients in the third study period. The order of the two interventions and standard care was randomized per center. Overall, 89% of all eligible patients were included and the total study population consisted of 5,939 patients. The day-28 mortality rate associated with standard care was 27.5%, and this rate was reduced by an estimated 3.5% (relative reduction of 13%) and 2.9% (relative reduction of 11%) during SDD and SOD, respectively. These reductions correspond to number needed to treat to prevent one casualty at day 28 of 29 and 34 for SDD and SOD, respectively. In this study, no attempts were made to measure the effects of SDD and SOD on the incidence of VAP. Overall intravenous antibiotic use (including the 4 days of cefotaxim during SDD) was 11.9% and 10.1% lower during SDD and SOD, respectively.

However, SDD has some potential drawbacks such as antibiotic resistance of gram-negative bacteria and the occurrence or selection of resistant gram-positive microorganisms. Although a number of studies reported no increased incidences of resistant bacteria (*244,248,250,254, 255,259–261,266,267*), overgrowth and even infections with gram-positive bacteria, resistant to the antibiotics used for SDD, have been reported in several trials (*185–189,249, 251,252,257,262,265,269,278–280*), as were increased colonization and infection rates due to gram-negative resistant bacteria (*245,249,251,252*). Moreover, the lack of cost-benefit analyses and of beneficial effects on mortality rates has further limited the widespread use of SDD (*281*).

In the before-mentioned multicenter cluster-randomized crossover study in 13 ICUs in the Netherlands, point- prevalence surveys were performed every third Tuesday of each month (277). On that day, rectal swabs and throat swabs were obtained from all patients present in the ICU, regardless whether they were receiving SDD or SOD. In all, 2,963 patients were included in these point-prevalence surveys, and the prevalence of carriage with antibiotic-resistant pathogens was <5% in all study periods, and was—for rectal carriage—lowest during SDD for all microorganism–drug combinations evaluated. In the respiratory tract, antibiotic resistance levels were similar for SDD and SOD, and lower than during standard care. Yet, when analyzed longitudinally, some unexpected findings emerged. For instance, rectal carriage with ceftazidime-resistant gram-negative bacteria was lowest during SDD, but was higher in study periods after SDD, than before SDD (282). Furthermore, respiratory tract carriage with ceftazidime-resistant gram-negative bacteria was lowest during SDD/SOD, but resistance prevalence gradually increased during these interventions. These findings demonstrated the ecological effects of SDD and SOD on the bacterial ecology in ICUs, with lowest levels of resistance during interventions. Yet, the data also suggest a rebound effect of intestinal carriage of ceftazidime resistance in the ICU after discontinuing SDD and a gradual increase of resistance in the respiratory tract during interventions.

In summary, SDD has been shown to decrease VAP; this effect seems mainly due to the SOD component in SDD. SOD has been shown to effectively decrease the incidence of VAP significantly. The largest SDD study up until now has shown reduced mortality of both SOD and SDD making it the standard of care in ICUs. Whether SDD or SOD has advantages in terms of development of antimicrobial resistance remains to be established.

Another way to achieve oropharyngeal decontamination, not using antibiotics, is the use of chlorhexidine. For instance, an oral rinse of 0.12% chlorhexidine reduced the incidence of respiratory tract infections among 353 cardiosurgical patients from 9% in control patients to 3% in patients receiving oropharyngeal decontamination with chlorhexidine (*283*), mainly due to a reduction of infections with gram-negative pathogens. This was repeated more recently in a study by Segers et al. randomizing 991 cardiosurgical patients. They found an ARR of 6.5%, which means that 16 patients need to be treated with oropharyngeal chlorhexidine gluconate to prevent one healthcare-associated pneumonia. Bacteremia, deep wound infections, and sternal infections were also significantly reduced (*284*). In a mixed ICU population, 2% chlorhexidine (CHX) alone or 2% chlorhexidine in combination with 2% colistin (CHX/COL) showed a reduced daily risk of VAP with hazard ratio of 0.35 for CHX and 0.45 for CHX/COL as compared to placebo. Moreover, CHX/COL provided significant reduction in oropharyngeal colonization with both gram-negative and gram-positive microorganisms, whereas CHX alone mainly affected gram-positive microorganisms (*285*). However, it is not known to what extent prolonged application of chlorhexidine will affect oral, esophageal, and gastric mucosa in critically ill ICU patients; the above-mentioned studies did not report serious complications. Moreover, the risk of chlorhexidine resistance after long-term application has scarcely been studied, although some studies report decreased susceptibility to chlorhexidine in some bacteria, however, with only slight increases in minimum inhibitory concentration (*284–289*).

Subglottic Secretions Drainage During MV, subglottic secretions and oropharyngeal fluids may accumulate above the inflated endotracheal cuff. This fluid will contain large amounts of microorganisms. Microaspiration of

these secretions along the tracheal cuff results in colonization and possibly infection of the lower respiratory tract. Drainage of subglottic secretions with specifically designed devices may therefore prevent VAP. This preventive measure has now been evaluated in five single-center studies all showing statistically significant or tendencies toward significant reductions in incidences of VAP (*14,*290,*291–293*). A meta-analysis of these studies concluded that subglottic secretions drainage was effective in reducing the rate of early-onset VAP (*294*). Recently, the first multicenter randomized controlled trial was published in which all study patients ($n = 333$) were intubated with a tracheal tube allowing drainage of subglottic secretions but were randomly assigned to undergo intermittent subglottic secretions drainage ($n = 169$) or not ($n = 164$). Moreover, diagnosis of VAP was performed by quantitative cultures of PSB or BAL. Microbiologically confirmed VAP occurred in 15% of study patients and 26% in the control group (RRR 42% and NNT approximately 10). Using a day-5 threshold, the beneficial effect of subglottic secretions drainage in reducing VAP was observed in both early- and late-onset VAP (*295*). Moreover, from a theoretical decision-model analysis, it was concluded that the use of endotracheal tubes allowing subglottic suctioning may result in cost savings in mechanically ventilated ICU patients (*296*). Pneumatikos et al. (*297*) determined the effects of subglottic secretion drainage in combination with decontamination of the subglottic area with nonabsorbable antibiotics (polymyxin, tobramycin, and amphotericin B). This combined intervention reduced the incidence of VAP with an RRR of 0.68.

In summary, subglottic secretion drainage appears to reduce VAP and the use of endotracheal tubes permitting subglottic secretion drainage should be considered by ICU physicians and physicians involved in pre-ICU care.

Body Position Enteral feeding increases gastric volume, especially in critically ill patients who often have reduced gastric motility and delayed gastric emptying due to the underlying disease or as a result of medication (*298*). In these patients, the risk of aspiration of gastric contents is enhanced. Torres and coworkers (*191*) analyzed gastroesophageal reflux in ventilated patients on enteral feeding, using radioactive-labeled gastric nutrition. They found that patients in the supine position had higher counts of radioactivity in endobronchial secretions compared with patients treated in a semirecumbent position. Moreover, the length of time in the supine position appeared to be a risk factor for aspiration of gastric contents. In a follow-up study in 15 patients by the same group, it was concluded that gastroesophageal reflux occurs irrespective of body position, and that the semirecumbent position does not protect completely from gastroesophageal reflux (*299*). These data confirmed the results reported by Ibáñez et al. (*190*) in a similar study. The semirecumbent patient position has been evaluated in a randomized design twice (*300*,301). In a small randomized trial, a semirecumbent position was associated with a significant reduction in the incidence of VAP as compared to the supine position (5% and 23%, respectively; $p = .018$). However, the combination of a supine position while receiving enteral feeding might have been responsible for this large difference (*300*). The study by van Nieuwenhoven et al. randomized 221 patients to standard care (supine position with backrest elevation of 10 degrees) or semirecumbent position (target backrest elevation of 45 degrees) and, importantly, backrest elevation was measured continuously. The most prominent conclusion was that a backrest elevation of 45 degrees for semirecumbent positioning was not feasible in daily practice. The target semirecumbent position of 45 degrees was not achieved for 85% of the study time, and these patients more frequently changed position than supine-positioned patients. The achieved difference in treatment position (average elevations of 10 degrees vs. 28 degrees) in this study did not prevent the development of VAP. The main conclusion regarding the preventive effect of body position on the incidence of VAP is that even in the presence of a dedicated team to control and maintain patient positioning, the semirecumbent treatment position with an aimed backrest elevation of 45 degrees is not feasible for mechanically ventilated patients (301).

In addition to the patient's position, gastroesophageal reflux may be influenced by the presence and even size of the nasogastric tube (*190,299,302*). However, the effects on incidences of VAP were not evaluated in any of these studies (301).

Other Preventive Strategies Intubation and MV clearly are the most important risk factors for VAP. Unnecessary intubation, therefore, should be avoided at all times. Noninvasive positive-pressure ventilation (NIPPV) using a face mask could be used as an alternative ventilation mode in ICU patients. The beneficial effects of NIPPV on the development of VAP and patient survival have been determined in randomized trials for patients with acute exacerbations with chronic obstructive pulmonary disease (COPD) (*303*), acute respiratory failure (*304*), and in immunosuppressed patients with pulmonary infiltrates, fever, and respiratory failure (*305*). In addition, the risk for VAP increases with duration of ventilation. As a result, strategies to reduce the duration of ventilation may decrease the risk for development of VAP. Examples of such strategies are protocols to improve methods of sedation administration (*306,307*), accelerate weaning (*308*), or combining these protocols (*236*). Furthermore, staffing levels may influence the length of stay of patients in ICU, with an inverse relationship between adequacy of staffing levels and duration of stay and subsequent development of VAP (*309,310*). Understaffing can also lead to lapses in infection control practices, facilitating transmission of antibiotic-resistant bacteria (*311*).

Bacterial contamination of the ventilator tubing circuit may predispose to the development of VAP (*224*). Frequent changing of these circuits (including inline suction catheters, heat and moisture exchangers, and heated humidifiers) may be beneficial to decrease the bacterial burden. On the other hand, frequent manipulation of ventilator tubing circuits may lead to introduction of healthcare-associated pathogens. Five studies have addressed the effects of lengthening intervals between circuit changes on colonization of the patient and circuits, and the incidence of VAP (*130,312–315*). They all concluded that decreasing the frequency of ventilator circuit changes did not increase incidences of VAP or patient and circuit colonization. Therefore, substantial reductions in the costs of MV can be

obtained without apparent adverse effect. Studies using a closed-suction catheter system for endotracheal suctioning found similar incidences of pneumonia compared with the open-suction system with single-use sterile suction catheters (*316–319*). During MV, heating and humidifying inspired gases are necessary. Heated humidifiers are used most frequently, but these cause accumulation of water in the circuit that may become colonized with bacteria (*224*). Heat and moisture exchangers are a possible alternative in which the formation of condensate in ventilation circuits is avoided due to the combination of humidification with antimicrobial filtering properties. However, heat and moisture exchangers failed to reduce the incidence of pneumonia in five studies comparing both methods (*320–324*). Kirton and coworkers (*325*) are the only investigators to report a significant reduction in late-onset VAP, but not early-onset VAP, with the use of heat and moisture exchangers. More recently, the effect of heat and moisture exchanger filters with a different composition of the condensation surface, either $CaCl_2$ or $AlCl_2$ based, was compared. No difference was observed in the incidence of tracheal colonization and VAP (*326*).

Administering probiotics has been advocated as a means to prevent various infections, including VAP. Probiotics may exert immunomodulatory properties and maintain the host's microbial balance in oropharynx and upper digestive tract, which potentially reduces the incidence of VAP. Several studies have been performed and five of those were critically reviewed in a meta-analysis of randomized controlled trials by Siempos et al. concluding that administration of probiotics was beneficial in terms of incidence of VAP, length of ICU stay, and respiratory tract colonization with *P. aeruginosa*. No effect on mortality was seen (327). More recently, Morrow et al. compared oropharyngeal and gastric administration of *Lactobacillus rhamnosus* with placebo in a blinded, randomized, controlled trial, using quantitative BAL cultures for diagnosis of VAP. In all, 138 highly selected critically ill ICU patients were randomized. The patients receiving probiotics were less likely to develop VAP (19.1% vs. 40%, $p = .007$) and had fewer days of antibiotics prescribed for VAP (5.6 days vs. 8.6 days, $p = .05$) when compared to patients treated with placebo. No adverse affects related to probiotic administration were identified (*328*). Given the increasing antimicrobial resistance, the use of probiotics as a preventive strategy for VAP deserves consideration.

The endotracheal tube contributes to the pathogenesis of VAP, which involves colonization of the endotracheal tube from which the oropharyngeal cavity becomes colonized, eventually leading to the development of VAP. Colonization of the endotracheal tube is facilitated by biofilm formation. To prevent bacterial colonization and biofilm formation, a silver-coated endotracheal tube was designed since silver, *in vitro*, has broad-spectrum antimicrobial activity, reduces bacterial adhesion to the tube, and blocks biofilm formation. Rello et al. (*329*) were the first to report that the silver-coated endotracheal tube was feasible and well tolerated and showed delayed colonization, reduced colonization, and lower maximal bacterial burden in tracheal aspirates. Kollef studied the silver-coated endotracheal tube in a large, prospective, randomized, single-blind, controlled trial with VAP as primary outcome. The incidence of VAP was reduced (7.5% in control group and 4.8% in the study group [$p = .03$]), and the occurrence of VAP was significantly delayed (330). Moreover, it was suggested that the use of silver-coated endotracheal tubes was associated with reduced mortality in patients with VAP, a finding that needs confirmation in future trials (*331*).

The Institute for Healthcare Improvement has come forward to assist healthcare institutions with programs to implement evidence-based practice guidelines. The standard component of these programs are "bundles" of care defined as a small, straightforward set of practices that when performed collectively and reliably, have been proven to improve patient outcomes. Specific to VAP, the "ventilator bundle" was put forward, consisting of four evidence-based practices to improve the outcomes of MV: (a) peptic ulcer disease prophylaxis, (b) deep venous thrombosis prophylaxis, (c) elevation of the head of the bed, and (d) daily sedation vacation and assessment of readiness to wean. Several studies, mainly before-after studies, have been performed on the influence of implementing the ventilator bundle on incidences of VAP. In general, the studies showed a decrease in the number of episodes of VAP after implementation of the bundle. However, as concluded in a systematic literature review, the lack of methodologic rigor of the studies precludes any conclusive statements about the bundle's effect on prevention of VAP. Moreover, whether the four practices, included in the ventilator bundle, are the best (evidence-based) practices regarding prevention of VAP is matter of debate (*332*). Recently, a European care bundle for prevention of VAP was presented with five practices including not implementing ventilatory circuit changes unless specifically indicated, the use of strict hand hygiene using alcohol, the use of appropriately educated and trained staff, the incorporation of sedation vacation and weaning protocols into patient care, and oral care with chlorhexidine. The validation of this bundle in a prospective study is ongoing (*333*).

CONCLUSION

It remains difficult to define firm conclusions after a critical assessment of the various studies on the prevention of VAP. Due to small numbers of patients studied, heterogeneous ICU populations, and differences in diagnostic criteria and quality of the studies, a comparison of the studies is hampered. Moreover, some strategies have scarcely been studied. Ideally, preventive strategies are studied in well-designed multicenter trials, including large numbers of comparable patients.

The use of SDD has been studied most frequently and seems to have the best potential to reduce the incidence of VAP. However, SDD was considered of unproven value by the ATS (category 3), and a strategy for which insufficient evidence is available by the CDC (Category UI). Large recent studies showed that SDD and SOD improve patient survival and reduce overall antibiotic use. However, such strategies may be contraindicated in ICU settings with high-levels of multiresistant microorganisms. In settings, where resistance levels are low, the long-term effects of antibiotic prophylaxis should be carefully monitored.

The various preventive strategies associated with enteral feeding and (prevention of) gastric aspiration are thought to be efficacious by ATS (category 2); very few studies on their efficacy have been performed, and the results are controversial. The CDC considers these recommendations to be an unresolved issue (category UI), although a semirecumbent body position during MV was strongly recommended (category IB), even though definitive scientific evidence for this recommendation is lacking. There is now one randomized trial favoring the semirecumbent position, while another showed that the semirecumbent position with backrest position at 45 degrees is not feasible in daily care.

Subglottic secretions drainage is regarded "promising in efficacy and being used by some hospitals on a regular basis" in accordance with an ATS category 2 recommendation, which is in line with the scientific evidence. Subglottic secretion drainage appears to reduce VAP and the use of endotracheal tubes permitting subglottic secretion drainage should be considered. However, the CDC considers this strategy to be a practice for which insufficient evidence or consensus regarding efficacy exists (category UI) in their last guideline.

Although preventive strategies aimed at ventilator circuits are categorized as promising in efficacy (category 2) by the ATS, the accessory guidelines in fact indicate that the proposed measures (i.e., heat and moisture exchangers; frequent, infrequent, or no change of circuits and closed-suction systems) do not seem to add to the risk of developing VAP. This is congruent with the categorization of the CDC (category UI) recommendation.

Finally, noninvasive ventilation, weaning and sedation protocols aimed to reduce endotracheal intubation and duration of ventilation have proven efficacious in preventing VAP. Evidence in support of the use of probiotics and silver-coated endotracheal tubes is compiling and should be considered. The use of the "ventilator bundle" appears attractive in many ways although the choice of practices incorporated in this bundle needs critical evaluation.

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CHAPTER 23

Healthcare-Associated Sinusitis

Marc J.M. Bonten

Healthcare-associated sinusitis (HAS) is a common, unrecognized cause of fever and even sepsis in mechanically ventilated patients. Underestimation of its incidence is at least partly due to the difficulty in diagnosing HAS. The reported cumulative incidence ranges from 1% to 83% in studies specifically designed to investigate HAS. Combined with pneumonia, catheter-related sepsis, and urinary tract infection, HAS has been considered as one of the four "horsemen" of clinically important healthcare-associated infections in critically ill patients *(1)*. HAS is most often caused by enteric gram-negative bacteria or *Staphylococcus aureus*. The infection is a result of disturbances of local anatomy, colonization of the upper respiratory tract with potentially pathogenic microorganisms, and the severity of underlying illness in critically ill patients. The most important risk factors are prolonged nasotracheal intubation, mechanical ventilation, and the presence of a nasogastric tube. Basic infection control procedures and avoidance of nasotracheal intubation seem to be most important for prevention of HAS.

DEFINITION

Because of the wide variation of definitions used for HAS, interpretation of the whole body of literature dedicated to this topic is difficult, mainly because of the problems encountered in diagnosing HAS. It is usually diagnosed using a combination of clinical suspicion of infection, with fever and leukocytosis, together with radiologic evidence of HAS. The latter may be based on radiographic, ultrasonographic, or computed tomography (CT) examinations. Finally, the diagnosis is confirmed by microbiologic cultures. The value of each of these diagnostic modalities is discussed later. In what probably is the most detailed prospective study of HAS, Rouby et al. (2) distinguished between radiologic maxillary sinusitis and infectious maxillary sinusitis (Fig. 23-1). Radiologic maxillary sinusitis was defined as total opacification of one or both maxillary sinuses or as the presence of an air-fluid level within one or both maxillary sinuses on CT image. Based on microbiologic cultures and Gram staining, the diagnosis of infectious maxillary sinusitis was established or refuted.

CLINICAL RELEVANCE OF HEALTHCARE-ASSOCIATED SINUSITIS

HAS was first described in 1974. Arens et al. *(3)* described four patients who had undergone nasotracheal intubation for coronary artery bypass surgery and who developed HAS. All patients had been intubated <36 hours, and evidence of HAS appeared in 6 to 10 days postoperatively. In later studies, HAS was usually described in patients who were still intubated. The true incidence of HAS and its relevance as a source of fever are unknown. Large studies determining prevalences and incidences of healthcare-associated infections, such as the National Nosocomial Infection Surveillance system from the Centers for Disease Control and Prevention or the European Prevalence of Infection in Intensive Care Study, did not include HAS as an infectious entity *(4,5)*. However, the cumulative incidence of HAS was remarkably high in several studies carefully analyzing causes of fever in mechanically ventilated patients, with the reported cumulative incidence ranging from 1% to 83% (Table 23-1). Meduri et al. (16) subjected 50 patients with a clinical suspicion of ventilator-associated pneumonia to a systematic diagnostic protocol, which included CT scanning of the sinuses and aspiration of the maxillary sinuses for microbiologic analysis when air-fluid levels or opacifications were encountered. A definitive source of fever was identified in 45 patients and HAS was diagnosed in 12 of them. HAS was in all cases accompanied by another infection, which in most cases (72%) was caused by pathogens other than those isolated from maxillary aspirates. In a large prospective study in medical intensive care unit (ICU) patients with endotracheal intubation, the cumulative incidence of HAS was 7.7%, with incidence rates of 12 cases per 1,000 patient-days and 19.8 cases per 1,000 nasoenteric tube days (11). Furthermore, cumulative incidences from 9% to 26% have been reported in neurosurgical ICU patients (13,14,*18*).

These studies suggest that HAS may occur often in selected patient groups. However, it is unknown to what extent HAS affects morbidity and patient outcome. Interestingly, HAS may occur concomitantly with other infections. For instance, Borman et al. *(21)* described 19 patients with

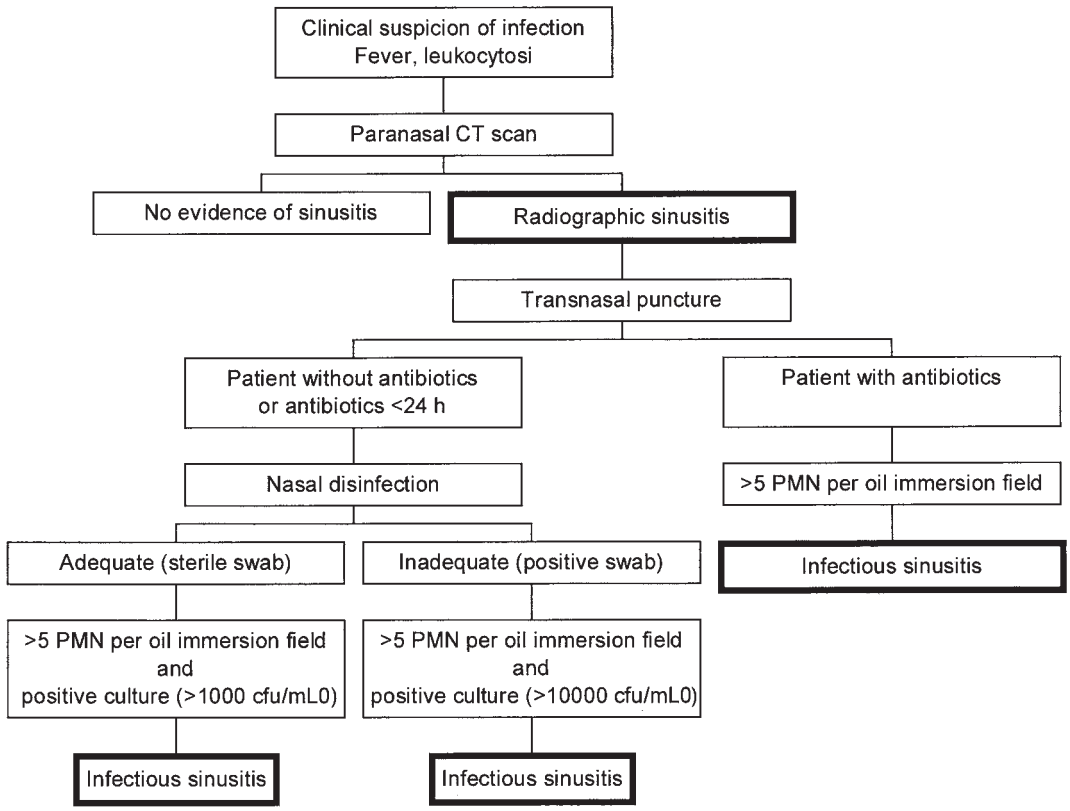

FIGURE 23-1 Possible diagnostic track for patients with a clinical suspicion of HAS. (Modified from Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of Healthcare-associated maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med* 1994;150:776–783, with permission).

radiographic evidence of HAS, and 10 of these patients had positive cultures of antral aspirates. Evaluation of causes of fever in these patients revealed that fever was definitely caused by HAS in only one patient, possibly in two, and definitely not caused by HAS in the remaining 16 patients.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Clinical Presentation

In previously healthy and ambulatory patients, acute sinusitis usually results in localized pain, nasal congestion, and purulent nasal drainage. Sinus disease is an inherent part of the common cold syndrome, and 87% of ambulatory patients with colds have sinus cavity disease *(22)*. In these patients, sinusitis is rarely associated with systemic symptoms or fever *(23)*. Pain cannot be expressed by most intubated patients, and findings of physical examination, such as tenderness and purulent nasal discharge, are often absent. As a result, physical examination usually does not contribute to establishing the diagnosis of HAS *(12)*. Nonspecific symptoms such as fever or leukocytosis often are the first signs of HAS. Because fever and leukocytosis, in this patient population, may have many other causes, both infectious and noninfectious, HAS may not be considered as the cause of infection by clinicians. Careful radiographic and microbiologic analyses are, therefore, mandatory.

Radiologic Examination

Sinus radiography usually includes three views *(24)*: the straight anterior–posterior view (Caldwell view) for examining the frontal and ethmoid sinuses; the Water's view to visualize the maxillary sinuses (also a straight anterior–posterior view with the patient's head tilted upward); and the lateral view to visualize the sphenoid sinus. Because of the complex labyrinthine structure of air cells separated by bony septa, the ethmoid sinus is difficult to evaluate. In addition, the sphenoid sinus is localized centrally and surrounded by bony structures and, therefore, is also difficult to evaluate. In critically ill patients, the diagnostic yields of conventional radiography are further diminished by the use of portable equipment, difficulties in placing patients in the upright position, and interference of nasogastric and nasotracheal tubes with x-ray images. Conventional multiview plain sinus radiographs, therefore, are regarded as inaccurate for diagnosing HAS (6).

Computed axial tomography displays bony details and can distinguish soft tissue swelling or fluid within the sinuses. In healthy subjects, sinuses are aerated. Signs suggestive for infection include maxillary mucosal thickening, total opacification, or the presence of an air-fluid level in one or both maxillary sinuses (2). CT scanning definitely has multiple advantages over conventional radiography for diagnosing HAS. However, mucosal thickening or fluid accumulation within sinus cavities are not proof of infection, and CT scan is unable to distinguish between blood and other fluids, which may be problematic in patients

TABLE 23-1

Cumulative Incidence of Healthcare-Associated Sinusitis According to Patient Population and Diagnostic Techniques Used

Study (Ref)	*No. of Patients*	*No. of Cases*	*Cumulative Incidence*	*Population Studied*	*Diagnostic Criteria*
Kaups et al. (6)	100	1	1%	Surgical ICU 54% multiple trauma 90% mechanically ventilated	Unexplained fever Bedside ultrasonography Positive antral puncture
Caplan and Hoyt *(7)*	2,368	32	1.3%	Trauma unit All patients admitted	Opacification or air-fluid level on bedside radiography with purulent nasal discharge or purulent aspirate from the involved sinus
Mevio et al. *(8)*	1,126	27	2%	ICU	Unexplained fever Imaging evidence of fluid in maxillary sinus Antral puncture
Bert and Lambert-Zechousky *(9)*	4,509	103	2.3% (0.1–8.8%)	Six ICUs All patients admitted	Clinical suspicion of HAS Positive transnasal culture
Aebert et al. *(10)*	171	4	2.3%	Trauma ICU Nasotracheal intubation	Unexplained fever or purulent nasal discharge Opacification or air-fluid level on bedside radiography Purulent aspirate from the involved sinus
George et al. (1)	366	28	7.7%	Medical ICU Expected mechanical ventilation >3 d	Opacification or air-fluid level on bedside radiography or CT evidence of HAS ≥1 micro-organism in culture of aspiration fluid
Bell et al. *(12)*	139	11	7.8%	Trauma ICU Intubated and ventilated	Unexplained fever Opacification or air-fluid level on bedside radiography or CT evidence of HAS Purulent aspirate from the involved sinus
Korinek et al. (13)	123	11	9%	Neurosurgical ICU Intubated and ventilated	Unexplained fever Opacification or air-fluid level on CT Purulent aspirate from the involved sinus
Westergren et al. (14)	15	2	13%	Neurosurgical ICU >7 d on mechanical ventilation	Unexplained fever Bedside ultrasonography Positive antral puncture after sinoscopy
Holzapfel et al. (15)	300	54	18%	Mixed ICU Expected duration of intubation >7 d	CT evidence for maxillary sinusitis Quantitative cultures from transnasal puncture
Meduri et al. (16)	50	12	24%	Medical ICU Intubated and ventilated >48 h	CT evidence for maxillary sinusitis Cultures from transnasal puncture
Bach et al. (17)	68	17	25%	Postoperative patients Mechanically ventilated >4 d	Opacification or air-fluid level on bedside radiography with purulent nasal discharge or purulent aspirate from the involved sinus
Deutschman et al. *(18)*	43	11	26%	Neurosurgical ICU Nasotracheal intubation and ventilated >72 h No surgery or trauma of paranasal sinuses	Clinical suspicion of HAS or unexplained fever Radiography or CT evidence of HAS Positive culture from transnasal puncture
Rouby et al. (2)	162	51	31%	Surgical ICU Intubated and ventilated on admission	CT evidence for maxillary sinusitis Quantitative cultures from transnasal puncture
Holzapfel et al. (19)	199	80	40%	Mixed ICU Expected duration of intubation >7 d	Opacification or air-fluid level on CT, purulent nasotracheal sinus aspiration with $\geq 10^3$ CFU/mL in quantitative culture
Guerin et al. *(20)*	30	25	83%	ICU Nasotracheal intubation >6 d	Evidence for sinusitis on routine CT scan Cultures from transnasal puncture

ICU, intensive care unit; HAS, healthcare-associated sinusitis; CT, computed tomography.

with facial trauma. Even total opacification of one or both maxillary sinuses or an air-fluid level within one or both maxillary sinuses had specificities for infectious maxillary sinusitis ranging from 38% to 69% (2,15,*21*). Furthermore, CT scan is costly and requires transport of patients, which may, in itself, be a risk factor for healthcare-associated infections *(25)*.

Bedside sinus ultrasonography may be a reliable, noninvasive, and cheap alternative to CT scanning. This method, when compared with culture of antral aspirates as a gold standard, has been demonstrated to be accurate in ambulatory adults and children (26). However, clinical experience in mechanically ventilated patients is limited (6,14,27,28). In one study, 100 patients were examined with bedside sinus ultrasonography on admission and every 48 hours thereafter. CT scanning of the head was performed at the discretion of attending physicians and was performed in 61 patients. Fifteen patients had fluid within the maxillary sinus detected by ultrasonography, and in nine other patients sinus fluid was detected by a head CT scan but not by bedside sinus ultrasonography. None of these nine patients, however, had clinical sepsis without another clearly documented source. The authors concluded that the head CT scan is more sensitive but may detect abnormalities that have little clinical significance (6). In another study, left and right paranasal sinuses were examined by ultrasonography in the supine and semirecumbent position in 15 neurosurgical ICU patients in whom HAS was suspected on clinical grounds. Findings of ultrasonography were compared with observations made by sinoscopy. Sensitivities of ultrasonography for the presence of fluid and edema were higher in the semirecumbent position (91% and 81%, respectively). However, specificity was only 25% for the presence of fluid. Moreover, edema and/or secretions were demonstrated in 29 of 30 sinus cavities examined, but microorganisms were cultured from only two antra (14). In a third study, A-mode ultrasonography of maxillary and frontal sinuses was performed in 50 comatose patients that needed cerebral CT for another reason than suspicion of sinusitis (28). With CT images as gold standard, ultrasonography had a specificity of 72% to 98% and sensitivity of 63% to 86% for maxillary sinuses, and of 96% to 99% and 14% to 57%, respectively, for frontal sinuses. With areas under the receiver-operating characteristic curves of 0.89 and 0.76, for maxillary and frontal sinuses, respectively, the authors concluded that ultrasonography was an accurate tool to detect secretions in maxillary sinuses (28). In addition, excellent agreement levels (with kappa statistic >0.9) between B-mode ultrasonographic examination of both maxillary sinuses and CT imaging have been reported (27). In a subsequent study, it was demonstrated that ultrasound evidence of sinusitis was highly predictive for receiving fluids (for microbiological cultures) after transnasal puncture (29). These data suggest that ultrasonography may be a useful screening test, but whether it can be used as the sole diagnostic method remains to be established.

Microbiologic Analysis

The problem of microbiologic analyses in many ICU-acquired infections is distinguishing between colonization and infection. Colonization of the upper respiratory tract (e.g., nares, oropharynx, and trachea) is universal in mechanically ventilated patients. Nasal swab cultures will grow upper respiratory tract flora and are believed to be of little value to determine pathogens causing sinusitis (30). Mucociliary clearance and drainage may keep the sinuses clean. Therefore, antral aspirate cultures are regarded as the gold standard. The frontal, ethmoid, and sphenoid sinuses can only be drained surgically and are not amenable to aspiration at the bedside. However, the maxillary sinuses can be drained, and these cavities are most often involved. CT imaging demonstrated that the maxillary sinuses are involved in almost all ICU patients who develop HAS, and radiographic evidence of maxillary sinusitis was associated with radiologic abnormalities of ethmoid and sphenoid sinuses in >80% of ventilated patients. However, according to Rouby et al.'s (2) study, 50% of the patients with normal maxillary sinuses on CT had radiologic signs of ethmoid and/or sphenoid sinusitis, as did 92% of patients with mucosal thickening in maxillary sinuses. The contribution of infection of the ethmoid and sphenoid sinuses has never been studied.

Aspiration cultures from maxillary sinuses are representative for microorganisms causing pansinusitis, and irrigation at this site is often therapeutic. Insertion is performed with a specialized trocar, which has an inner needle obturator with an outer sleeve. Once inserted, the needle can be removed and irrigation can be performed via the hollow sleeve *(24)*. Because of colonization of the nares, even transnasal cultures can be falsely positive because of introduction of pathogens into the sinus cavity. Adequate disinfection, therefore, has been recommended (2). Disinfection of the nares with a povidone-iodine solution proved to be totally adequate (sterile cultures) in 51%, partially effective (decrease in nasal bacterial burden) in 38%, and completely ineffective (increase in nasal bacterial burden) in 11% (2). In Rouby et al.'s study, patients underwent transnasal puncture of the affected maxillary sinus after nasal disinfection. The diagnosis was changed to infectious maxillary sinusitis when there were more than five polymorphonuclear leukocytes per oil immersion field and a positive culture from sinus aspirate. In patients who did not receive antibiotics, the diagnosis of infectious maxillary sinusitis was established by quantitative cultures depending on the effectiveness of nasal disinfection (cutoff points were $>10^3$ colony forming units [CFU]/mL with adequate nasal disinfection [sterile nasal swab] and $>10^4$ CFU/mL with inadequate nasal disinfection [positive nasal swab]) (2). Two studies reported poor correlations between endoscopically guided middle meatal cultures and cultures from antral lavage aspirates or taps in patients with clinical suspicion of HAS (31,32).

A diagnostic scheme incorporating clinical, radiographic, and microbiologic evaluation is depicted in Fig. 23-1. It should be mentioned that few studies prospectively determined the incidence of HAS and that the clinical relevance of this infection largely remains unknown. The schemes, therefore, should be viewed merely as a possible approach to the diagnosis of sinusitis. Whether such an extensive diagnostic approach influences patient care or will be cost-effective remains to be established.

Recent guidelines for evaluating fever in critically ill patients, developed by the Task Force of the Society of Critical Care Medicine and the Infectious Diseases Society of America, recommend that a CT scan be performed when clinical evaluation suggests that HAS could be the source of

fever. If CT findings are consistent with sinusitis, puncture and aspiration of the sinuses should be performed under sterile conditions, and the aspirate should be Gram stained and cultured for aerobic and anaerobic bacteria and yeasts *(33)*. This clinical guideline has been evaluated by Holzapfel et al. (19). They randomized 399 patients to receive either standard evaluation of fever occurring during the course of ICU stay or a specific diagnostic strategy directed at the possibility of HAS. The strategy included sinus CT scans on days 4 and 8 after tracheal intubation and thereafter every 7 days if fever was present. When CT scan showed an air-fluid level and/or opacification of the maxillary sinus, transnasal puncture was performed for culture, drains were placed, and antibiotics were adjusted according to culture results. Radiographic evidence of HAS was observed in 55% of the patients randomized to this diagnostic strategy and 80 patients (40%) fulfilled microbiologic criteria of HAS. In the control group, no patient was treated for HAS. Interestingly, the incidence of healthcare-associated pneumonia and mortality at 2 months after randomization were lower in study patients. Although striking, the absence of a mechanism explaining this favorable outcome and the fact that all patients were nasotracheally intubated, which is not the standard of care in most ICUs, warrants a cautious interpretation of these results *(34)*.

CAUSE

The cause of HAS closely resembles the spectrum of pathogens causing other healthcare-associated respiratory tract infections and differs from the etiologic spectrum of acute community-acquired sinusitis in ambulatory patients. Acute sinusitis is usually caused by streptococci or *Haemophilus influenzae (35,36)*, whereas gram-negative enteric bacteria (e.g., *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, *Enterobacter* species), *Acinetobacter* species, *Pseudomonas aeruginosa*, and *S. aureus*, are most often isolated from patients with HAS. *Candida* species also have been identified as the cause of HAS, especially in long-term intubated patients receiving broad-spectrum antibiotics *(37,38)*. One case of HAS resulting from *Legionella pneumophila* has been reported in a patient with acquired immunodeficiency syndrome (AIDS) *(39)*. An analysis of microorganisms isolated from patients with HAS as described in 33 studies yielded 723 pathogens and revealed that 60% of the pathogens were gram-negative bacteria, 31% were gram-positive bacteria, and 9% were yeasts *(38)*. A considerable proportion (20–50%) of patients with HAS have polymicrobial infection, usually containing a mixture of the aforementioned pathogens. When analyzed quantitatively, 60% of the microorganisms isolated from sinus aspirates from patients with infectious maxillary sinusitis grew in concentrations $\geq 10^3$ CFU/mL. Concentrations $<10^3$ CFU/mL were found exclusively in patients on antibiotic therapy, and concentrations $>10^4$ CFU/mL were only found in patients not treated with antibiotics (2).

PATHOGENESIS AND RISK FACTORS

To humidify and clear inspired air, the nose and paranasal sinuses secrete approximately 1 L of mucus daily *(24,40)*. Via ciliated columnar epithelial lining, the mucus flows in a specific pattern through the natural ostium of each individual sinus posteriorly toward the nasopharynx. Patency of the sinus ostia is essential for this flow to occur. Obstruction of this flow, leading to mucus stasis, may result in infection. In healthy people, obstruction may occur because of an anatomic deformity or mucosal inflammation. HAS is a result of local factors such as disturbances of anatomy and colonization of the upper respiratory tract with potentially pathogenic microorganisms and systemic factors such as the severity of underlying illness in critically ill patients.

Local Factors

In ICU patients, several local factors predispose to HAS. Intubation in itself impairs reflex mechanisms, such as coughing, sneezing, and nose blowing that help to cleanse the nasal passage. Avoiding intubation, for example, by using noninvasive positive-pressure ventilation, will probably reduce the incidence of HAS *(41)*. Nasotracheal intubation is considered as the most important risk factor for HAS, and the risk of HAS increases with the duration of intubation (2,*42*). Nasotracheal intubation may be preferred over orotracheal intubation, because it provides greater stability of the tube, less difficulty with removal of oral secretions, decreased vocal cord injury because of less tube motion, and less patient discomfort *(24,43–46)*. However, nasotracheal intubation will ultimately cause irritation of the nasal mucosa, resulting in edema and possibly sinus obstruction. A large tube may directly obstruct drainage from sinus cavities. Moreover, as compared with orotracheal intubation, nasotracheal intubation took more time and was more often accompanied by nasal bleeding in cardiac surgery patients randomized to either of the intubation routes. After the procedure, bacteremia with microorganisms usually colonizing nose, mouth, and throat was demonstrated in 9% of the patients with nasotracheal and 2% of the patients with orotracheal intubation *(47)*.

When compared with nonintubated healthy subjects, radiologic evidence of HAS, such as thickening of maxillary mucosa, fluid levels in, and opacification of sinuses on CT images are clearly related to any kind of intubation, whether it be naso- or orotracheal intubation (14). Sixteen patients with nasotracheal intubation were prospectively studied with CT scanning of the paranasal sinuses on the second or third day and again on the eighth day after intubation. At day 2, three patients had signs of maxillary sinusitis and three of sphenoid sinusitis, and at day 8 all patients had radiographic sinusitis of at least one sinus cavity *(48)*. In another study, paranasal sinusitis, diagnosed by CT scan and aspiration, developed in 13 of 31 (42%) patients with nasotracheal intubation and in 3 of 65 (5%) patients with orotracheal intubation. However, these patients were not randomized to the routes of intubation *(43)*. Associations between nasotracheal intubation and HAS have been further established in a series of studies comparing the effects of both routes of intubation (Table 23-2). Strict comparison of the different studies is hampered because of differences in study populations and diagnostic criteria and modalities used. Rouby et al. (2) randomized 40 patients with no evidence of maxillary sinusitis on baseline CT scan to nasotracheal or orotracheal intubation. In addition, gastric tubes were placed accordingly. After 7 days, radiologic maxillary sinusitis was demonstrated in all but one patient

TABLE 23-2

Randomized Studies Comparing Nasotracheal and Orotracheal Intubation In Relation to Healthcare-Associated Sinusitis

Study (Ref.)	*No. of Patients Included*		*Cumulative Incidence of Radiographic HAS*		*Outcome Measures of Radiographic HAS (95% Confidence Interval)*		*Cumulative Incidence of Infectious HAS*		*Outcome Measures of Infectious HAS (95% Confidence Interval)*	
	OT	*NT*	*OT (%)*	*NT (%)*	*ARR*	*RRR*	*OT (%)*	*NT (%)*	*ARR*	*RRR*
Rouby et al. (2)	18	22	4 (22)	21 (95)	0.73	0.76	—	—	—	—
Holzapfel et al. (15)	151	149	33 (22)	45 (30)	0.08	0.27	25 (17)	29 (19)	0.02	0.11
Bach et al. (17)	32	36	15 (47)	25 (69)	0.25	0.32	2 (6)	15 (42)	0.36	0.86
Michelson et al. *(50)*	24	20	15 (63)	19 (95)	0.32	0.34	2 (8)	7 (35)	0.27	0.77
Salord et al. *(45)*	53	58	1 (2)	25 (43)	0.41	0.95	—	—	—	—
Total	278	285	68 (24)	137 (47)	0.23 (0.15–0.31)	0.49 (0.33–0.65)	29 (10)	51 (18)	0.08 (0.01–0.15)	0.44 (0.07–0.8)

HAS, healthcare-associated sinusitis; OT, orotracheal intubation; NT, nasotracheal intubation; ARR, absolute risk reduction (incidence NT – incidence OT); RRR, relative risk reduction (1 – [incidence OT/incidence NT]).

with nasotracheal intubation and in only four patients with orotracheal intubation. However, the results of cultures of maxillary sinus aspirates for these patients were not reported. All patients with radiologic maxillary sinusitis also had radiologic evidence of ethmoid and/or sphenoid sinusitis.

Holzapfel et al. (15) randomized 300 ICU patients to nasotracheal (n = 149) and orotracheal (n = 151) intubation. CT scans were performed every 7 days or earlier when HAS was clinically suspected. Radiographic sinusitis was observed in 45 (30%) and 33 (22%) of patients with nasotracheal and orotracheal intubation, respectively (p = .08). The radiographic suspicion of HAS was microbiologically confirmed in 29 (19%) and 25 (17%) of the patients with nasotracheal and orotracheal intubation, respectively (15).

Bach et al. (17) randomized 68 postoperative patients, without infection at baseline, to nasotracheal or orotracheal intubation. Sinus radiographs were performed at regular intervals and transnasal needle punctures were performed when HAS was suspected. Radiologic findings suggestive for HAS were found in 47% of patients with orotracheal and in 69% of patients with nasotracheal intubation. Infectious sinusitis was confirmed by microbiologic cultures in 6% and 42% of the patients, respectively (p < .01).

Michelson et al. *(50)* randomized 20 mechanically ventilated patients to nasotracheal intubation and 24 to orotracheal intubation. With the patient in the semirecumbent position, maxillary sinuses were sonographically examined daily for signs compatible with sinusitis. Diagnostic aspirates were performed in patients with abnormal findings on sonography. Nineteen (95%) patients with nasotracheal and 15 (63%) patients with orotracheal intubation had sonographic evidence of sinusitis after approximately 2 days in both groups. Diagnostic aspiration was performed in 22 patients (13 nasally and 9 orally intubated) and pathogenic microorganisms were cultured in 7 of 13 and 2 of 9 cultures, respectively.

Salord et al. *(45)* randomized 111 adult patients to orotracheal (n = 53) or nasotracheal (n = 58) intubation. All patients were ventilated for at least 2 days, and HAS was diagnosed by complete opacification or an air-fluid level in the maxillary sinus on bedside radiography (reversed Waters' view). HAS occurred in 2% of the patients in the orotracheal group and in 43% of the patients with nasotracheal intubation.

When the results of these studies are summarized, orotracheal intubation is, when compared with nasotracheal intubation, associated with a reduced incidence of radiologic HAS, but the beneficial effects on the development of infectious HAS are much smaller. Orotracheal intubation results in an absolute risk reduction for the occurrence of radiographic HAS of 0.23 (95% confidence interval 0.15–0.31) and a relative risk reduction of 0.49 (95% confidence interval 0.33–0.65). For the occurrence of infectious HAS, orotracheal intubation has an absolute risk reduction of 0.08 (95% confidence interval 0.01–0.15) and a relative risk reduction of 0.44 (95% confidence interval 0.07–0.81) (Table 23-2).

Nasogastric tubes are probably less harmful than nasotracheal tubes, because they are smaller and, therefore, cause less irritation (*49*). Secretions were more often found in sinuses adjacent to a nasal cavity with a nasotracheal tube than in sinuses adjacent to a nasogastric tube (8). In addition, facial and head trauma can lead to accumulation of blood and debris in the sinuses and can disrupt mucosal structures. This provides a favorable medium for proliferation of microorganisms. Furthermore, patient immobility in the supine position may further predispose to sinusitis. The role of gravity and positional changes facilitate mucus drainage in physiologic circumstances. Finally, the supine position may decrease venous blood flow from the head and neck to the heart, leading to nasal congestion and narrowing of the maxillary sinus ostia *(51)*. This effect can be exacerbated by mechanical ventilatory support with positive inspiratory and end-expiratory pressure by virtue of increasing central venous pressure. However, patient positioning and modes of mechanical ventilation on development of HAS have never been studied. Recently, it was demonstrated that HAS was associated with inhibition of epithelial expression of nitric oxide synthases (NOS2), which generates NO that has a major role

in the nonspecific host defense (52). The decrease in NO activity may impair nonspecific host defenses. Appropriate treatment of sinusitis (with drainage, lavage, and removal of the nasogastric tube) was associated with increased maxillary and nasal NO concentrations (53).

Systemic Factors

Because of the severity of their underlying illnesses, mechanically ventilated patients are prone to develop any healthcare-associated infection, and there is no reason to assume that this does not hold true for HAS. Corticosteroids may further suppress immune function in these patients. As mentioned earlier, colonization of the upper respiratory tract (e.g., nares, oropharynx, and trachea) is universal in mechanically ventilated patients, and nasal colonization with enteric gram-negative bacteria was an independent risk factor for HAS in a recent study (11). In addition, the use of sedatives and a Glasgow Coma Score ≤7 at admission were independent risk factors in that study.

ASSOCIATION WITH HEALTHCARE-ASSOCIATED PNEUMONIA

Because of the resemblance of the etiologic spectrum of pathogens causing HAS and healthcare-associated pneumonia, a causal relationship between both infections has been suggested (15,17,54). Incidences of pneumonia were found to be higher among patients with HAS as compared with unaffected patients—14/26 (54%) versus 4/85 (5%) *(45)*—and HAS increased the risk for pneumonia by a factor of 3.8 in multivariable analysis in another study (15). In this study, pneumonia was diagnosed in 16 of 54 patients with HAS, and the same microorganism was isolated from the lungs and sinus in 9 of 16 episodes (15). In a third study, incidences of pneumonia demonstrated within 7 days after evidence of maxillary sinusitis on CT scan were 67% and 43% for patients with and without pathogens isolated from sinus aspirates. However, identical pathogens were isolated from the distal airways in only 38% of the patients with previous infectious maxillary sinusitis (2). Among 271 ICU patients with bacteriologically documented HAS (cultures obtained by maxillary sinus puncture), the percentage of concurrent episodes of pneumonia (cultures obtained via bronchoscopic techniques) caused by similar pathogens ranged widely. More than 25% of episodes of sinusitis caused by *S. aureus*, *P. aeruginosa*, *Acinetobacter baumannii*, *E. coli*, and *Hemophilus* species were followed by episodes of pneumonia caused by the same pathogens. In contrast, HAS caused by coagulase-negative staphylococci, streptococci, enterococci, *Klebsiella* species, *Proteus* species, *Enterobacter* species, and yeasts were succeeded by pneumonia caused by these pathogens in <10% of the cases *(55)*. A similar pattern of concurrent recovery of pathogens from sinus cavities and lungs was reported by Rouby et al. (2). It has been hypothesized that differences between microorganisms in their capacity to adhere to mucus surrounding endotracheal tubes might influence increased colonization of the tracheobronchial tree from the sinus reservoir *(56)*. Whether HAS really leads to pneumonia or whether sinusitis just reflects extensive airway colonization and infection has not been elucidated. A recent study of patients with nasotracheal intubation suggested that early treatment of episodes of HAS was associated with a reduction in incidence of healthcare-associated pneumonia and improved patient survival (19).

COMPLICATIONS

Failure to diagnose HAS as the cause of sepsis may lead to bacteremia and even hemodynamic instability. Because of the anatomic location of the sinuses, infectious complications are prone to extend to orbital or intracranial spaces (Table 23-3). The frontal and ethmoid sinuses are separated from the orbit by a thin bony plate. Infection, therefore, may extend directly via vascular channels or neurologic foramina, resulting in periorbital cellulitis, muscle edema, and even ophthalmoplegia. When pus collects between the periorbital structures and the bony wall of the orbit, a subperiosteal abscess develops. Orbital extension of infection causes fat necrosis and may lead to orbital abscess formation.

The venous system draining the nose, paranasal sinuses, and the orbital system has no valves, facilitating spread of orbital infection to the cavernous sinus. This should be suspected in case of spread of orbital cellulitis to the opposite eye, severe retinal venous engorgement, and rapid clinical deterioration. In addition to direct spread of pus, thrombosis may develop.

Secondary intracranial complications may also occur along preformed pathways resulting from retrograde thrombophlebitis or by direct hematogenous spread. Meningitis is the most common intracranial complication, most often caused by sphenoid infection. Meningitis occurs less often after ethmoidal, frontal, or maxillary sinusitis *(24)*. Kaufman et al. *(57)* described 17 cases of subdural empyema

TABLE 23-3

Potential Complications of Paranasal Sinusitis

Orbital complications
Periorbital (preseptal) edema
Orbital cellulitis
Subperiosteal abscess
Orbital abscess
Cavernous sinus thrombosis
Intracranial complications
Meningitis
Epidural abscess
Subdural empyema
Venous sinus thrombosis
Brain abscess
Other complications
Bacteremia
Sepsis, severe sepsis, septic shock
Osteomyelitis of the skull
Pneumonia
Thoracic empyema

(Modified from Seiden AM. Sinusitis in the critical care patient. *New Horizons* 1993;5:261–270.)

induced by community-acquired sinusitis. This complication occurred most often in young men, possibly because during maturation the posterior wall of the sinus may be an incomplete barrier to intracranial spread of microorganisms. The empyemas, therefore, were usually located directly behind the sinuses.

Veins from the frontal sinus communicate directly with the dura. Spread of infection may result in epidural abscess when pus collects superficial to the dura, and a subdural empyema may result from collection of pus between the dura and pia arachnoid. Because there is little resistance to the spread of infection, cerebral abscesses may develop at multiple locations. CT scanning will establish most of the diagnoses, and surgical exploration should be considered if abscess is demonstrated.

PREVENTION

Measures to prevent the development of HAS can be subdivided into general measures, device-related measures, and patient-specific measures.

General measures include the principles of conventional infection control policies *(58)*. Colonized and infected patients and environmental contamination or common sources of microorganisms should be identified as reservoirs of pathogens. When identified, environmental contamination should be cleared by cleaning and disinfection, and common sources should be eliminated. In addition, transmission from patient to patient should be prevented by improving compliance with standard infection control practices in the ICU, such as hand washing. Barrier precautions (gloves, gowns) should be used to prevent cross-transmission of multiply resistant bacteria or when taking care of a patient with open wounds.

The most important device-specific measure to prevent HAS is to avoid intubation *(41)* and especially nasotracheal intubation. In addition, the duration of orotracheal and nasogastric intubation should be minimized. Whether the mode of mechanical ventilation influences the development of HAS is unknown; therefore, no advice on how best to ventilate patients can be provided.

With regard to patient-specific preventive measures, the relevance of adequate treatment of the underlying illness is obvious. Corticosteroids should be administered only when indicated, and antibiotic prescription policy should be restrictive and rational. The relationship between antibiotic use and subsequent colonization and superinfection with antibiotic-resistant microorganisms and/or pathogens that are difficult to treat (such as yeasts) should be known to all intensivists.

Based on the pathogenesis of HAS, several preventive strategies may be hypothesized, although clinical experience is scarce or completely absent. These measures are discussed but are not (yet) recommended. Prevention of colonization of the upper respiratory tract is likely to reduce the incidence of HAS. Application of topical antibiotics in the oropharynx, usually in combination with nonabsorbable antibiotics administered via the nasogastric tube and systemic antibiotics during the first days of ventilation (selective decontamination of the digestive tract [SDD]), decreases the incidence of healthcare-associated respiratory tract infection *(59)*, and has been associated with improved patient outcome in some settings *(60,61)*. Few studies testing the SDD concept determined its effects on HAS. In one double-blind, placebo-controlled study, neurosurgical patients were randomized to receive topical antibiotics (tobramycin, polymyxin E, amphotericin B) in the oropharynx and in the stomach. Vancomycin was added to the oropharyngeal paste. HAS diagnosed by CT scan and microbiologic cultures occurred in 2 of 63 (3%) study patients and 9 of 60 (15%) control patients ($p < .02$) (13). However, objections against widespread use of SDD include the threat of selection of antibiotic resistance *(62)*. The same objections apply to the prophylactic use of systemic antibiotics in high-risk patients for HAS, such as trauma patients with facial fractures.

Recently, the preventive effects of locally applied nasal decongestant agents and corticosteroids were determined in 79 mechanically ventilated trauma patients (63). Patients were randomized to receive either two drops twice/day of xylometazoline nasal solution 0.1% and 100 μg budesonide or placebo, and radiological (CT scanning) maxillary sinusitis was detected in 54% of treated and 82% of the control patients ($p < .01$). Infectious sinusitis was detected in 8% of the treated and 20% of control patients ($p = .11$).

Based on the physiology of mucociliary clearance from the sinus cavities, a supine position of the patient may be associated with an increased risk for development of HAS. In this position, the physiologic process of mucociliary clearance may be diminished and ostia may be narrowed because of nasal congestion resulting from decreased venous blood flow to the heart. However, it is unknown to what extent a change in nursing care (e.g., placing patients in semirecumbent position as soon as possible) affects incidence of HAS.

CONCLUSION

An increasing number of studies suggest that the incidence of HAS among mechanically ventilated ICU patients is underreported. However, the true incidence and clinical relevance of this infection still are unknown. HAS is usually caused by those microorganisms known to colonize the upper and lower respiratory tract in ICU patients such as Enterobacteriaceae, *P. aeruginosa,* and *S. aureus*. Development of HAS is a result of disturbances of local anatomy, colonization of the upper respiratory tract with potentially pathogenic microorganisms, and severe underlying illness. Nasotracheal intubation has been convincingly demonstrated to be the most important risk factor and should, therefore, be avoided. Other preventive measures include prevention of cross-colonization by standard infection control measures and avoidance of unnecessary use of antibiotics and corticosteroids. Future studies should determine the incidence of HAS in large patient populations and elucidate its role as a risk for the subsequent development of pneumonia. Based on these findings, the need for specific regimens for prevention of HAS can be judged. In addition, cost-benefit analyses of the different diagnostic tracks are warranted. An excellent review of the clinical entity of HAS has been published by Westergren et al. *(64)*.

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CHAPTER 24

Healthcare-Associated Gastrointestinal Tract Infections

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Although infectious diarrhea is well recognized in the outpatient setting, enteric infections acquired in the hospital are less well studied. A number of factors associated with being admitted to a healthcare facility contribute to the occurrence of diarrhea including antibiotic use, change of diet and administration of feedings, procedures involving the gastrointestinal tract (e.g., endoscopic and surgical procedures) and underlying diseases; one or a combination of these factors leads to the development of diarrhea, either infectious or noninfectious. Furthermore, microorganisms that cause foodborne illnesses in the community have the potential for causing disease in hospitalized patients.

Certain forms of noncommunicable foodborne gastroenteritis or diarrheal disease, such as those originating from the ingestion of bacterial toxins derived from *Clostridium perfringens, Clostridium botulinum, Staphylococcus aureus*, and *Bacillus cereus*, as well as those produced by the ingestion of food contaminated with group A streptococci and *Vibrio parahemolyticus* may occur in the hospital with their control depending on adequate food handling practices. Other etiological agents, such as *Clostridium difficile*, nontyphoid *Salmonella*, diarrhea-producing *Escherichia coli*, *Shigella*, *Yersinia enterocolitica*, *Staphylococcus aureus*, rotaviruses, and noroviruses (NoVs), can be transmitted between hospitalized individuals and will be the subject of more detailed review in this chapter.

Enteric infections acquired in the hospital may occur in the form of epidemic clusters from exogenous sources. Hospitalized individuals who are admitted with infectious gastroenteritis can potentially transmit a virulent microorganism to other patients and hospital workers. Hospital personnel can also facilitate the spread, either as short-term intestinal carriers of microorganisms or via their hands when attending to different patients.

It is of importance to know the epidemiology of healthcare-associated diarrhea, as well as the mechanisms involved in the acquisition and transmission of disease. Several diagnostic techniques are available, and the effective treatment and containment of outbreaks depend on an accurate clinical assessment and appropriate management.

DEFINITIONS

Healthcare-associated diarrhea is defined as the passage of three or more soft or liquid bowel movements per day beginning at least 72 hours after admission to the hospital *(1)*. For infectious healthcare-associated diarrhea, an enteric infection has been acquired after hospitalization. Iatrogenic healthcare-associated diarrhea is defined as noninfectious diarrhea associated with an in-hospital exposure (e.g., medications, antibiotics, feedings, or procedures).

EPIDEMIOLOGY

The incidence of healthcare-associated diarrhea is estimated to be between 6% and 30% of hospitalized patients, with the majority occurring on the geriatric wards and critical care units. Healthcare-associated diarrhea can also be seen in children, showing an incidence of 1.2% to 2.1% for patients admitted to pediatric teaching hospitals *(2)* and 1.5% for children admitted to general pediatric wards *(3)*. Although it is commonly underreported, the incidence of infectious gastroenteritis in adult patients approximates 29.4% of hospitalized patients, with *Clostridium difficile* being the most important definable cause of the disease and other bacterial pathogens being found in a small percentage of cases (4). Norovirus infections have also been reported in hospital populations, with an incidence up to 1.19 per 1,000 admissions. In children, viral pathogens play a larger role. The incidence of viral pathogens in pediatric populations has been reported to be 4.6 cases per 1,000 admissions (with a range of 0.40–11.9) for norovirus and 4.04 cases per 1,000 admissions for rotavirus infections (5).

Healthcare-associated diarrhea represents not only a cause of morbidity but also of mortality, particularly in high-risk patients. The most important definable enteric cause of death is *C. difficile*, with 30-day mortality rates as high as 38% *(6)*. Death rates are far less from other pathogens and noninfectious causes. In pediatric patients, mortality due to healthcare-associated rotavirus infection is very low (7). There is evidence that patients who develop healthcare-associated diarrhea have an increased length of stay when compared with control cases. Patients with infectious gastroenteritis have longer lengths of stay when compared with those in which healthcare-associated diarrhea is from noninfectious causes (iatrogenic diarrhea) (4). Patients with infectious gastroenteritis tend to have more severe underlying conditions and be older than those with diarrhea from noninfectious causes.

Healthcare-associated infectious gastroenteritis also is associated with a measurable economic impact. A study done in Germany (8) showed that each *C. difficile* diarrhea (CDD) case costs an excess of approximately US$ 10,353 per patient. Rotavirus healthcare-associated outbreaks may also increase the cost of care by up to $3,546 per episode. Hospital outbreaks of diarrhea are particularly costly. According to one study in the United Kingdom (9), gastroenteritis outbreaks represented a national cost of $2,301,864 (United States) during a 1-year period. These costs included the days of empty beds when units were closed to new inpatient admissions and days of productivity lost by staff who acquired disease.

PATHOGENESIS

Predisposing Host Factors

Individuals in the hospital setting are admitted because of disease, and therefore have unique predisposing factors for enteric infection. Their immune systems may be impaired because of age, seen in infants and the elderly, underlying disease, such as HIV/AIDS, hematological malignancies or organ transplantation, or because of iatrogenic interventions, including the administration of enteral feedings, antibiotics, steroids, or chemotherapy. In a study of patients with renal transplantation, drugs and infectious agents contributed to the development of diarrhea, of which 14.6% were healthcare associated *(10)*. Other underlying medical conditions that can increase susceptibility to acquire infectious diarrhea include renal disease, liver disorders, and diabetes.

Defective intestinal defenses also represent a form of local immune impairment. Gastric acid plays a role in the defense against ingested microorganisms. A lower microorganism inoculum can produce enteric infection with reduced gastric acidity. Achlorydia or hypochloridia may be iatrogenically produced by the use of antacids such as H2 blockers or proton pump inhibitors. Antacids have been shown to greatly facilitate the colonization of the intestine with enteric vaccine strains as well as to increase the frequency of gastrointestinal acquisition of healthcare-associated strains of aerobic gram-negative rods. Anticholinergic medications may have similar effects.

Endoscopic evaluation of patients has become routine with more than eight million or more such interventions being performed annually in the United States. Although infectious gastroenteritis after endoscopic procedures is uncommon, they have been reported. The infectious agents having been acquired by this route include *Salmonella* sp., *C. difficile*, and *Campylobacter* spp. It is difficult to sterilize the instruments employed, since they have complex structures and fragile parts that do not tolerate aggressive sterilization procedures. Preventing transmission of pathogenic microorganisms is of utmost importance, and can be achieved through adequate training of the personnel in charge of this task, stressing meticulous cleaning, the use and adequate contact time with the appropriate disinfectant, and drying thoroughly all parts before storage. Specific guidelines for handling endoscopes have been published *(11,12)*. (see also Chapter 62)

Antibiotic use is perhaps one of the greatest factors in the development of healthcare-associated diarrhea. With the availability of broad spectrum antibiotics with suppressive effects on gut flora, antibiotic-associated diarrhea (AAD) has become an important medical problem in the hospital. Antibiotics such as macrolides and clavulanic acid can alter the motility of the gastrointestinal tract influencing the development of bacterial overgrowth. Microflora of the gut is also altered by antimicrobials, with reductions of anaerobe populations, which can cause an osmotic diarrhea by decreased breakdown of carbohydrates. Alterations of gut flora also predispose to infection by strains of *C. difficile*, which can be found in the hospital environment. While the first CDD cases followed use of clindamycin, essentially all antibiotics have been associated with development of CDD. It occurs in approximately 2% to 5% of hospital inpatients treated with a variety of antibiotics. The cephalosporins and fluoroquinolones may have the highest rate of CDD development. The rates of diarrhea associated with parenterally administered antibiotics, especially those with enterohepatic circulation, are similar to rates associated with other orally administered agents. Furthermore, AAD may occasionally be caused by other enteric pathogens, including *Salmonella*, *C. perfringens* type A, *S. aureus*, *Klebsiella oxytoca*, and possibly *Candida albicans*.

Admission to the hospital also causes individuals to become colonized with hospital microorganisms. Evidence suggests that hospitalized adults have rates of colonization with *C. difficile* up to 20% to 30% when compared with the outpatient population. Although *S. aureus* can also be a part of the gut microflora, it has been reported that 7% of patients with AAD have enteric infection with enterotoxin-producing strains. Interestingly, affected patients often can be shown to be carriers of *C. difficile* (13).

Environmental Factors

As mentioned before, the hospital setting represents a unique environment. Several studies have demonstrated that increasing lengths of stay in the hospital are a risk factor for acquiring infections unique to this environment. There have also been studies that demonstrate high rates of environmental contamination by *C. difficile* in hospitals, as well as high rates of colonic colonization associated with hospitalization. *C. difficile* colonization rates of adult outpatients is seen in 2% to –3%, which increases to 20% to 30% with hospitalization and even higher with longer stays. Hospital food may rarely be a source of healthcare-associated diarrhea, especially outbreaks due to inadequate handling of food. However, the sanitary standards in most hospitals in industrialized countries are high and such outbreaks are unusual. Hospital outbreaks caused by *Bacillus cereus (14)*, *Salmonella* spp. *(15)*, and *C. perfringens (16)* have been reported. Crowding and staffing factors play a key role in the transmission of infectious gastroenteritis between patients. A ratio of staff to patients that is insufficient encourages deficiencies in effective hand washing and isolation techniques, especially in critical care areas. Even with careful hand washing, there is still some risk of transmission by direct and successive patient contact. Although most of the time crowding is associated with

low staff to patient ratios, it may also be an independent factor. There is an increase in the incidence of CDD in patients who have physical proximity to other *C. difficile*–infected patients (17).

DIAGNOSIS

Healthcare-associated diarrhea ranges in severity from mild illness to a fulminant picture of pseudomembranous entoerocolitis with sepsis and death. Patients can present with abdominal cramps or pain, loss of appetite, hematochezia, and fever. Children with acute diarrhea can also present with significant volume loss. The yield of stool cultures for healthcare-associated diarrhea is low. Enteropathogenic bacteria other than *C. difficile* are grown from 2.6% to 6.4% of stool cultures when patients are admitted with diarrhea and in only 0.6% of stool cultures obtained 3 days or more after admission. Therefore, performing stool cultures in patients after 72 hours of admission is unlikely to yield an enteric pathogen and should not be routinely performed. In special situations, the microbiologic yield for stool cultures may be higher, particularly in HIV-positive individuals, neutropenic patients receiving chemotherapy, and in individuals 65 years or older with an existing comorbid condition (18) and during a defined outbreak in the hospital. While a majority of patients with healthcare-associated diarrhea will not have an etiologic agent detected in stool samples, CDD is responsible for the majority of adult diarrhea cases with definable etiology. The specific diagnostic studies required in making an etiologic diagnosis are presented later when specific etiologic agents are considered.

CDD AND COLITIS

Clinical and Microbiological Features

CDD follows enteric infection by *C. difficile*, a spore forming, gram-positive, strictly anaerobic bacteria that produces one or two toxins, toxin A, an enterotoxin and toxin B, a cytotoxin. Both toxins are toxic to human enterocytes. The clinical presentation is broad, and the severity ranges from mild diarrhea to pseudomembranous colitis, sepsis, and death. Between 10% and 20% of all cases of AAD are secondary to *C. difficile* infection. The likelihood of *C. difficile* causing disease is higher in persons with more severe disease, particularly when illness is associated with pseudomembranous colitis. Risk factors for CDD include antibiotic exposure resulting in depletion of colonic bacterial flora, hospitalization with its exposure to spores of the microorganism, and host debility (advanced age or other infirmity). The antibiotics showing the highest risk for CDD include the cephalosporins, penicillins, and fluoroquinolones. Traditionally, clindamycin has been an important offender. CDD can also occur in patients who have been exposed to short prophylactic courses of antibiotics *(19)*. Elderly patients >65 years of age have as much as a 20-fold higher risk than younger patients. Other risk factors include underlying disease severity, nonsurgical gastrointestinal procedures, and possibly the use of proton pump inhibitor drugs that cause hypochlorhydria. Patients with a suppressed immune system or poor response to *C. difficile* toxin are also at increased risk of CDD and disease recurrence.

When a hospitalized patient develops important diarrhea, especially when the illness occurs in an elderly and infirm patient or when fever, dysentery, or leukocytosis are found, a stool should be collected and tested for *C. difficile* toxins. The most sensitive tests include the cell cytotoxicity test for toxin B, culture of the microorganism followed by testing of isolates for toxigenicity or commercial PCR test. These tests cannot be performed quickly, and they are technically demanding *(20)*. Enzyme immunoassays (EIAs) for detection of toxins A and B are less sensitive (around 70% positivity in known infection), since up to 100 to 1,000 pg of toxin is needed for detection, and can have a false-negative rate up to 40% of cases when compared to cell cytotoxicity assay or culture *(21)*. While culture has very high sensitivity *(22)*, its specificity is low, since the rate of carriage of toxigenic and nontoxigenic strains of *C. difficile* is high in hospitalized patients. Sensitivity of the EIAs can be increased by repeating the test with other collected stool samples. Glutamate dehydrogenase (GDH) testing does not assay for the toxins but is very sensitive for CDD and can be used to identify true *C. difficile*-negative cases of diarrhea, while the positive tests need to be confirmed with a toxin-based assay such as an EIA or cytotoxicity assay *(23)*. Other diagnostic modalities include radiographic imaging (CT) and endoscopy, but they are expensive and nonspecific. Finding pseudomembranous colitis at endoscopy is diagnostic, although there are other less common causes of this condition (24).

Epidemiological Considerations and Control

Spores of *C. difficile* can be found in the environment of hospitals and long-term care facilities. Thus, it is not surprising that patients in these facilities have higher rates of *C. difficile* colonization; rates are 10% to 25% among hospitalized patients and 4% to 20% among residents of long-term care facilities, compared with a rate of 2% to 3% for noninstitutionalized adults. In the pediatric population, over half of all healthy neonates are asymptomatic carriers of *C. difficile*, but disease in this population is rare. Although direct patient-to-patient spread of *C. difficile* is uncommon, the microorganism is easily spread from infected and colonized patients to the environment. Most transmission to previously uninfected patients is thought to occur through hand carriage by healthcare workers. Hand washing with antiseptic soaps may not kill *C. difficile* spores. Outbreaks of CDD have also been reported among geriatric populations in general hospitals or long-term care facilities *(25)*.

Several measures for infection control have been outlined (26). They include (a) performing *C. difficile* toxin assays on all patients with healthcare-associated diarrhea and those admitted from an outside hospital with diarrhea in attempting to diagnose most infected patients in the hospital; (b) practicing strict contact precautions for everyone entering a patient's room, including healthcare workers and visitors; (c) placing patients with CDD in single rooms with a designated toilet or commode, with designated staff to minimize the risk of cross-infection

to other patients; (d) wearing of disposable gloves and gowns by persons with contact with infected patients and employing meticulous hand washing methods by persons in contact with patients with CDD, ideally using soap and water. While alcohol-based soaps, gels, and wipes do not kill *C. difficile* spores, their general use has not increased the occurrence of healthcare-associated CDD; (e) cleaning of hospital rooms at least once a day and more often if environmental fecal soiling has occurred. The rooms of patients with CDD should be carefully disinfected after patient discharge, using a sporocidal agent, ideally a 1:10 dilution of sodium hypochlorite; (f) use of dedicated medical equipment and devices for patients with CDD, with all equipment being carefully cleaned and disinfected with disposal of single patient use items once the patient is discharged; and (g) use of antibiotic stewardship programs that decrease general use of particularly high-risk drugs for development of CDD and decrease the use of predisposing drugs in *C. difficile*–infected patients whenever feasible (see also Chapter 37).

STAPHYLOCOCCAL ENTEROCOLITIS

Clinical and Microbiological Features

Prior to the discovery of *C. difficile* as the cause of pseudomembranous enterocolitis (PMC), *S. aureus* was considered as the important cause of antibiotic-associated PMC. The infecting microorganisms did not appear to be transmissible from person to person, but healthcare-associated spread occasionally was identified. Methicillin-resistant *S. aureus* (MRSA) strains may cause outbreaks of enteric disease *(27)*, occasionally complicated by septicemia *(28)*. In certain hosts in whom there is impaired resistance due to surgery, antimicrobial therapy, alcoholism, or diabetes mellitus, staphylococci may grow to large numbers in the intestinal tract and be responsible for morphologic damage to the intestinal mucosa resulting in diarrhea and fever of varying severity. Like CDD, intestinal involvement in staphylococcal enteritis varies widely from minimal and self-limiting enteritis to fulminating PMC *(29)*. Patients with enteritis have diarrhea of a variable nature, often mild and watery, and may have low-grade fever, but they are not extremely toxic. PMC usually presents with fulminating and dehydrating dysentery with toxemia, fever, and leukocytosis. The entire colon may be involved with *S. aureus* disease of the gut, and there may be involvement of the small intestine. Mortality in such patients is high, ranging from 10% to 50%. The diagnosis is established by documenting abundant polymorphonuclear leukocytes together with sheets of gram-positive cocci in stool specimens by Gram stain, which on subsequent culture grows large numbers of *S. aureus*. Proctologic examination shows a white membrane that reflects areas of mucosal necrosis in those with pseudomembranous colitis.

Control

Prompt cessation of previously administered antibiotics and administration of oral vancomycin to patients with more serious staphylococcal enterocolitis may prevent the disease from progressing to pseudomembranous changes. Large numbers of *S. aureus* are often disseminated from patients with these diseases, and Contact Precautions should be strictly enforced.

DIARRHEAGENIC STRAINS OF *ESCHERICHIA COLI*

Clinical and Microbiologic Features

Enteropathogenic *E. coli* (EPEC) are rare causes of infectious healthcare-associated diarrhea. EPEC has previously been considered a common cause of nursery outbreaks, which sometimes were explosive, with a high attack rate and fulminant course *(30)*. Reports of such outbreaks have not been common in the United States in recent years. This may relate in part to failure to recognize the etiologic agent due to the decreasing availability of serotyping procedures in hospital diagnostic laboratories. During any hospital outbreak of diarrhea, particularly when it has occurred in the newborn nursery, EPEC should be considered in the differential diagnosis. The clinical expression of disease varies considerably, from minimal watery diarrhea to fulminating disease with septicemia. Incubation periods of EPEC disease are commonly 24 to 48 hours.

Enterotoxigenic *E. coli* (ETEC) is even a less common cause of hospital nursery outbreaks than EPEC strains *(31)*. ETEC is very rarely transmitted from person to person due to the high microorganism inoculum required to produce illness in humans.

Control of Outbreak Disease in Newborn Nurseries

Infection control measures in the nursery *(32)* unit include isolating patients with asymptomatic as well as symptomatic *E. coli* enteric infections in separate facilities. Contact Precautions should be routine. In nurseries in which Contact Precautions for individual cases is not possible, cohort systems should be used to minimize the risk of cross-infection. Infants who are ill or colonized with the epidemic microorganism can sometimes be grouped together in a cohort that is physically separated from noninfected infants. Personnel caring for infected infants should not care for noninfected ones. Only milk packaged in sterile containers should be used, common equipment shared among babies should be removed, and infants should be confined to their own bassinets or isolettes. To prevent additional spread of infection, infants born outside the hospital should not enter the nursery during an epidemic of diarrhea. Unnecessary contact with babies by hospital personnel or other infants should be avoided. Also, infected patients should be discharged home as soon as their condition permits in-home management. Uninfected infants should be discharged from the hospital as soon as possible.

SALMONELLA INFECTIONS

Microbiologic, Clinical, and Epidemiological Features

There are more than 2,000 serotypes of *Salmonella enterica*. The four most common serotypes isolated in 2006, seen in 45% of cases of salmonellosis include *S. typhimurium*,

S. enteritidis, *S. newport*, and *S. heidelberg (33)*. In general, the isolation of *Salmonella* from a stool culture is sufficient to make a diagnosis of salmonellosis, since these bacteria are highly pathogenic and their long-term carriage is unusual. The isolation of *Salmonella* in a symptom-free patient should be reported as a healthcare-associated infection only if previous cultures during hospitalization were negative.

Transmission of *Salmonella* can occur through the hands of healthcare workers or from person-to-person spread between aged, debilitated, or newborn patients. The communicability of this microorganism to hospital personnel is low since a relatively large inoculum is required to produce disease in healthy people, and precautions used routinely in hospitals when handling *Salmonella*-infected patients are usually effective. However, outbreaks of intestinal salmonellosis can occur among institutionalized patients. Between 1963 and 1972, 112 (28%) of the total number of reported *Salmonella* outbreaks occurred in institutions (hospitals, nursing homes, and custodial institutions) *(34)*. The economic burden of hospital outbreaks caused by *Salmonella* spp. can be significant. One outbreak can cost up to $52,463, with individual charges to the patient calculated at $1,588.78 ± $1,460.37 when compared to uninfected controls *(35)*.

Patients who are at special risk for *Salmonella* infection include the elderly, HIV-infected individuals, cancer patients, and the chronically debilitated. Patients with malignancy have a high risk of *Salmonella* bloodstream invasion. Newborns and infants <3 months of age have a special predisposition to *Salmonella* infection, particularly to systemic *Salmonella* infection. In a nursery outbreak, up to 50% of exposed infants can become infected with *Salmonella*, with a high rate of symptomatic infection once the infection is introduced into the nursery. Cultures may remain positive for up to a year in infants.

A common source is usually the initial focus of outbreaks of *Salmonella* in the hospital. Potential sources are products from the central kitchen such as previously contaminated raw or undercooked meats, other animal products like dairy or eggs, and/or food that has been contaminated after cooking because of microorganisms on equipment or surfaces in the kitchen. Rarely *Salmonella*-contaminated medications can be the vehicle of transmission in the hospital, especially enzymes and hormones of animal origin. Less frequent sources of healthcare-associated salmonellosis include yeast, dried coconut, carmine dye, and inadequately disinfected equipment. In homes for the elderly common source outbreaks of salmonellosis can occur from ingestion of contaminated foods, with secondary cases of infection occurring by way of the contaminated hands of healthcare workers.

Control

Safe food handling practices are especially important in the prevention of healthcare-associated outbreaks. The prompt identification and removal of common sources is essential, as well as the implementation of outbreak management measures as outlined earlier in this chapter. Prophylactic antibiotics are not recommended.

SHIGELLOSIS

Microbiologic, Clinical, and Epidemiological Features

Isolation of *Shigella* in asymptomatic individuals should be reported as healthcare-associated infection if other cultures obtained during hospitalization are previously negative. The incidence of healthcare-associated *Shigella* infections in industrialized regions is rare. The main risk factor for the occurrence of outbreaks is living under crowded conditions where poor personal hygiene prevails. This is especially important in facilities for chronic care of the mentally retarded. According to data from the National Healthcare-associated Infection Surveillance system, shigellosis was reported in only 1 of 3,363 patients with healthcare-associated enteric infections during the period between 1986 and 1989. *Shigella* has the potential of being transmitted efficiently between individuals, and a low inoculum can cause infection in exposed persons. Because of its striking clinical appearance, identification by the clinician is prompt and adequate measures are usually instituted. The usual sources of *Shigella* are short-term carriers of the microorganism who are either ill or convalescing from the disease. Long-term *Shigella* carriers are rare.

Control

Antibiotics are effective in eradicating susceptible strains of *Shigella* from the gastrointestinal tract. Thus, treatment of culture positive patients should be coupled with Contact Precautions to prevent spread of antibiotic resistant strains.

VIRAL GASTROENTERITIS

Rotaviruses have been shown to be important causes of healthcare-associated gastroenteritis in infants and young children. Viruses account for 91% to 94% of all causes of pediatric healthcare-associated diarrhea with rotaviruses being the single major etiologic agent (31–87% of cases in various outbreaks). Evidence has been provided to show that NoVs account for up to 17% to 46% of healthcare-associated diarrhea among the pediatric population (36).

ROTAVIRUS

Clinical Characteristics

Rotavirus strains are usually introduced to pediatric wards after hospitalization of children with community-acquired infection and/or following an exposure in the emergency department before hospitalization (37). Usually they become apparent between the second and sixth day of hospitalization. Typical symptoms are fever (60–100% of cases), together with vomiting and diarrhea with acute onset. Asymptomatic rotavirus infection is frequent in neonates and young infants (<3 months). Risk factors for acquiring viral gastroenteritis include duration of hospitalization, young age, prematurity, low birth weight, severe immunodeficiencies, and malnutrition. Other risk factors related to the hospital are low

staff to patient ratio, poor hygiene procedures, limited availability of disposable equipment, and the presence on the ward of individuals not involved in patient care, such as parents and relatives (38).

Rotavirus disease is highly infectious, and it can be spread from patients with disease to susceptible individuals by direct contact. The amount of viral particles required to cause disease is small, and rotavirus is excreted in very high concentrations in stools of infected children. Upper gastrointestinal secretions may be infectious. Airborne transmission (through respiratory droplets) has been suggested but remains controversial *(39,40)*.

Infected infants admitted to the hospital seem to be the primary source of healthcare-associated outbreaks. Transmission can be perpetuated through the hands of healthcare workers as well as person-to-person spread from patients with disease to susceptible patients. Adult hospital personnel in general are immune and are neither affected nor known to carry the virus. Since fluid rehydration is a standard practice in all hospitals, morbidity seems to be more related to diminished quality of children's lives, along with increased direct and indirect costs.

Control

Rotaviruses are highly immunogenic, and indeed a high level of immunity is seen in children and adults older than 5 years of age. Therefore, vaccination could theoretically achieve ultimate control of disease. Meanwhile, appropriate hand washing remains the most important and effective control measure *(41)*, especially with the routine use of alcohol-based hand sanitizers *(42)*. Unfortunately, in many settings compliance continues to be low. Other effective measures include physical barrier protection (gowns, masks, gloves) and physical isolation of children with diarrhea.

NOROVIRUSES

Microbiological and Clinical Characteristics

NoVs are single-stranded RNA viruses, enclosed in a nonenveloped protein coat belonging to the *Caliciviridae* family. Great diversity exists among NoV strains, and human strains have been classified according to their sequences in three genogroups (GI, GII, and GIV). NoV gastroenteritis develops after an incubation period of 10 to 51 hours and begins with vomiting, followed by abdominal cramps, fever (37–45% of cases), watery diarrhea, and other constitutional symptoms such as headache, chills, and myalgias. The illness normally lasts only 2 to 3 days, but it can last up to 4 days in healthcare-associated outbreaks and among children younger than 11 years of age. Shedding of the virus in stool usually lasts 8 weeks, although in certain patient populations fecal excretion can last longer than a year.

Healthcare-associated outbreaks of NoV have been reported (5,*43*). Transmission occurs in this setting via the fecal–oral route. Also, a low infectious dose is required for disease acquisition (18–1,000 viral particles) *(44)*. This enables the virus to spread more efficiently through droplets, fomites, person-to-person contact, and environmental contamination. The virus is shed in 30% of people before the onset of symptoms and continues for several weeks after symptoms improve, allowing secondary spread. The virus can also withstand a high variety of temperatures and persist on environmental surfaces, making decontamination difficult. Also, since there are a great variety of strains, mounting immunity against one particular strain does not protect against another strain.

Prevention and Control

Prevention and control of NoV epidemics once introduced is challenging. Contacts that become infected after exposure to contaminated food or water can spread the virus rapidly by person-to-person contact. Preventing the secondary spread of the virus through person-to-person contact and from contaminated environmental surfaces are critical to stopping the continuation of outbreaks such as those occurring in hospital wards and aboard cruise ships. Enforcing personal hygiene, using Contact Precautions, and decontaminating environmental surfaces may help. The effectiveness of alcohol-based hand sanitizers against NoVs is unsettled *(41,42,45,46)*. Washing with soap and water may be the most effective method to remove NoV from hands.

MANAGEMENT OF HEALTHCARE-ASSOCIATED INFECTIOUS GASTROENTERITIS

Infection Control

It is important to understand that the most important mode of cross-infection for enteric bacterial pathogens in the hospital is the fecal–oral route, by which indirect contact spread of microorganisms occurs from patient to patient on the hands of personnel. Hand washing remains the most effective measure to prevent infection, yet compliance continues to be low among healthcare workers and professionals. Although it will not remove the pathogen in its entirety, hand washing will reduce the amount present on the hands. Since some patients are highly susceptible to infection, other measures should be taken in order to avoid their contact with pathogens. Alcohol-based sanitizers may be sufficient to stop an outbreak due to certain pathogens. This approach is unlikely to influence the rate of *C. difficile* transmission in the hospital (Table 24-1).

Active surveillance is another key component in infectious diarrhea control. A program must be in place that is tailored to clinical patterns of infection in the hospital along with bacteriological monitoring. Such a program can detect outbreaks before they have reached important levels and can implement early appropriate control measures.

Prompt investigation of cases is the key to controlling outbreaks in the hospital setting. The occurrence of two or more cases of healthcare-associated diarrhea should prompt a review of the exposures common to these cases. Active epidemiological investigation measures include case–control studies, microbiological sampling of foods, medications, and equipment and culture surveys of asymptomatic patients and healthcare workers. Since hospital outbreaks can be caused by patients or hospital personnel who are short-term carriers of the pathogens, comparison

TABLE 24-1

Principles of Infection Control for Healthcare-Associated Diarrhea

Individual Measures	*Environmental Measures*	*General Epidemiologic Measures*	*Outbreak Management*
Hand washing Alcohol-based hand rub Meticulous hand washing with soap and water (*C. difficile*)	Prompt and thorough cleaning and disinfection of patient areas	Active surveillance	Prompt reporting and investigation of suspicious cases Case–control studies Judicious sample collection Use of molecular techniques
Use of protective clothing (gowns, aprons, etc.)	Thorough cleaning of contaminated toilets and/or bassinets	Periodic screening and early diagnosis	Isolation Individual rooms or patient cohorting Contact Precautions Dedicated nursing staff to infected or healthy patients only Avoidance of unnecessary contact
Individual isolettes and bassinets	Prompt notification to cleaning personnel of fecal soiling	Continuous education and communication (general awareness campaigns)	Reinforcement of hygienic measures
Individual medical equipment	Avoid crowding	Antibiotic stewardship	Implementation of specific policies Admission and discharge Patient placement Unit staffing
Use of disposable items whenever feasible	Safe and hygienic handling of food products		

of the exposure of cases and controls to specific personnel and review of the results of culture surveys may yield valuable information. Occasionally, environmental factors such as air, dust, mattresses, and equipment can serve as vehicles to spread pathogens, and their culture and epidemiological association can identify a common vehicle of dissemination. On certain occasions, epidemiological studies may identify the source in the central kitchen. Infected or ill food handlers should be removed from duty immediately in order to prevent disease transmission among patients.

Outbreak Management

Patients suspected of having an enteric disease with potential for spread should be segregated appropriately, with individual commodes, toilets, equipments, and rooms, with the lowest staff-to-patient ratio possible. If this is not possible, infected patients should be cohorted and cared for by the same personnel in order to avoid indirect transmission of disease. Adequate protective wear should also be worn by healthcare workers when working with patients, including gowns, gloves, and aprons that are discarded in the patient's room. In nurseries, only milk packaged in sterile containers should be used, and common equipment shared by babies should be removed. Infants should be confined to their own bassinettes, and infants born outside the area should not enter the nursery during an epidemic of diarrhea. Finally, the care of babies should be limited to essential personnel, and the number of people in the unit should be reduced as much as possible. This may include reductions in visitors to the unit.

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CHAPTER 25

Healthcare-Associated Burn Wound Infections

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Burn patients are among the patients at highest risk for healthcare-associated infections. These patients have lost a portion of their integument that would ordinarily be a strong barrier to invasion by microorganisms. In addition, the necrotic tissue in the burn eschar combined with the presence of serum proteins provides a rich culture medium for microorganisms. Added to the loss of integument is the adverse effect of thermal injury on both local and systemic immunity *(1,2)*. Given these effects of burn trauma, it is easily understood why burn patients are at risk for healthcare-associated burn wound infections.

There are approximately 2 million fires in the United States annually leading to 1.2 million burn injuries. About 100,000 patients with moderate to severe burns require hospitalization, and about 5,000 of these burns are fatal *(3–7)*.

Data submitted from burn intensive care units (BICUs) to the National Nosocomial Infections Surveillance (NNIS) system at the Centers for Disease Control and Prevention indicate that the cumulative incidence for burn wound infections is 4.5% and the incidence rate is 6.8 cases per 1,000 patient days (R. Gaynes, personal communication, 1998). Infections are the most common cause of death in burn patients, and the most common sites of infection are the lungs and the burn wound *(8)*. The burn wound may also initiate and perpetuate a mediator-induced septic response accompanied by multiple-organ failure in the absence of an identifiable focus of infection and with negative blood culture results *(9)*. Thus, proliferation of microorganisms in the burn wound followed by invasion of subjacent viable tissue or the mediator-induced septic response may cause the clinical manifestations of sepsis.

Although the most important cause of death in burn patients is infection, the current overall mortality rate due to infections in the burn patient is unknown *(10)*. However, data from the NNIS system on patients with burn wound infection who died, and for whom the relationship of infection to death was reported, indicated that 18 (12.6%) of 143 deaths were caused by burn wound infection. Burn wound infection contributed importantly to death in 104 patients (72.7%), and the burn wound infection was unrelated to death in the remaining 21 patients (14.7%) (R. Gaynes, personal communication, 1998). It has also been observed that mortality in burn patients is significantly increased by bacteremia due to gram-negative bacilli *(11)*.

TYPES OF BURNS

Most burns are due to thermal injury. According to the National Burn Repository, for cases with a known etiology, 40% of cases are due to fire/flame injuries and 30% of cases are due to scald injuries. Nine percent of injuries are due to contact with a hot object. The remaining cases are due to electrical injury (4%) and chemical injury (3%) *(12)*.

PATHOGENESIS OF BURN WOUND INFECTIONS

Loss of the integument combined with the immune defects that accompany thermal injury place the burn patient at high risk for burn wound infection. Microorganisms are present on the skin at the time of burning and are readily acquired from the patient's gastrointestinal tract after the thermal injury has been sustained. Microorganisms are rapidly acquired from the environment of the burn care facility as well as from other burn patients cared for in the same unit.

In addition to the loss of the skin barrier, the rapid colonization of the burn wound from endogenous and exogenous sources, and the excellent culture medium provided by the burn wound, thermal injury has a substantial suppressive effect on the immune system. The nonspecific immune system is involved with long-term suppression of the neutrophil oxidative burst (13) and impairment of neutrophil chemotaxis (14). Abnormalities in cellular immunity are reflected by a decreased ratio of helper to suppressor lymphocytes and a decrease in natural killer cell activity *(2,15)*. Changes in monocyte function are reflected by an early release of high mobility group box protein 1 (HMGB1) after a burn injury and release of the cytokines IL-6, IL-8, and IL-10 (16). Higher levels of HMGB1 and IL-10 on admission were predictive of a fatal outcome. Another dysfunction of monocytes that occurs after burn injury is decreased production of human leukocyte antigen-DR (mHLA-DR) (17). Severe burn injury induces a marked decrease in the production of mHLA-DR by circulating monocytes. The marked reduction of mHLA-DR expression in severely burned patients leads to septic complications and a fatal outcome.

Thermal injury leads to local accumulation of cytokines in the areas of burn injury that "spill over" into the systemic circulation *(18)*. Thus, local accumulation of multiple cytokines in the area of injury that mediate the reparative process has a marked suppressive effect on host defenses when these cytokines enter the bloodstream and are distributed throughout the body.

With the loss of the integument, immunosuppression, and availability of nutrients for microbial proliferation, microorganisms contaminating the surface of the burn wound may multiply to high concentrations. Early colonization of the wound in the first 48 hours takes place with gram-positive microorganisms from within the depths of the sweat glands and hair follicles *(10,15,19)*. Between 3 and 21 days, the wound becomes colonized with gram-negative bacilli from the patient's own gastrointestinal tract or from other patients in the burn care facility *(10,15)*. If microorganisms reach a concentration of at least 10^5 colony-forming units (CFU) per gram of tissue, they may spread from the hair follicles along the dermal subcutaneous junction *(19)*. Perivascular colonization may result in thrombosis, vascular occlusion, and necrosis of the remaining viable elements. The resultant ischemia and bacterial autolysis may convert a partial-thickness injury to a full-thickness injury. In burn wounds with unexcised eschar, invasion of the subeschar viable subcutaneous tissue results in burn wound infection or burn wound sepsis and may be complicated by bacteremia.

CLINICAL MANIFESTATIONS OF BURN WOUND INFECTIONS

In burn wounds with unexcised eschar, clinical manifestations of burn wound infection appear when microorganisms reach high concentrations in the burn eschar and invade subjacent viable tissue. Clinical signs of infection may depend, to some extent, on the type of infecting microorganism. Hyperthermia and leukocytosis tend to be more marked in patients with gram-positive infection. Infections with gram-positive microorganisms are also more often associated with irrational behavior and mental confusion. The appearance of a wound infected by gram-positive microorganisms may be characterized by maceration with a ropy tenacious exudate and surrounding cellulitis *(19)*.

Patients with gram-negative burn wound infection are more likely to have hypothermia and leukopenia. Although they may have altered mental status with confusion, some patients with gram-negative burn wound infection may remain lucid until near death *(19,20)*. Patients with gram-negative infection may also have glucose intolerance with hyperglycemia, ileus and abdominal distention, respiratory distress syndrome, and oliguria *(20)*.

The wound infected by gram-negative microorganisms is characterized by (a) focal gangrene that coalesces and spreads throughout the wound; (b) conversion of a partial-thickness wound to a full-thickness wound; (c) hemorrhagic discoloration of subeschar tissue; (d) focal, multifocal, or generalized dark brown, black, or violaceous discoloration of the burn wound; and (e) changes in unburned skin at the wound margins characterized by edema and violaceous discoloration *(19,20)*. Bacteremia is a common complication of burn wound infection, but absence of bacteremia does not rule out burn wound infection. In fact, fatal burn wound infection may occur in the absence of bacteremia, particularly when the infection is caused by gram-negative microorganisms *(19)*.

DIAGNOSIS OF BURN WOUND INFECTION

Clinical Diagnosis

Examination of the burn wound and clinical signs and symptoms provide important clues to the diagnosis of burn wound infection. As noted above, changes in the wound characterized by dark brown, black, or violaceous discoloration; unexpectedly rapid separation of the eschar; hemorrhagic discoloration of subeschar tissue and edema; and violaceous discoloration of unburned skin at the wound margin suggest burn wound infection *(20)*. Clinical suspicion of infection is heightened when these local wound manifestations are accompanied by hypothermia (<36°C), hyperthermia (>38°C), hypotension (systolic blood pressure ≤90 mm Hg), oliguria (<20 mL/h), ileus with abdominal distention, glucose intolerance and hyperglycemia, or altered mental status *(20,21)*.

Microbiologic Diagnosis of Burn Wound Infection

In a study wherein about 80% of burn wound biopsies were obtained from patients with local signs of burn wound infection, Pruitt and Foley *(22)* observed that 75% of patients with more than 10^5 CFU/g of burn wound tissue died. When this density of microorganisms in the burn eschar was combined with a grade 6 histologic diagnosis ("invasive infection with microbial penetration into viable tissue beyond the depth of original necrosis"), the mortality rate was 100%. In another study comparing quantitative burn wound cultures and histopathologic examination of the same tissue, McManus et al. *(23)* observed that growth of at least 10^5 CFU/g of tissue identified burn wound infection diagnosed by histopathologic assessment of tissue 96.1% of the time. However, 64.3% of biopsies that showed negative results histopathologically also had at least 10^5 CFU/g of tissue. Thus, quantitative burn wound cultures have a high sensitivity (96.1%) but a low specificity (35.7%). Stated another way, burn wounds with $<10^5$ CFU/g of tissue are highly unlikely to be infected, whereas only about one-third of burn wounds with at least 10^5 CFU/g of tissue will be infected.

Although the threshold of at least 10^5 CFU/g of burn wound tissue has a high sensitivity and low specificity for burn wound infection, a threshold of over 10^8 CFU/g of tissue is highly suggestive of burn wound sepsis and impending death in the untreated patient *(24,25)*. Thus, even though the definitive diagnosis of burn wound infection may be made by histopathologic examination of a full-thickness biopsy of the burn wound (see below), it would appear that burn wound biopsies containing $<10^5$ CFU/g of tissue suggest that burn wound infection is unlikely and that biopsies with more than 10^8 CFU/g of tissue are highly suggestive of burn wound sepsis.

One problem with the interpretation of quantitative cultures of burn wound biopsies has been the uneven distribution of microorganisms, both qualitatively and quantitatively, throughout the burn wound. In a study wherein culture results were not correlated with clinical manifestations, appearance of the burn wound, or histopathologic examination of the tissue taken for culture, Woolfrey et al. *(26)* concluded, "Quantitative results derived from burn wound biopsy cultures are unreliable and may be significantly misleading when used for decision-making relative to patient care." These authors divided each biopsy specimen and cultured the two portions separately. Between the two segments, an average of 4.8 microorganism types was recovered. At the 10^5 CFU/g of tissue breakpoint, the paired quantitative results agreed within the same log increment for only 38% of biopsies. Although it is clear from the data of Woolfrey et al. that there may be large qualitative and quantitative differences in burn wound microbiology between immediately adjacent areas of the wound, it is unclear how their results relate to the appearance of the burn wound (and whether biopsies were taken from areas of the wound that appeared infected on clinical examination), histopathologic examination of the tissue taken for culture, and the clinical course of the patient.

Surface swab cultures, either qualitative or quantitative, have been used in the diagnosis of burn wound infections. Steer et al. *(27)* compared qualitative results and quantitative bacterial counts of 141 surface swabs and 141 wound biopsies taken from 74 burn patients. They observed a significant correlation between the total bacterial counts of surface swabs and the total bacterial counts of biopsies ($p < .001$), but the predictive value of the counts obtained by one method to predict the counts obtained by the other method was poor. The qualitative correlation was also poor, and only 54% of the biopsy/swab pairs yielded the same microorganism on culture. There were two exceptions to the latter observation. When *Staphylococcus aureus* was present in the burn wound biopsy, it was present on surface culture 95% of the time, and when *Pseudomonas aeruginosa* was recovered from the burn wound biopsy, it was cultured from the surface swabs 92% of the time. Thus, although *S. aureus* and *P. aeruginosa* in the burn wound may be detected by surface swabs, qualitative and quantitative surface cultures are generally not useful for predicting the qualitative and quantitative microbiology of the burn wound.

When the diagnosis of burn wound infection is made by histopathologic examination of a full-thickness burn wound biopsy (see below), quantitative culture of a portion of the biopsy may identify the causative microorganism(s) and provide antimicrobial susceptibility data for the selection of appropriate antimicrobial therapy. McManus et al. *(23)* observed a 100% concordance between microorganisms seen on histopathologic examination and those recovered on culture. Thus, burn wound biopsies should be both cultured and examined histopathologically. Although quantitative cultures may not be necessary for identification of the causative microorganism(s), quantitation might be useful in separating microorganisms on and in the nonviable tissue from those invading viable tissue. It would be unlikely that microorganisms recovered at a concentration below 10^5 CFU/g of tissue would be causing burn wound infection *(23)*.

Although some investigators have found a good correlation between the results of quantitative Gram-stained preparations and quantitative cultures of biopsy tissue *(28,29)*, others have not *(30)*. Even with a good correlation between quantitative Gram-stain and culture results, the results of microscopic examination of Gram-stained tissue should not be used for diagnosis of burn wound infection, because definitive diagnosis of burn wound infection requires histopathologic examination and culture.

Histopathologic Diagnosis of Burn Wound Infection

In burn wounds with unexcised eschar, the diagnosis of burn wound infection may be made by histopathologic examination of a full-thickness burn wound biopsy. The biopsy should be taken from the area of the wound with the most pronounced local changes (see above). A lenticular tissue sample should be obtained using a scalpel. The biopsy should measure from $0.5 \times 0.5 \times 0.5$ cm to $1 \times 1 \times 1$ cm and should weigh between 100 and 500 mg. The biopsy must include underlying or adjacent unburned tissue in addition to the eschar. The specimen should be divided; one half should be cultured quantitatively, and the other half should be placed in 10% neutral buffered formalin solution for processing for histopathologic examination. The tissue should be stained with hematoxylin and eosin stain, Brown Hopps Gram stain, and periodic acid-Schiff stain *(20,31)*.

Histopathologic examination may show microorganisms localized to the burn eschar surface or various degrees of penetration of the eschar. Burn wound infection or sepsis develops when microorganisms invade through the eschar and into viable tissue subjacent to the eschar. These histopathologic manifestations of burn wound infection were carefully described 47 years ago by Teplitz et al. *(32)* using rats as an experimental model. Their findings in the animal model appear to parallel those observed in humans with thermal injury.

Kim et al. *(33)* have described a frozen section technique for rapid evaluation of burn wound biopsies for burn wound infection. This technique reduces the time of processing from 4 hours (rapid technique) to 30 minutes. Application of the frozen section technique to burn wound biopsies had not been possible in the past because of the hardness of the eschar. However, advances in this technique, which made frozen sections of bone and cartilage possible, have permitted its application to burn wound biopsies as well. Frozen section diagnosis should always be confirmed by examination of permanent sections (rapid section technique).

DEFINITIONS OF BURN WOUND INFECTION

Although burn wound infection may be diagnosed by histopathologic examination of a full-thickness burn wound biopsy, and the causative agent may be established by culture of the biopsy or by histopathologic examination of the burn wound biopsy using special stains for microorganisms (e.g., periodic acid-Schiff stain for fungi), such studies may not be available in all burn care facilities. Further, when the

TABLE 25-1

Definitions for Burn Wound Infections

Burn infections must meet at least one of the following criteria:

1. Patient has a change in burn wound appearance or character, such as rapid eschar separation, or dark brown, black, or violaceous discoloration of the eschar, or edema at wound margin
   and
   histologic examination of burn biopsy shows invasion of organisms into adjacent viable tissue
2. Patient has a change in burn wound appearance or character, such as rapid eschar separation, or dark brown, black, or violaceous discoloration of the eschar, or edema at wound margin
   and
   at least **one** of the following:
   a. organisms cultured from blood in the absence of other identifiable infection.
   b. isolation of herpes simplex virus, histologic identification of inclusions by light or electron microscopy, or visualization of viral particles by electron microscopy in biopsies or lesion scrapings.
3. Patient with a burn has at least **two** of the following signs or symptoms with no other recognized cause: fever (>38 °C) or hypothermia (<36°C), hypotension, oliguria (<20 cc/h), hyperglycemia at previously tolerated level of dietary carbohydrate, or mental confusion
   and
   at least **one** of the following:
   a. histologic examination of burn biopsy shows invasion of organisms into adjacent viable tissue
   b. organisms cultured from blood
   c. isolation of herpes simplex virus, histologic identification of inclusions by light or electron microscopy, or visualization of viral particles by electron microscopy in biopsies or lesion scrapings.

Comments

- Purulence alone at the burn wound site is not adequate for the diagnosis of burn infections; such purulence may reflect incomplete wound care.
- Fever alone in a burn patient is *not* adequate for the diagnosis of a burn infection because fever may be the result of tissue trauma or the patient may have an infection at another site.
- Surgeons in Regional Burn Centers who take care of burn patients exclusively may require Criterion 1 for diagnosis of burn infection.
- Hospitals with Regional Burn Centers may further divide burn infections into the following: burn wound site, burn graft site, burn donor site, burn donor site-cadaver; NHSN, however, will code all of these as BURN.

(Reprinted from Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332, with permission from Elsevier.)

burn wound has been excised, there may be no tissue to biopsy. Thus, case definitions are needed for surveillance and outbreak investigation that make use of other, more easily obtained data such as clinical observations, blood cultures, viral cultures, and microscopic examination of lesion scrapings for viral inclusions. Table 25-1 (34) shows case definitions for burn wound infections used by the National Healthcare Safety Network (NHSN).

One element missing from the NHSN definitions is that of the causative agent. Thus, if one were selecting a definition for burn wound infection in a suspected outbreak of burn wound infections caused by *S. aureus*, it would be appropriate to include culture of *S. aureus* from the burn wound in the case definition of infection. The source from which a culture must be taken to establish the cause of a burn wound infection is not described in the NHSN definitions. For bacterial infections, the culture should be taken from a full-thickness burn wound biopsy and not the surface of the burn wound. Another acceptable source is blood if no other possible site of infection can be identified. Although fungi may be cultured from a full-thickness burn wound biopsy, most fungal burn wound infections will probably be diagnosed by histopathologic examination of burn wound biopsies. Herpes simplex may be cultured from scrapings from the burn wound surface; viral inclusions may also be seen microscopically in burn wound scrapings.

The NHSN definitions are based on burn wounds containing unexcised eschar. Since burn wounds are treated in many centers now by early excision and coverage of the wound with autograft, cadaveric allograft, temporary biologic dressings, or dermal replacement (Integra) (35), definitions are needed for infections in surgically created wounds such as excised burns and donor sites. Further, definitions are needed for other types of infections related to the burn wound such as burn wound impetigo and burn wound cellulitis (36). For the purposes of surveillance, the NHSN lumps all wounds related to thermal injury and its treatment together as burn infections. However, when an outbreak occurs involving sites other than burn wound containing unexcised eschar, it will be necessary to use case definitions specific to the type of infection involved in the outbreak (Table 25-2).

TABLE 25-2

Proposed Definitions for Burn Wound Infections (Including Burn Wound Impetigo, Open Burn-Related Surgical Wound Infections, Cellulitis, and Infection of Unexcised Burn Wounds)

Infection	*Criterion (Must Meet the Following)*
Burn wound impetigo	Infection involves loss of epithelium from a previously reepithelialized surface such as grafted burns, partial-thickness burns allowed to close by secondary intention, or healed donor sites *and* Is not related to inadequate excision of the burn, mechanical disruption of the graft, or hematoma formation *and* Requires some change of or addition to antimicrobial therapy It may or may not be associated with systemic signs of infection such as hyperthermia (temperature >38.4°C) or leukocytosis (white blood cell count >10,000/m^3)
Open burn-related surgical wound infection	Infection occurs in surgically created wounds such as excised burns and donor sites that have not yet epithelialized *and* Has a purulent exudate that is culture positive *and* Requires change of treatment (which may include change of or addition to antimicrobial therapy, removal of wound covering, or increase in frequency of dressing changes) *and* Includes at least one of the following: 1. Loss of synthetic or biologic covering of the wound 2. Changes in wound appearance such as hyperemia 3. Erythema in the uninjured skin surrounding the wound 4. Systemic signs such as hyperthermia or leukocytosis
Burn wound cellulitis	Infection occurs in uninjured skin surrounding the burn wound or donor site *and* Is associated with erythema in the uninjured skin progressing beyond what is expected from the inflammation of the burn *and* Is not associated with other signs of infection in the wound itself *and* Requires change of or addition to antimicrobial therapy *and* Includes at least one of the following: 1. Localized pain or tenderness, swelling, or heat at the affected site 2. Systemic signs of infection such as hyperthermia, leukocytosis, or septicemia 3. Progression of erythema and swelling 4. Signs of lymphangitis and/or lymphadenitis
Invasive infection in unexcised burn wounds	Infection occurs in deep partial-thickness or full-thickness burn that has not been surgically excised *and* Is associated with change in burn wound appearance or character, such as rapid eschar separation, or dark brown, black, or violaceous discoloration of the eschar *and* Requires surgical excision of the burn and treatment with systemic antimicrobials *and* May be associated with, but not dependent on, any of the following: 1. Inflammation of the surrounding uninjured skin, such as edema, erythema, warmth, or tenderness 2. Histologic examination of the burn biopsy specimen that shows invasion of organism into adjacent viable tissue 3. Organism isolated from blood culture in absence of other identifiable infection 4. Systemic signs of infection such as hyperthermia or hypothermia, leukocytosis, tachypnea, hypotension, oliguria, hyperglycemia at previously tolerated level of dietary carbohydrate, or mental confusion

(Reprinted from Peck MD, Weber J, McManus A, et al. Surveillance of burn wound infections: a proposal for definitions. *J Burn Care Rehabil* 1998;19:386–389.)

ETIOLOGIES OF BURN WOUND INFECTIONS

Burn wound infections may be caused by bacteria, fungi, or viruses. Although not invariably the case *(37)*, bacteria probably cause the majority of infections in most burn care centers. Almost all burn wound infections caused by bacteria are due to aerobic microorganisms. Anaerobes cause up to 2% of all burn wound infections *(38,39)*.

Bacteria

S. aureus continues to be one of the most important bacterial causes of burn wound infections (40,*41*,42). More importantly, methicillin-resistant *S. aureus* (MRSA) continues to be an important pathogen for burn wound infections (43,*44*,*45*). More recently, there is evidence that community-acquired MRSA is beginning to enter some burn care facilities (46) but not others (47). In one center, 25 of 206 (12.1%) of patients colonized or infected with MRSA had USA300 (46). Differences between patients colonized or infected with USA300 community-acquired MRSA and healthcare-associated MRSA were that patients with community-acquired MRSA had frequent abscesses involving their burn wounds. Nasal colonization was present in only 31.6% of patients infected with community-acquired MRSA (46). Occasionally, strains of *S. aureus* that produce toxic shock syndrome toxin and exfoliative toxin cause burn wound infection (*48*,*49*,50,*51*). Although much less common, β-hemolytic group A streptococci may occasionally cause outbreaks of burn wound infection *(52)*. However, groups A, B, and G streptococci are the third most common cause of burn wound infections in the burn unit at the Karolinska Hospital in Stockholm *(53)* (see also Chapter 32).

P. aeruginosa continues to be a common cause of burn wound infections. *Pseudomonas* infections tend to occur more often in patients with burn wounds of >60% total body surface area (TBSA) and after 2 weeks of hospitalization *(54)*.

Acinetobacter baumannii has become the most frequently isolated pathogen in many BICU in civilian and military populations (*54–58*,59). *A. baumannii* is the most common microorganism isolated from war wounds including burn wounds *(57)*. *A. baumannii* becomes highly resistant to antimicrobial agents and forms biofilms that appear to increase its pathogenicity *(58)*. It is unclear at present whether or not *Acinetobacter* infections in burn patients are associated with an increase in mortality *(54,55,57)*.

Similar to healthcare-associated infections in other body sites, enterococci have become an important cause of burn wound infection. This is likely due to the widespread use of third-generation cephalosporins to which enterococci are resistant. In 1986, Jones et al. *(60)* reported on a series of cases of burn wound sepsis caused by enterococci. Enterococcal infection was diagnosed by recovery of at least 10^5 CFU/g of tissue on burn wound biopsy or by recovery of enterococci from blood cultures. They identified 38 enterococcal burn wound infections in 26 months. Twenty patients developed enterococcal bacteremia, and 10 of these patients died. Enterococci appear to be not only common but also virulent burn wound pathogens. In a more recent study, 97 isolates of vancomycin-resistant enterococci (VRE) and 652 isolates of vancomycin-susceptible enterococci (VSE) were recovered from burn patients *(61)*. No mention was made of infections caused by VSE, but none of the patients colonized by VRE developed VRE infections. As has been noted in other patient populations in the hospital, VRE have been reported to cause an outbreak of VRE colonization and infection in a BICU (62). Four cases of bacteremia due to VRE occurred during that outbreak.

While each of the genera among the Enterobacteriaceae still contribute pathogens as a cause of burn wound infections, only *Klebsiella pneumoniae* joins *S. aureus*, *A. baumannii*, and *P. aeruginosa* as one of the four most common causes of burn wound infections *(54)*. Those strains of *K. pneumoniae* that produce extended-spectrum beta-lactamase (ESBL) may result in higher mortality (63). Although the authors could not directly relate ESBL production to mortality, multivariate analysis did indicate that ESBL producing *K. pneumoniae* may be related to mortality in patients who are older and who are more badly burned.

Fungi

As bacterial burn wound infections have come under better control with use of topical antimicrobial agents, better isolation techniques, and, perhaps, early burn wound excision, the relative importance of fungal burn wound infections has increased. In a recently published autopsy series from the U.S. Army Institute of Surgical Research, the most common causes of fungal burn wound infection were *Aspergillus* species and *Candida* species *(64)*. Two publications from the same institution showed that fungal burn wound infection, not burn wound colonization, is significantly associated with mortality *(65,66)*.

Candida Species Invasive candidiasis occurs in 2% to 21% of burn patients (67). Mucosal disruption occurs in burn patients, which leads to fungal translocation. Mucosal atrophy in the gastrointestinal tract is related to the extent of the burn, and ileus complicates burns with >25% TBSA burned (67). *Candida albicans* is the most common species of *Candida* recovered from blood (65% of cases) with *Candida parapsilosis* causing 25% of cases and *Candida tropicalis* causing 10% of cases *(68)*. The most common source for *Candida* bloodstream infection is the burn wound and the risk increases with increasing size of the burn wound and with delay in burn wound excision *(69)*. The attributable mortality for candidemia in burn patients has been reported to range from 14% to 70% (67). However, whether or not *Candida* infections in burn patients are related to mortality remains controversial. In a recently published retrospective matched case–control study using prospectively collected data, no difference in mortality was observed between the patients with candidemia and the control group *(68)*.

Filamentous Fungi The great preponderance of burn wound infections caused by fungi is due to filamentous fungi. The filamentous fungi that most often cause burn wound infections are *Aspergillus* species, Zygomycetes (*Mucor* species, *Rhizopus* species), *Alternaria* species, and *Fusarium*

species. Less commonly isolated are *Cladosporium* species, *Penicillium* species, and *Trichosporon* species (43,*64,65*). Burn wounds may be colonized or infected by fungi, but only burn wound infection is significantly associated with mortality *(66)*. However, this relationship between burn wound infection and mortality is observed only in those patients with TBSA of 30% to 60% *(66)*. Importantly, 15.4% of patients with burn wound colonization progressed to burn wound infection and made up 40.7% of all patients with burn wound infection.

Viruses

Herpes Simplex Herpes simplex infections may occur in burn patients. Most of these infections appear to be reactivation infections and may be symptomatic or asymptomatic. Asymptomatic infections are detected by a fourfold or greater rise in antibody titer *(70)*. Symptomatic infections most commonly involve the burn wound and tend to occur in healing partial-thickness burn wounds that involve the face *(71–73)*. The infection, which apparently reactivates in the healing skin after burn injury, may disseminate to involve liver, adrenal glands, lungs, spleen, gastrointestinal tract, and urinary bladder *(71)*. No data are available on the incidence of herpes simplex infections of burn wounds. In one study, 25% of children with burns had serologic evidence of herpes simplex infection, and all were reactivation infections *(70)*. Only one of these children had a burn wound infection due to herpes simplex.

In one study of adult burn patients, 40% had serologic evidence of herpes virus infection, but apparently, there was no herpetic involvement of their burn wounds *(74)*. About 90% of these infections were reactivation infections, and about 10% appeared to be primary infections.

Cytomegalovirus In one published study of burn patients with a mean age of 29 years, the incidence of cytomegalovirus (CMV) infection was 33% *(74)*. These infections were due to reactivation of latent infections in 76% of the patients. There was no evidence that transfusion of blood products increased the incidence of primary or reactivation CMV infections. These infections were apparently asymptomatic, and none involved the burn wound. In a second study, 29% of the burn patients developed CMV infection, but again, none had any clinical manifestations of infection *(75)*.

In a series of pediatric burn patients, 33% of the patients developed CMV infections *(70)*. Unlike the adult patients, some pediatric patients developed fever and hepatitis. In a second study from the same institution, CMV infection was found to have caused initially unexplained fevers in four patients *(76)*. None of the patients in these two reports had involvement of the burn wound by CMV. In the former study, a few patients had adenovirus infections and reactivated Epstein–Barr virus and varicella-zoster virus (VZV) infections, but none of these infections involved the burn wound. In a more recent study cytomegalovirus was identified as a cause of pneumonia in a burn patient but the patient had no skin lesions suggestive of cutaneous involvement (*77*).

In pediatric burn hospitals, infections in patients due to VZV occur uncommonly but may cause serious disease such as VZV pneumonia *(78)*. Although there has been no significant involvement of the burn wound in these cases, pneumonia may be fatal. The lower morbidity, particularly involving the burn wound, may be due to the ready availability of acyclovir and varicella-zoster immune globulin. Due to the high degree of communicability of VZV, prompt detection and isolation of cases is very important in preventing spread among burn patients. That VZV can be effectively controlled in a pediatric burn hospital was shown by Sheridan et al. *(78)* (see also Chapter 43).

EPIDEMIOLOGY OF BURN WOUND INFECTIONS

The epidemiology of burn wound infection involves a reservoir or source for the causative microorganisms, a means of transmission of these microorganisms to the burn wound surface, and the presence or absence of certain factors (risk factors) that may promote colonization, multiplication, and invasion of wound surfaces by newly deposited microorganisms.

Reservoirs or Sources

Burn Wounds of Patients The collective burn wound surfaces of the patients in a burn treatment facility may make up an important reservoir of microorganisms that cause burn wound infections. The burn wound has been shown to be a reservoir for *P. aeruginosa, E. coli*, *K. pneumoniae*, *A. baumannii*, *Streptococcus pyogenes*, MRSA, and enterococci including VRE (40,*41,54*,62). Given the shift in the etiology of burn wound infections over the last 3 to 4 decades and the continuing trend toward early burn wound excision and closure, it is unclear how important the collective burn wounds of patients in burn care facilities are today as a reservoir for microorganisms that cause burn wound infections. With the improvement in control of bacterial pathogens as causes of burn wound infection, yeast and fungi have assumed a prominent role as causes of burn wound infections in the 21st century *(66,69)*.

Gastrointestinal Tract There is substantial evidence that microorganisms that colonize the burn patient's bowel may contaminate the burn wound and lead to burn wound infection *(78–80)*. In past years when *P. aeruginosa* was a common burn wound pathogen, the areas of the burn wound most often contaminated by feces (buttocks, perineum, lower abdomen, inside of the upper thighs) were the areas most often infected by *P. aeruginosa*. The previous species name for *P. aeruginosa* was *Pseudomonas pyocyanea*, and burns in the areas most often contaminated by feces were called pyocyaneus-prone burns *(81). P. aeruginosa* may reach the bowel by ingestion of these microorganisms as a result of cross-contamination from one burn patient's wound surface to the oropharynx of a patient in a nearby bed or by ingestion of food contaminated by *P. aeruginosa (78,79)*. It has also been suggested that gut flora may contaminate the burn wound by translocation from the gastrointestinal tract *(82)*.

Environment Microorganisms that cause burn wound infections have been recovered from a number of inanimate sites in the environments of burn care facilities *(83–91)*. Among the most important inanimate reservoirs or sources for microorganisms that cause burn wound infections is hydrotherapy equipment *(92)*.

Endogenous Flora Early burn wound infections caused by gram-positive cocci are due to microorganisms from the endogenous skin flora (42,*54*). Routine antibiotic prophylaxis to prevent these early infections, given in many burn treatment centers, has eliminated infections from this source. Within 8 to 72 hours, endogenous gram-negative bacteria from the patient's respiratory and gastrointestinal tracts colonize the burn wound *(54)*. After initial colonization with endogenous flora, the burn wound becomes colonized with *Pseudomonas*, *K. pneumoniae*, and *A. baumannii* from other patients and the environment *(54)*.

Modes of Transmission

Hands of Healthcare Workers As with other healthcare-associated infections, there is evidence that microorganisms are transmitted between patients on the hands of their caregivers *(7,8,83,84,87,88)*. Microorganisms may be transmitted directly between patients by the hands of medical personnel (patient to hands to patient) or they may be indirectly transmitted by contaminated hands (patient to hands to inanimate environmental surface to hands to patient).

Another source of hand contamination for healthcare workers in burn units is nonsterile examination gloves *(93)*. *Bacillus cereus* was disseminated among patients in a burn unit. When infection control measures failed to halt spread of the microorganism, cultures of unopened boxes of nitrile gloves revealed the source. The outbreak was cleared by use of latex and vinyl gloves.

Gastrointestinal Tracts of Patients As noted above, microorganisms that gain entrance to the gastrointestinal tract of a patient may be carried to the patient's burn wound surface by feces. The gastrointestinal tract may be inoculated with a burn wound pathogen by contact of the patient's oropharynx with the contaminated hands of a healthcare worker or by ingestion of contaminated food *(79)*. Contaminated food may carry the burn wound pathogen directly to the patient's gastrointestinal tract or may contaminate utensils used for food preparation, leading to secondary contamination of food *(79)*.

Hydrotherapy After hydrotherapy equipment becomes contaminated, subsequent patient contact with the equipment during hydrotherapy treatments may transfer the microorganisms to a burn patient's wounds *(83–86,88, 89,92)*.

Inanimate Environmental Surfaces Environmental surfaces frequently become contaminated with the microorganisms that cause burn wound infections. Other than hydrotherapy equipment and mattresses, it has been difficult to document transfer of microorganisms from environmental surfaces directly to the burn wound surfaces of patients.

Risk Factors for Burn Wound Colonization and Infection

After microorganisms are transmitted to the surface of the burn wound, there are several factors that determine whether the microorganisms will survive, colonize the surface, and invade the burn wound. These factors that promote colonization and burn wound invasion may be considered risk factors for burn wound infection.

Duration of Hospitalization Using Cox model survival analysis to analyze data from a retrospective study of bacterial wound colonization and duration of hospital stay, one group of investigators *(94)* observed a significant positive association between length of stay and colonization with Enterobacteriaceae or a combination of *S. aureus* and *P. aeruginosa*. Although the relationship observed by these workers was between duration of stay and wound colonization (not infection), it is likely that duration of stay is related to burn wound infection, since colonization is a necessary first step in the development of wound infection.

Burn Wound Size Intuitively, it would seem likely that the larger the burn wound, the more likely it would be contaminated and colonized with microorganisms. In a prospective study of 53 pediatric patients with burns in which the data were analyzed by multivariable analysis, Fleming et al. *(82)* showed a significant relationship between colonization of burn wounds with microorganisms from patients' fecal flora and the size of their burn wounds. Again, it is likely that risk factors for colonization also place the burn wound at greater risk for infection.

In a retrospective study in which data were analyzed by multiple regression analysis, Merrell et al. *(95)* found a significant relationship between burn wound size and subsequent occurrence of fatal sepsis. Fifty-four percent of the fatalities were due to burn shock. Graves et al. *(96)* also observed a significant relationship between burn wound size and infection in a retrospective study wherein data were analyzed by logistic regression analysis. Sites of infection in the latter two studies included burn wound *(95,96)*, lungs *(92,93)*, multiple organs *(93)*, and abdomen *(93)*. In a prospective cohort study in pediatric burn patients analyzed by multivariable techniques, Gastmeier et al. *(97)* observed a significant relationship between burn wound infections and percentage of TBSA affected. The authors also noted a significant relationship between duration of ventilation and pneumonia and duration of urinary catheter use and urinary tract infections.

Transfusions Graves et al. *(96)*, using multivariable analysis, also found a significant relationship between number of blood transfusions and infections. Although they recognized that the relationship may only be due to the possibility that more frequent transfusion identifies patients at a higher level of severity of injury and therefore at a higher risk of infection, the authors also noted that the relationship may be due to a specific depression of resistance to infection caused by the transfusions. In an investigation of an outbreak in a burn unit caused by *A. baumannii*, Simor et al. (59) identified receipt of blood products as a risk factor for acquisition of the outbreak strain. In the multivariable model, the odds ratio was 10.8 with a 95% confidence interval of 3.4 to 34.4, $p < .001$. Thus, blood transfusions may further suppress host defenses already impaired by the burn injury.

Hyperglycemia Poor plasma glucose control and the effect of hyperglycemia on the occurrence of infections and on mortality in pediatric burn patients were investigated

by Gore et al. *(98)* in a retrospective study with analysis of data limited to univariate statistics. Quantitative cultures of burn wound were done, and poor plasma glucose control was defined as >40% of glucose values ≥7.8 mmol/L and adequate control was indicated by ≤40% of glucose values of ≥7.8 mmol/L.

There was no association between adequate glucose control and wound infections defined as $>10^5$ CFU/g of burn wound tissue. There was no association between glucose control and bacteremia. However, patients with poor glucose control had a significantly higher rate of fungemia. When controlled for length of stay, patients with poor glucose control had significantly more bacteremia and fungemia, more skin-grafting procedures, and a lower percentage of graft takes for each procedure. Mortality was also significantly higher in patients with poor glucose control.

Although hyperglycemia did not appear to affect the incidence of burn wound infections, wound closure was apparently more difficult in patients with hyperglycemia, and patients with hyperglycemia had significantly more bacteremias and fungemias and a higher mortality rate.

Hypermetabolic Response Severe thermal injury defined as involvement of more than 40% of the TBSA leads to a hypermetabolic response that may last for 1 to 2 years (99). The primary mediators of this response are catecholamines and corticosteroids. For burns >40% TBSA, there is a 10- to 50-fold surge of plasma catecholamine and corticosteroid levels that last up to 9 months postburn. Immediately after the burn, cytokine levels peak and return to normal levels at 3 to 6 months postburn. The changes that occur in the immune response in catabolic patients lead to a further diminution in the burn patient's already suppressed immunity. Development of sepsis leads to further catabolism and energy expenditures. Early excision and grafting of burn wounds markedly reduce the hypermetabolic response.

Resistance of Microorganisms to Topical Antimicrobial Agents When microorganisms in a burn patient population become resistant to the topical antimicrobial agent used for suppression of growth of microorganisms in and on the burn wound, for any given patient the risk of uncontrolled growth of bacteria or fungi in the wound increases and invasion of viable tissue resulting in burn wound infection becomes more likely. Hendry and Stewart *(100)* observed that colonization of burn wounds by silver- and sulfonamide-resistant bacteria may occur within 2 weeks of admission.

Five outbreaks of burn wound infection or colonization due to gram-negative bacilli resistant (or relatively resistant) to topical antimicrobial agents have been reported *(83,87,101–103)*. The epidemic isolates from these outbreaks have been resistant to gentamicin *(83)*, silver sulfadiazine *(87)*, or silver nitrate *(101,103)*. No outbreaks due to mafenide acetate–resistant microorganisms have been reported.

Resistance of Microorganisms to Systemically Administered Antimicrobial Agents Resistance to systemically administered antibiotics may also result in a selective advantage for the resistant microorganisms and place patients at greater risk for burn wound infection. Although it has been generally assumed that antimicrobial agents do not achieve therapeutic concentrations in the avascular burn eschar, Polk et al. *(104)* showed that gentamicin and tobramycin frequently reached therapeutic concentrations in both the superficial and the deep layers of the unexcised burn wound. Reporting on data from the same study, Mayhall et al. *(105)* observed that when the concentration of antibiotic in burn wound tissue exceeded the minimum bactericidal concentration of the microorganisms present in the tissue, the microorganisms usually were eliminated from the wound. In no case was a microorganism eliminated from tissue when its minimum inhibitory concentration (MIC) was higher than the concentration of antibiotics in tissue. Of particular importance was their observation that, during therapy, six patients developed superinfection of the burn wound with *Serratia marcescens* and that five of these isolates were highly resistant to the antibiotic being administered. In the five patients for whom tissue levels were available, the MICs of these strains exceeded concentrations of antibiotic present in the burn wound. Thus, when a microorganism present on the wounds of patients in a burn care unit becomes highly resistant to an antibiotic used frequently to treat burn wound infection, particularly when used empirically, use of this antibiotic may place patients at risk for burn wound infection.

Risk Factors for Burn Wound Colonization and Infection with Multidrug-Resistant Microorganisms

Methicillin-Resistant S. aureus Several studies have been published recently that report on risk factors for burn wound infections caused by MRSA. In a case–control study analyzed by univariate statistics, the risk factors included a long duration of stay, diabetes mellitus, and residence in a long-term care facility in the previous year (40). In two case control studies analyzed by multivariable analysis, risk factors included treatment with vancomycin, burns involving the head and the number of burn wound excisions *(44,45)*. One of the latter studies found older age (50.8 ± 21.9) to be protective when compared with younger age (35.9 ± 22.3) *(45)*. In a study of the community-acquired USA 300 strain of MRSA on a burn-trauma unit Wibbenmeyer et al. (46) reported on a case–control study analyzed by univariate analysis. Risk factors for acquisition of the USA 300 strain included age, comorbidities, hospitalization in the prior 6 months, and having had a surgical procedure in the prior 6 months.

Vancomycin-Resistant Enterococcus Although enterococci have been reported to cause serious burn wound infection *(60)*, burn wound infections due to VRE, to the author's knowledge, have not been reported. In one outbreak of burn wound colonization in a burn unit, four cases of bacteremia were identified and were caused by the same strain of VRE that colonized patients' burn wounds (62). In another study, patients who acquired VRE in a burn surgery step-down unit developed no burn wound infections due to VRE, but two patients acquired VRE urinary tract infections *(45)*. Reported risk factors for VRE colonization include presence of diarrhea, receipt of an antacid, extent of TBSA burn, and presence of a Foley catheter while in the burn unit (*45*,*61*,62). In one study, it appears that a greater depth of burn injury and administration of vancomycin

were protective against VRE acquisition *(61)*. Colonization of the burn wound with VRE does not appear to cause burn wound infection, but the colonized burn wound may be an important reservoir for development of VRE infections at other body sites, particularly at sites of indwelling devices.

PREVENTION AND CONTROL

There is good evidence that improvements in the prevention and control of infections in burn patients have led to improvements in patient survival *(3,106)*. The approach to control of infections in burn patients may be conveniently divided into the following categories: (a) use of barrier techniques to prevent cross-contamination of patients; (b) prevention of cross-contamination of patients during hydrotherapy treatments; (c) application of topical antimicrobial agents to the burn wound to diminish the colonization and growth of microorganisms on the surface of the burn wound; (d) appropriate use of systemically administered antimicrobial agents to reduce the pressure for selection of resistant microorganisms; (e) early excision and closure of the burn wound; (f) control of hyperglycemia; and (g) management of the hypermetabolic response.

Barrier Techniques

Barrier techniques and other related techniques for preventing cross-contamination between patients in burn care facilities have been shown to be effective in diminishing infection rates in burn patients *(107,108)*. The most important barrier techniques are those used to prevent contact transmission of microorganisms from patient to patient by the contaminated hands and clothing of personnel who provide direct patient care. Use of gloves and an apron made of impermeable material has been shown to decrease cross-contamination of burn patients *(108,109)*. Hands should be washed before donning gloves and after removing gloves. Gloves need not be sterile for routine noninvasive patient care, including dressing changes *(110)*. In order for personnel to practice frequent hand hygiene, there must be enough alcohol gel dispensers and hand-washing sinks appropriately located within the burn care unit to minimize the amount of time required for personnel to practice hand hygiene *(106,107)*. Given the evidence that gram-negative microorganisms may be difficult to remove from the hands of healthcare workers in intensive care units, alcohol gel dispensers and hand-washing agents containing antiseptics effective against gram-negative bacilli should be provided in a suitable dispenser at each sink *(111)*. Hand hygiene should be strictly enforced *(109)*.

Patients should have surveillance cultures performed on admission and at least weekly to identify patients who are colonized with multiply-resistant microorganisms. This will permit early identification of patients colonized with resistant microorganisms so that they may be promptly placed on Contact Precautions *(109,112)*.

Prevention of Cross-Contamination from Inanimate Surfaces and Food

Given the frequent contamination of inanimate surfaces in burn care facilities, attention must be paid to preventing cross-contamination via these surfaces. Each patient should be assigned his or her own stethoscope, blood pressure cuff, box of clean disposable gloves *(110)*, and container(s) of topical antimicrobial agent. Items of equipment that must be shared between patients should be thoroughly cleaned and disinfected between patients. Particular attention should be paid to mattress covers, since two outbreaks in burn units have been related to damaged mattress covers that led to contamination of the mattress foam *(90,91)*. Covers on mattresses should be inspected between patients, and mattresses with damaged covers should not be used for subsequent patients.

A recently discovered source of microorganisms for colonization of burn wound surfaces is that of computer keyboards. Neely et al. *(113)* noted an increase in the number of their patients being colonized with *A. baumannii* and recovered the microorganism from the plastic covers over keyboards on bedside computers. Control measures included having personnel put on gloves before using the computer and having the plastic covers over the keyboards cleaned on a daily basis.

Environmental surfaces in every patient's room and in any treatment rooms need to be thoroughly cleaned and disinfected every day. In the author's hospital, the patient's room surfaces are cleaned by environmental services staff, the equipment attached to patients is cleaned and disinfected by clinical equipment services staff and respiratory therapists clean and disinfect the ventilators. Extensive cleaning and disinfection of the burn patients environment is well supported by scientific studies conducted over the past 15 years (62,*114–116*,117). Although all but one of these studies were not conducted in burn units, they likely apply to burn units since burn patients have extensive burn surfaces heavily colonized with bacteria and burn unit environments are likely contaminated with bacteria from the patients.

Environmental surfaces should be cultured periodically to verify that decontamination is effective. This is particularly important when one or more of the patients is colonized or infected with a microorganism that is highly resistant to antimicrobial agents.

Since raw vegetables have been shown to be a source of *P. aeruginosa* microorganisms that cause burn wound infections *(79)*, burn patients should not be fed raw fruits and vegetables. Attention should also be paid to avoiding contamination of kitchen utensils with raw fruits and vegetables that may later contact uncontaminated foods before they are served to burn patients.

Prevention of Cross-Contamination from Convalescent Patients

McManus et al. *(107)* showed that convalescent burn patients may be a reservoir of microorganisms for cross-contamination and infection of burn patients in the acute phase of care. They caution that patients in nonintensive care areas of burn treatment facilities should be included in microbial surveillance and infection control programs. These patients are the least likely to become infected but may be ignored as a reservoir for patients in intensive care. Consideration might be given to assignment of nursing staff to either the intensive care unit or convalescent care area without crossover of nursing staff between these two patient care areas.

Hydrotherapy

Prevention of cross-contamination in the hydrotherapy treatment area also includes use of barrier techniques but is considered separately from barrier techniques because of the unique risks for cross-contamination encountered in this area. Hydrotherapy is provided in a common area using common equipment and involves exposure to water. Effective decontamination of complex equipment between patients in a limited period may be a major challenge to burn care personnel. Unlike the hands of personnel and inanimate surfaces, water in hydrotherapy tanks contacts the entire burn wound surface. To decrease the contamination of the burn wound surface that occurs with immersion hydrotherapy, many burn care facilities have replaced immersion hydrotherapy with showering patients on a flat surface *(89)*. In two studies, the lowest rates of burn wound colonization and infection occurred when all wound care was done at the patients' bedsides *(86,89)*.

Topical Antimicrobial Agents

Topical antimicrobial agents are applied to the burn wound surface to diminish colonization and multiplication of microorganisms on the surface of the wound. Multiplication of microorganisms on the burn wound surface may lead to invasion of the wound. For burn wounds with unexcised eschar, continued multiplication of microorganisms may lead to invasion of the subeschar space and then to invasion of the subeschar viable tissue and burn wound sepsis.

The most commonly used agents are silver sulfadiazine, mafenide acetate, and silver nitrate. Silver sulfadiazine is the most commonly used agent among these *(118)*. Cerium nitrate–silver sulfadiazine is used in some centers but is not commercially available in the United States *(119)*. Silver sulfadiazine has the fewest side effects of the three most commonly used agents; these side effects include rare crystalluria and methemoglobinemia and common but mild transient leukopenia *(118)*. Since there is an association between the use of the sulfonamide component and kernicterus, it should not be used during pregnancy or in infants *(119)*. Microbial resistance has been reported for all of the topical agents, but resistance to mafenide acetate has been uncommon. Other less commonly used topical agents include sodium hypochlorite (Dakin's solution), bacitracin, neomycin and other aminoglycosides, and mupirocin. Many of these topical antimicrobial agents are also used in pediatric burn patients *(120)*. Although topical antimicrobial agents are frequently effective against microorganisms that are resistant to antibiotics, a recent study indicates that multiply-resistant microorganisms are more resistant to topical antimicrobial agents than are microorganisms that are not multiply resistant to antibiotics *(121)*.

It should be kept in mind that resistance to the topical antimicrobial agent(s) in use in a burn care facility may develop and may be associated with an outbreak of infections caused by the resistant microorganism(s). When confronted with an outbreak, healthcare epidemiologists and IPs should keep in mind the possibility that the epidemic strain may be resistant to the topical antimicrobial agent in use at the time of the outbreak. Testing the outbreak strain for resistance to the topical antimicrobial agent in use prior to onset of the outbreak should be considered *(100,102,103)*.

Systemic Antimicrobial Agents

The extensive use of systemically administered antimicrobial agents in burn care facilities for the treatment of burn wound infections frequently leads to selection of resistant microorganisms.

Continued use of the same antibiotics provides a selective advantage for these microorganisms, and they are able to proliferate and displace the susceptible microorganisms in and on the burn wounds of the patients in the unit. Continued colonization of patients with large numbers of multiply resistant microorganisms with an epidemiologic advantage may lead to an outbreak. Polk et al. *(104)* showed that systemically administered antimicrobial agents penetrate the avascular burn wound, and Mayhall et al. *(105)* observed that susceptible microorganisms in the wound may be rapidly replaced by highly resistant gram-negative bacilli.

Thus, prevention of the emergence of such resistance depends on the appropriate use of antimicrobial agents. Use of antibiotics should be limited to clearly indicated situations, and their selection should be based, when possible, on the results of cultures and antimicrobial susceptibility tests. During outbreaks, control efforts should include examination of prescribing patterns, and appropriate changes and limitations in the use of antibiotics should be implemented. Detection and treatment of superinfection of burn wounds by multiply resistant microorganisms may require culture of burn wound biopsies.

There are currently no data in support of administration of antimicrobial agents for prophylaxis of burn wound infections *(122)*. There is evidence that perioperative antibiotics may prevent bacteremia during burn wound excision *(123)*. However, the authors observed that there were no cases of bacteremia in patients who had wound cleansing or wound excision in the first 10 days post burn and a TBSA burn <40%.

Hypermetabolic Response

Modulation of the hypermetabolic response is important for decreasing infections in burn patients because of its immunosuppressive effects superimposed on the immunosuppression due to the burn injury (124). Early burn wound excision and grafting has had a major effect on reducing the hypermetabolic response. Other important interventions include thermoregulation by increasing the ambient temperatures in the operating rooms and patient rooms, aggressive early enteral feeding, and an early exercise training program. Other effective therapies have been developed for controlling other manifestations of the hypermetabolic response. The latter are well described in a recent review of the topic (124).

Insulin Therapy

Recently published data indicate that intensive insulin therapy has a significant impact in reducing infections, other morbidities, and mortality (125,126). In a study with historical controls, Hemmila et al. studied the control group using standard glucose control methods. In the second year of the study, patients had intensive insulin therapy with a goal to maintain blood glucose levels between 100 and 140 mg/dL. After adjusting for patient risk, the group with intensive glucose therapy had significantly fewer cases of pneumonia, ventilator-associated

pneumonia, bacteremia, urinary tract infections, and burn wound infections (125). A minimum glucose of 70 mg/dL was not associated with an increased risk of mortality. A blood glucose >200 mg/dL was associated with increased risk of complications. In a prospective randomized trial of intensive insulin therapy in severely burned pediatric patients, Jeschke et al. (126) observed that patients in the intensive insulin therapy group had significantly fewer infections. Mortality was 4% in the intensive insulin therapy group and 11% in the control group.

Burn Wound Excision and Closure

Theoretically, early excision and closure of burn wounds should diminish the incidence of burn wound infection. If early excision and closure does reduce the rate of burn wound infections, it could be considered an important modality for prevention of burn wound infections. However, there is no scientific evidence that such treatment of burn wounds does reduce infection rates. Several studies have shown apparent reductions in burn wound infection rates related to early burn wound excision and closure *(127–130)*. However, these studies suffer from a number of flaws such as use of small study populations, absence of randomization, use of historical controls, and failure to define burn wound infection or nonuniformity of definitions. These are important deficits, because many aspects of burn care improved while early excision and wound closure were being introduced.

There have been three randomized prospective studies of early burn wound excision and closure versus nonoperative or exposure treatment published. In a study in which patients with burns of <20% TBSA were randomized to either early excision and grafting or nonoperative treatment, Engrav et al. *(131)* make no mention of burn wound infection in either group. Sørensen et al. *(132)* randomized burn patients with burns of all sizes to either acute excision or exposure treatment. They observed a significantly lower rate of burn wound infections only in patients with burn wounds of 1% to 15% of body surface area. Herndon et al. *(133)* randomized patients with >30% TBSA second-degree and >20% TBSA third-degree burns to early excision or conservative therapy. They noted no difference in the number of septic days between patients treated with early excision and those treated conservatively. They specifically noted that early excision did not prevent septic episodes in large burns.

McManus et al. *(37)* have made the point that if excision of the burn wound is to be cited as the reason for improvement in the survival of burn patients, this conclusion can be validated only by studies that include concurrent controls. They further note that the extent to which the reduction in the rate of burn wound infections can be attributed to burn wound excision is unclear.

In spite of the fact that early burn wound excision has not been scientifically proven to be an effective modality for the prevention of burn wound infections, it is a widely held belief among burn surgeons that early burn wound excision and closure significantly reduces burn wound infection and mortality from thermal injury *(134–138)*. In the absence of randomized clinical trials, two recent publications provide evidence that early excision does reduce the incidence of burn wound infection *(139,140)*.

In the first study, the authors prospectively studied 20 children with burns *(139)*. Patients admitted to the authors' hospital within 24 hours of burn injury had early burn wound excision. Patients transferred from other hospitals at 7 ± 2 days had burn wound excision at the time of admission. At the time of burn excision, specimens were taken from excised burn eschar and excised burn wound bed for quantitative cultures. The 12 patients in the early excision group had less than approximately 10^4 CFU/g of tissue in burn eschar and less than approximately 10^2 CFU/g of tissue in the excised wound bed. For the eight patients in the late excision group, burn eschar had more than approximately 10^5 CFU/g and in some cases had 10^6 CFU/g of tissue. Bacterial counts in the excised wound bed were less than approximately 10^4 CFU/g of tissue.

None of the patients in the early excision group had burn wound infections or graft loss. In the late excision group, three patients had infections and graft loss and two patients had sepsis after surgical excision of the burn wound. High bacterial counts and infection rates were associated with delayed excision ($p < .01$). Although this study was not a controlled trial and differences in potentially important variables between groups of patients could not be controlled for, this study lends further support to the widely held belief that early excision significantly reduces the incidence of burn wound infections.

In the second prospective study, the authors investigated the effects of early versus delayed wound excision on hypermetabolism, catabolism, and sepsis in children with burns *(140)*. The authors measured resting energy expenditure, skeletal muscle protein catabolism, and the concentration of microorganisms in burn wound tissue. Patients were divided into three groups: an early group (arrival within 72 hours of injury), a middle group (arrival 3–10 days after injury), and a late group (arrival at least 10 days after injury). The authors noted increased muscle catabolism in 1 to 3 weeks in the middle and late excision groups compared to the early excision group. Sepsis appeared to increase as excision and aggressive feeding were progressively delayed among the treatment cohorts ($p = .07$). The concentration of microorganisms in quantitative cultures taken 1 week after initiation of surgical and nutritional therapy was progressively increased with treatment delay ($p < .05$). Again, although not a controlled study, the data from this investigation show the benefit of early burn wound excision for reducing burn wound infections and muscle catabolism. In the absence of controlled clinical trials, these two studies provide further evidence that early burn wound excision significantly reduces the incidence of burn wound infections. However, it remains unclear how early burn wound excision and wound closure affect the epidemiology of burn wound infections in burn care facilities.

Currently, the rationale for early burn wound excision and wound closure is based on observed improvements in the altered physiology due to thermal injury (35). The positive effect of burn wound excision amelioration of the abnormal physiologic states such as the hypermetabolic response likely contributes to improvement in the immune response, which may reduce the incidence of burn wound infection.

Selective Decontamination of the Digestive Tract

Selective decontamination of the digestive tract (SDD) has been suggested as a preventive measure for burn wound infections. It is postulated that the elimination of potentially pathogenic microorganisms from the gastrointestinal tracts of burn patients by the oral administration of nonabsorbable antibiotics will diminish colonization and infection of burn wounds.

The first of only two randomized studies included only 27 patients and found no evidence that SDD decreased or delayed the colonization of the burn wound by enteric microorganisms *(141)*. On the contrary, *Pseudomonas* appeared earlier on the wound and in blood cultures of the treated group when compared with the control group. Enteric microorganisms appeared earlier in the blood cultures of the treatment group than in those of the control group. Thirty-three percent of the treated group had complications severe enough that prophylaxis had to be discontinued early. One study of 48 patients was uncontrolled *(142)*, and another study of 91 patients compared two regimens for SDD but contained no placebo control group *(143)*. In a prospective, nonrandomized study, Jarrett et al. *(144)* assigned 20 patients to receive SDD and compared them to 10 patients assigned to receive no SDD. No placebo was used for the control group. All of these patients were also treated in a laminar airflow burn unit using strict reverse isolation techniques. These authors observed a significant delay in burn wound colonization in the SDD group, but no significant differences were found in burn wound biopsies that yielded positive results ($>10^5$ CFU/g of tissue) or in the occurrence of bacteremia, burn wound sepsis, urinary tract infections, pneumonitis, or cellulitis. Mackie et al. *(145)* studied 64 patients in a nonrandomized study wherein 31 patients given SDD were compared with 33 historical control subjects. They noted a marked reduction in positive fecal culture results for Enterobacteriaceae and *Pseudomonas* and a significant decrease in burn wound colonization with gram-negative microorganisms in the SDD group. In addition, they noted significant reductions in respiratory infections and in septicemia. The mortality rate was also significantly lower in the SDD group. The authors did not report any differences in burn wound sepsis. No increase in antimicrobial resistance was observed after introduction of SDD.

The best study on SDD published to date is that of Barret et al. *(146)*, who carried out a prospective, randomized, double-blinded, placebo-controlled clinical trial. The treatment regimen was a suspension containing polymyxin E, tobramycin, and amphotericin B. The suspension was given by a nasogastric tube four times a day for the duration of the study. The placebo solution was Ringer's lactate. Oral nystatin was administered as "swish-and-swallow" to prevent oral and esophageal candidiasis. Routine cultures of sputum, urine, blood, wound, stool, and gastric aspirates were taken on admission and twice weekly during the study. Eleven patients were randomized to the treatment group and 12 to the placebo group. There were no significant differences in infections at various sites and no significant differences in results of cultures between the two groups. There was however a significant difference in the occurrence of diarrhea (82% in the SDD group vs. 17% in the placebo group, $p = .003$).

More recently, de La Cal et al. *(147)* published a randomized, placebo-controlled, double-blind trial on SDD in critically ill burned patients. These investigators observed significantly fewer cases of pneumonia and urinary tract infections in the group that received prophylaxis. There was no difference in the rate of burn wound infections between the groups.

From the available published data, it must be concluded that SDD is unproven as an effective modality for prevention of burn wound infection. Further, the side effects of such therapy may well outweigh any benefit. Finally, data are insufficient to determine whether such prophylaxis will lead to selection of resistant microorganisms in burn care facilities.

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CHAPTER 26

Healthcare-Associated Eye Infections

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Worldwide, 314 million people are visually impaired and 45 million are blind (1). Cataracts account for nearly half of all cases of blindness, while uncorrected refractive error, glaucoma, and age-related macular degeneration (AMD) are the next three most common causes of vision loss worldwide (1). The most important infectious causes of blindness are trachoma and onchocerciasis, which cause 4% and 1% of blindness worldwide, respectively (1). Ophthalmia neonatorum due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis* blind several thousand children each year. Although 75% of worldwide blindness can be treated or prevented, approximately 90% of blind patients live in poverty and have limited access to healthcare.

Healthcare-associated eye infections are currently a small cause of vision loss worldwide, but will become increasingly important as access to healthcare improves. Cataract surgery, for example, would restore sight to over 20 million blind people worldwide and improve sight in many millions more, were this surgery available to them. A vision-threatening complication of cataract surgery is bacterial endophthalmitis, which occurs in approximately 0.1% of cataract surgeries in the developed nations. This is a small percentage but would be a large absolute number of cases if all needed cataract surgeries could be performed.

Regardless of the number of people affected, healthcare-associated eye infections cause significant morbidity in those patients affected. Sight is important to everyone, and losing sight to a preventable infection is a tragedy.

SURVEILLANCE DEFINITIONS

The Centers for Disease Control and Prevention (CDC) defines a healthcare-associated infection (HAI) as a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent or its toxin, provided that there is no evidence of the infection at the time of admission to the acute care setting *(2)*. The source of these infections may be exogenous or endogenous. Infections occurring in infants that result from passage through the birth canal, such as ophthalmia neonatorum (i.e., neonatal conjunctivitis), are also considered HAIs. An infection that occurs after surgery is considered HAI if it occurs within 30 days after the operative procedure if no implant is left in place, and within 1 year if an implant is placed "and the infection appears to be related to the operative procedure" *(2)*.

Eye-related HAIs are divided into only two categories by the CDC for reporting to the National Healthcare Safety Network (NHSN): (a) "conjunctivitis" and (b) "eye, other than conjunctivitis" *(2)*. For the second category, the eye infection must meet one of the following criteria: either (a) positive cultures of the anterior chamber, posterior chamber, or vitreous, or (b) at least two of the following three symptoms, eye pain, visual disturbance, or hypopyon (layer of white blood cells in the anterior chamber), *and* either physician diagnosis of eye infection, positive antigen test on blood (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*), or microorganisms cultured from blood *(2)*.

There are two areas of uncertainty in the CDC criteria. The first is that these surveillance criteria will identify nearly all eye-related HAIs, but not all. For example, a patient who develops candidemia from an indwelling central catheter may develop classic chorioretinal lesions due to fungemic seeding of *Candida* in the eye. This would be easily diagnosed as a *Candida* endophthalmitis by the ophthalmologist based on examination of the eye, but may be asymptomatic. A vitreous culture would not be necessary in this case, so there would be no intraocular cultures to fulfill the first criterion nor symptoms to fulfill the second, yet this case of *Candida* endophthalmitis would clearly be a HAI. We recommend including such cases as HAIs in local facility surveillance data even though they do not meet the CDC criteria outlined above.

The second area of uncertainty is whether to extend from 30 days to 1 year the window of time that a postcataract endophthalmitis case qualifies as an HAI. Nearly all cataract surgeries implant an intraocular lens (IOL), so the 1-year window would seem to apply. However, nearly all major studies of postcataract endophthalmitis use 6 weeks or less as the postoperative cutoff. For example, a major National Eye Institute–sponsored randomized trial of postcataract endophthalmitis used 6 weeks *(3)*.

POSTSURGICAL EYE INFECTIONS

Eye surgery is commonly performed in the United States, and each procedure may result in a postoperative HAI. Surgeries may be divided into those of the anterior segment

TABLE 26-1

Infections Following Eye Surgery

Surgery Type	*Infection*
Anterior segment surgery	
Corneal transplant	Keratitis, endophthalmitis
Keratoprosthesis (artificial cornea)	Keratitis, endophthalmitis
LASIK	Keratitis, endophthalmitis
Glaucoma surgery	
Filtering bleb	Blebitis, endophthalmitis
Ahmed shunt	Orbital abscess, endophthalmitis
Cataract surgery	Endophthalmitis
Posterior segment surgery	
Scleral buckle	
For retinal detachment repair	Orbital abscess, endophthalmitis
Intravitreal injections	
For AMD, DME	Endophthalmitis
Vitrectomy	
E.g., for diabetic retinopathy, retinal detachment repair	Endophthalmitis

LASIK, laser *in situ* keratomileusis; AMD, age-related macular degeneration; DME, diabetic macular edema.

(structures from the lens forward) and those of the posterior segment (vitreoretinal surgery). The major types of eye procedures and their infectious complications are listed in Table 26-1 and will be considered here.

Infections After Corneal Transplant

Corneal transplant, or keratoplasty, is performed in over 40,000 patients in the United States each year. The major indications for transplantation include keratoconus, pseudophakic bullous keratopathy, Fuch's dystrophy, herpetic corneal infection, and trauma *(4)*. In the United States, cadaver donor corneas are stored by local eye banks in an antibiotic-containing solution by protocols established by the Eye Bank Association of America (EBAA).

The traditional corneal transplant is a penetrating keratoplasty (PK), or full-thickness transplant. During this transplant procedure, the surgeon trephines a central disk from a donor cornea and uses this to replace the central disk of the patient's native cornea. The donor cornea is sutured to the residual rim of the patient's native cornea. The patient typically uses topical corticosteroid eye drops for months to years postoperatively to prevent rejection; many patients are continued on these indefinitely. Sutures are left in place for months to years. Healthcare-associated infections include donor–host transmission of systemic infections, keratitis (infection of the cornea), and endophthalmitis (infection of the vitreous).

Systemic donor infections have rarely been transmitted through PK. Premorbid bacterial sepsis in the donor appears to have no effect on the incidence of posttransplantation endophthalmitis in the recipient *(5,6)*. Diseases transmitted from donors to recipients via corneal transplantation that have been reported in the literature include three cases of Creutzfeldt–Jakob disease *(7,8)*, eight cases of rabies *(9–14)*, and two cases of hepatitis B virus from the same donor *(15)*.

The possibility of transmission of herpes simplex virus (HSV) from donor cornea to recipient has been demonstrated in some cases and suspected in others *(16,17)*. HSV in the donor cornea may cause primary graft failure and keratitis after transplantation *(18)*. Cases of healthcare-associated herpetic graft infection are rare, however. Other viruses that potentially could be transmitted through PK include human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), adenovirus, and rubella *(19)*. The EBAA requires review of the donor's medical history and recommends serologic screening for hepatitis B, hepatitis C, and HIV-1 and HIV-2 *(20)*. Patients who have died from progressive encephalopathy are also excluded as cornea donors. The recommended screening is highly effective. Eye banks affiliated with EBAA provided over 400,000 corneas during a 12-year period, and there were no cases of donor to recipient transmission of a systemic infectious disease during this time *(20)*.

A more common infectious complication after PK is infectious keratitis. Many cases occur beyond the postoperative time period and would not be considered healthcare-associated. A retrospective review of 885 transplants performed over a 16-year period revealed a 4% overall incidence of infectious keratitis, but a 1.5% incidence over the initial 2 months postoperatively *(21)*. A similar study of 285 patients who received transplants over a 5-year period found a 2.5% incidence of keratitis in the first 3 months, but an overall incidence of 7% *(22)*. Bacteriology in these studies was not specified by time of onset of infection, but *S. pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Serratia marcescens* were the most common pathogens. Risk factors for keratitis included persistent corneal epithelial defects and suture abscesses. Suture abscesses may develop months after surgery. One study of 18 suture abscesses found they developed 1 to 53 months postoperatively (mean: 21 months), so few would be considered healthcare-associated *(23)*. A recent study from India of 37 patients with suture-related corneal graft infection found that 31 developed the infection within 1 year postoperatively *(23a)*. The median time to onset of corneal infiltrates in the latter group was 87 days.

Endophthalmitis, or infection within the eye involving the vitreous and/or aqueous humor, is a rare but potentially devastating complication of PK that occurs in 0.2% to 0.4% of recipient eyes (24,25). Onset of symptoms is within 2 months of surgery, but most cases occur within 2 weeks. Both bacterial and fungal endophthalmitis have resulted from PK. In a US study of 1,010 corneal transplants, streptococci caused three cases and *Candida* one case of posttransplant endophthalmitis *(25)*. A study from Saudi Arabia reported a cluster of endophthalmitis that developed in four patients 1 week after PK (three *Enterococcus faecalis*, one *Candida glabrata*) *(26)*. Contamination of the donor corneas during storage was the likely source of infection. Endophthalmitis due to aminoglycoside-resistant *Alcaligenes* has been described, and this is significant because aminoglycosides are the only antibiotics present

in standard tissue storage media *(27)*. Eye bank corneal storage media contain either gentamicin (McCarey-Kaufman media) or gentamicin plus streptomycin (Optisol GS). No antifungal agent is present, and candidal endophthalmitis has occurred in patients who received *Candida*-contaminated corneal tissue *(28,29)*.

The source of infection in nearly all cases of post-PK endophthalmitis is thought to be microbial colonization of the donor cornea. Most corneal surgeons routinely culture the unused rim of the donor cornea at the time of surgery in an attempt to predict patients at risk for endophthalmitis. The value of this practice is controversial, as the incidence of culture-positive donor rims is high but post-PK endophthalmitis is low. This was illustrated by a study of 774 donor corneal rim cultures in which 5% were positive, yet no patient who received these corneas developed endophthalmitis *(30)*. The only two patients in this study who did develop endophthalmitis received culture-negative corneas. However, Wilhelmus and Hassan found that positive donor rim cultures did have predictive value (24). They performed a meta-analysis of studies involving 17,614 corneal grafts and found that 14% had positive donor rim cultures and only 0.2% developed endophthalmitis. However, using Bayesian analysis, they showed that positive donor rim cultures predicted a 1% endophthalmitis risk overall, and donor rims that were culture positive for fungi predicted a 3% probability of developing fungal endophthalmitis. The significance of a positive donor rim fungal culture was also seen in a study from New York Eye and Ear Infirmary *(29A)*. In that study, 13% of nearly 2,500 donor rim cultures were positive during a 5-year period, and 28 of these (8.6%) grew fungi. All were *Candida* species, and 4 of the 28 recipient eyes (14%) developed fungal infections. The Medical Review Subcommittee of the EBAA reviewed 121 culture-positive post-PK endophthalmitis cases reported to eye banks from 1994 to 2003, and found that 49% had concordant donor and recipient microbial isolates (29b). The prevalence of concordance was greater in fungal than bacterial post-PK endophothalmitis cases. Longer storage times increase the risk of developing post-PK endophthalmitis, and this may be especially true of *Candida* endophthalmitis. Another study from the EBAA found that the chance of developing fungal endophthalmitis was 3.4 times that of bacterial endophthalmitis when donor corneas had been preserved 4 days or longer *(29C)*. It is unknown whether prophylactic antifungal eye drops should be prescribed to eyes that receive donor corneas with rim cultures positive for fungi, but these studies suggest that may be a consideration.

New Corneal Transplantation Techniques In the past several years, new techniques have been developed that allow transplantation of only a portion of donor cornea to replace the specific level of diseased cornea in the patient's eye. Some patients have an abnormality of their corneal endothelium, the single-cell-thick layer of the cornea that abuts the aqueous humor. Conditions that require endothelial replacement include Fuch's endothelial dystrophy, pseudophakic bullous keratopathy, and failed previous graft. These patients may be helped by a posterior lamellar keratoplasty procedure, such as Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) or Descemet's Membrane Endothelial Keratoplasty (DMEK). The first procedure, DSAEK, has become the preferred treatment for endothelial dysfunction over PK, because it allows faster visual recovery and retains the strength of the eye better than PK. In 2007, 85% of corneas provided by the EBAA for patients with endothelial dysfunction were used in endothelial keratoplasty procedures *(31)*. The second procedure, DMEK, was first used in humans in 2006 *(32)*. A recent prospective multicenter study found that DMEK provided a higher rate of 20/20 vision compared with DSAEK, although donor preparation and attachment were more challenging than that with DSAEK *(31)*. A case each of *Candida* keratitis and endophthalmitis has been reported after DSAEK *(33,34)*.

Other patients have a surface abnormality but a normal corneal endothelium; these patients may need only the anterior layers of their cornea replaced, by Deep Anterior Lamellar Keratoplasty (DALK). In DALK, the patient's corneal endothelium is functional and only the more superficial layers require transplanting. With DALK, banked donor corneas that would be unsuitable for PK due to endothelial deficiencies can be utilized, or even the same cornea that supplied the endothelium for DMEK could supply the anterior layers for DALK. In a study from France, nearly 50% of donor corneas at one eye bank would have been unusable for PK, but over 70% of these were used for DALK *(35)*.

Eye bank technicians now routinely dissect corneas for DSAEK. This may increase the risk of contamination of tissues to airborne bacteria during microkeratome processing (36).

Infections After Keratoprosthesis (Artificial Cornea)

A keratoprosthesis (KPro) is an artificial cornea implanted in eyes that are blind from corneal disorders but in whom corneal transplants have failed. A major complication of KPro is endophthalmitis, which occasionally occurs during the first year postoperatively so would be considered healthcare associated, but usually occurs abruptly years later. It is similar in that regard to bleb-related endophthalmitis (see below). A widely used type of KPro is the Boston KPro, a plastic implant shaped like a collar button that replaces the central part of a corneal transplant. The rate of endophthalmitis in patients with a Boston KPro is now very low since these patients use long-term daily prophylactic antibiotic eye drops (e.g., vancomycin plus a quinolone) (37).

Infections After Laser *In Situ* Keratomileusis

Laser *in situ* keratomileusis (LASIK) is one of the most commonly performed eye surgeries. Unlike other eye surgeries, LASIK is performed in patients who have normal eyes except for refractive error, i.e., the need for glasses. Over 1 million LASIK procedures were performed in the United States in 2000, up from 400,000 procedures in 1998 and 200,000 in 1997 *(38,39)*. The LASIK uses a microkeratome to cut a thin, hinged flap across the corneal surface, exposing the corneal stroma beneath. A laser then ablates some of this central stroma and the flap is replaced, leaving a flattened cornea. The procedure is often performed using only semisterile technique (e.g., the microkeratome blade is sterile but the microkeratome handle is not).

The procedure is an outpatient procedure and is often performed in free-standing LASIK centers. Many centers are owned by the ophthalmologist who performs the procedures, so underreporting of complications is likely.

The most common complication of LASIK is keratitis, both infectious and noninfectious. In a study from Salt Lake City, Utah, of approximately 10,500 LASIK procedures, the incidence of post-LASIK keratitis was 2.66%, and 88% of these cases were noninfectious *(40)*. Most noninfectious keratitis cases in this study and others were due to diffuse lamellar keratitis (DLK). This syndrome, also called "sands of the Sahara" because of the granular appearance of the corneal flap/stroma interface, occurs in 1% to 5% of eyes *(39)*. The etiology is unknown, and cultures are negative. One outbreak in 52 patients in which cultures were negative was thought to be related to endotoxins *(41)*. Sterilizers used at the center were found to have reservoirs contaminated with gram-negative bacterial biofilms, and it was postulated that these biofilms produced endotoxins that contaminated the instruments during sterilization.

Infectious keratitis occurred in 0.3% of eyes in the Utah study, and viruses caused 70% of these 33 cases *(40)*. All 18 cases (55%) due to adenoviral keratitis recovered 20/20 vision, while all 5 (15%) of the eyes with herpes simplex keratitis lost one to two lines of visual acuity. Ten cases (30%) had a bacterial, fungal, or parasitic etiology. A study of 204,586 LASIK procedures from a private ophthalmologic institution with 19 centers in Spain found that infectious keratitis developed in 72 eyes (63 patients) during the first 6 months postoperatively, for an incidence of 0.035% (42). A majority (60%) of patients developed symptoms within 7 days of the procedure; the mean time to presentation was 16 days. Cultures were obtained in 54 eyes and were positive in 21, and all were due to gram-positive bacteria: *S. epidermidis* (nine cases), *S. pneumoniae* (eight cases), *viridans* streptococci (two cases), *S. pyogenes* (one case), and *S. aureus* (one case). There were no case clusters in this study. Khan et al. *(39)* reviewed the world literature through 2001 and found that in the 31 eyes with positive cultures, rapidly growing nontuberculous mycobacteria, primarily *Mycobacterium chelonae*, accounted for 29%. *S. aureus* (31%) and molds such as *Aspergillus* and *Curvularia* (16%) were other important etiologies, although the high incidence of molds likely reflected the contributions of reports from tropical areas. Nontuberculous mycobacteria and *S. aureus* were also the major pathogens in a study of 13 patients (15 eyes) with post-LASIK keratitis referred to an eye institute in Miami from centers in Florida and South America *(43)*. Nontuberculous mycobacteria (e.g., *M. chelonae*, *Mycobacterium abscessus*) caused six of 15 cases, whereas *S. aureus* caused four. Two cases involved gram-negative bacilli (*Pseudomonas*, *Stenotrophomonas*). Excluding two patients with late (>6 months) onset of keratitis due to molds and related to trauma, patients developed keratitis symptoms an average of 16 days postoperatively (range 2–65 days).

Nontuberculous mycobacteria have been the cause of several outbreaks. Freitas described an outbreak of 10 cases of *M. chelonae* that occurred in a center in Brazil during a 2-week period in 2000 *(44)*. Corneal infiltrates appeared during the third postoperative week. The CDC investigated a California cluster of *M. chelonae* post-LASIK keratitis and then emailed members of the American Academy of Ophthalmology to solicit reports of other cases of nontuberculous mycobacterial keratitis *(45)*. Forty-three additional cases were reported, including 31 that were part of 2 unrelated LASIK-associated outbreaks.

Post-LASIK *S. aureus* keratitis likely represents contamination from normal colonizing eye flora, and the incidence may be increased in patients with chronic meibomian gland dysfunction (e.g., marginal blepharitis). These patients should be free of any signs of eyelid disease at the time of the procedure to minimize infectious complications. The nontuberculous mycobacterial infections likely represent environmental contamination at the time of the procedure. For this reason, some authors recommend that LASIK be performed with sterile technique, including sterile instruments, sterile plastic bags covering portions of the laser that can't be sterilized, sterile gloves and drapes, eyelid antisepsis with povidone iodine, and prophylactic topical antibiotics *(43)*.

A rare complication after LASIK is endophthalmitis. A recent case was reported following a retrobulbar injection of saline to assist with globe suction by the microkeratome *(46)*. Ten days postoperatively, the patient presented with visual acuity of count fingers and presumed bacterial endophthalmitis. At surgery, a perforation site was found in the inferonasal retina. Following intravitreal antibiotic therapy, vision returned to 20/20.

Infections Related to Glaucoma Surgery

Glaucoma that is refractory to medical therapy may be controlled by placement of a filtering bleb. This is a surgically created defect in the sclera that allows excess aqueous to filter out of the eye and into the systemic circulation. The bleb may become infected (blebitis) and bacteria may rapidly enter the eye and cause endophthalmitis. Bleb-related endophthalmitis usually occurs abruptly, months to years postoperatively. Early-onset cases are rare. One study of 988 procedures in China found only one case of early-onset infection *(47)*. A retrospective review of 49 cases found that endophthalmitis developed an average of 2 years after bleb placement (range 1 month to 8 years) *(48)*. Most cases of bleb-related endophthalmitis are therefore not considered HAIs.

Another way to control severe glaucoma is through use of glaucoma drainage implants, such as the Ahmed shunt. These plastic devices have a tube, inserted into the anterior chamber, that directs aqueous humor out of the eye and into a perforated reservoir ("plate") sutured to the superior surface of the globe. Aqueous humor then leaks slowly out of this reservoir into the overlying conjunctiva and thereby the systemic circulation. Endophthalmitis is a rare complication of glaucoma drainage implants, and as in filtering blebs, most cases occur beyond the postoperative period so are not HAIs. In a retrospective study of Ahmed shunts placed in 542 eyes between 1994 and 2003 at one eye hospital in Saudi Arabia, endophthalmitis had developed in 9 eyes (1.7%) *(49)*. Eight of the nine cases occurred more than 6 weeks postoperatively (range 30–330 days). *S. pneumoniae*, other streptococci, and *H. influenzae* were the primary pathogens, accounting for six of the infections, similar to the situation in bleb-related endophthalmitis.

Postcataract Endophthalmitis

Cataracts are the leading cause of blindness worldwide and affect nearly half of all people over age 65. A cataract is a clouding of the lens, and this occurs naturally over time with exposure to ultraviolet light. Other factors may also lead to cataracts, including trauma, diabetes, chronic use of corticosteroids, and chronic inflammation in the eye (e.g., uveitis).

Cataract Surgery Cataract surgery is one of the most common surgical procedures performed in the United States, with over 2 million cases annually. Surgery has been performed on an ambulatory basis since 1985, when Medicare instituted a policy that covered only outpatient cataract surgery. Surgery involves making a small incision through either the sclera or cornea, removing the native lens pulp (leaving the posterior lens capsule intact), and replacing it with a synthetic IOL. The most common technique for native lens removal is phacoemulsification, in which the lens is ultrasonically broken up and aspirated. This allows for a very small incision that may be left unsutured, as it self-seals. "Clear cornea" surgery, where the incision is made through the cornea rather than tunneled through the sclera, was first described in 1992 but is now commonly performed. The incision is small (4 mm or less in width) and self-sealing. The stroma of the cornea remains swollen for up to 24 hours postoperatively so aids in this sealing process *(50)*.

Incidence, Pathophysiology, Risk Factors for Endophthalmitis Endophthalmitis is the major infectious complication of cataract surgery, occurring in approximately 0.1% of cases (range 0.08–0.3%) *(51–54)*. This incidence has been stable for decades. Onset of symptoms is usually within days of surgery: 75% present within 1 week of surgery. Symptoms include eye pain, redness, and decreased vision, but the patient otherwise feels well. Patients are afebrile, the white blood count is normal or only slightly elevated, and blood cultures are negative.

Nearly all cases are due to microorganisms introduced into the aqueous humor at the time of surgery from the patient's own ocular surface flora. Contamination of the aqueous humor during surgery with surface flora is common, with between 8% and 43% of aqueous cultures positive at the end of surgery in uncomplicated cases *(55–58)*. Endophthalmitis is rare, however, presumably because of aqueous turnover rate (every 100 minutes) and the immune system's ability to clear small inocula of bacteria from the aqueous *(59)*. The vitreous is gel-like and permanent, so it is much less resistant to infection than the aqueous.

Risk factors for developing postcataract endophthalmitis include surgical complications, such as inadvertent bleb creation, wound leak, or posterior capsule break. The last allows communication with the vitreous ("vitreous wick"), increasing the risk of endophthalmitis 14-fold *(60)*. Clear corneal incisions may carry a higher risk of postoperative endophthalmitis than does traditional scleral tunnel surgery *(61)*, although clinical features, microbiology, and outcomes of endophthalmitis resulting from either type of incision are similar *(62)*. In one large European study, the use of clear corneal incisions was associated with a 5.88-fold increase in risk over scleral tunnel incisions *(63)*. That study also found that the use of a silicone IOL rather than acrylic IOL had a threefold increased risk of developing endophthalmitis.

Microbiology The bacteriology is well defined. In a study of 420 patients with acute postcataract bacterial endophthalmitis, cultures of vitreous or aqueous were negative in 30% (*3*,64). In the 70% with positive cultures, gram-positive cocci caused 94% of cases, with coagulase-negative staphylococci the most common etiology (70% of culture-positive cases). *S. aureus* (10%), streptococci (9%), and gram-negative bacilli (6%) were other causes. Visual outcome depends on the etiology, with streptococci of any type producing the worst outcomes, followed by *S. aureus* and gram-negative bacilli. Infections due to coagulase-negative staphylococci, or culture-negative cases, fare best.

Chronic Postcataract Endophthalmitis While most cases of postcataract endophthalmitis present acutely, there are rare cases that present subacutely or chronically. These are usually due to *Propionibacterium acnes* or fungi. Cases due to *P. acnes* usually present with low-grade, chronic inflammation in the aqueous that mimics anterior uveitis. The diagnosis may not be suspected until months postoperatively. Fungal endophthalmitis following cataract surgery is rare, but more common in tropical countries than those with temperate climates.

Outbreaks Clusters of endophthalmitis cases due to contaminated instruments or ophthalmic solutions have been described, but are rare. Three outbreaks due to *P. aeruginosa*, two in Europe and one in the United States, have been linked to use of a contaminated phacoemulsifier *(65–67)*. In all three outbreaks, the outbreak pathogen was found contaminating the internal pathways of the phacoemulsifier. Intrinsically contaminated fluids or lenses used in ocular surgery have led to outbreaks with *P. aeruginosa* or *Bacillus* species *(68)*, *P. aeruginosa (69)*, or *Paecilomyces lilacinus (70,71)*. Contamination of trypan blue solution used to mark the anterior lens capsule during cataract surgery in Spain led to an outbreak of 6 cases of *Pseudomonas* postcataract endophthalmitis at one center within 4 months *(72)*. A cluster of 20 cases of a multidrug-resistant *Pseudomonas* endophthalmitis occurred during a 2-month period in 2008 at an eye center in southern India *(73)*. *Pseudomonas* was recovered from the phacoemulsifier's tubing, the povidine-iodine solution, and the operating room's air conditioning system; most strains tested similar to the air conditioner's strains. Contamination of humidifier water in a ventilation system with *Acremonium kiliense* led to four cases of endophthalmitis in an ambulatory surgical center *(74)*. *Aspergillus* endophthalmitis occurred in five patients during a period of hospital construction, which again demonstrates the need to follow standard guidelines during renovation or new construction *(75)* (see Chapter 83). An outbreak in Thailand from 1997 to 1998 in which 9.4% of patients developed postoperative endophthalmitis was determined to be due to inadequate sterilization procedures and use of multidose intraocular irrigating solution *(76)*.

Prevention The optimal method to prevent postcataract endophthalmitis is unknown. A number of nonrandomized or retrospective studies have tried to determine efficacy of various interventions. Speaker and Menikoff *(77)*, in an open-label nonrandomized trial, compared 5% povidone-iodine topical solution as prophylaxis in one operating room suite with silver protein solution prophylaxis in another suite. Surgeons continued to use "their customary prophylactic antibiotics." The study found a significantly lower incidence of culture-positive endophthalmitis in the suite using the povidone-iodine (0.06% vs. 0.24%). Since this study was published, it has been generally accepted that 5% povidone-iodine solution should be used on the conjunctiva during preoperative preparation. Whether the iodine should be then flushed with sterile saline is unknown.

Other nonrandomized studies have advocated intraoperative irrigation of the anterior chamber with antibiotics, antibiotic injection into the aqueous at the end of the case, postoperative subconjunctival antibiotic injections, and perioperative topical antibiotics. Preoperative and postoperative topical antibiotics are routinely used, with topical moxifloxacin and gatifloxacin most commonly used for this purpose in the United States A retrospective study of 20,000 cataract surgeries performed at the John A. Moran Eye Center at the University of Utah found an overall incidence of postcataract endophthalmitis of 0.07%, with no significant difference between groups that used moxifloxacin versus gatifloxacin eye drops *(78)*. In another retrospective study, the Utah group found that prophylaxis with fourth-generation quinolone eye drops was more effective than third-generation quinolone eye drops (ofloxacin, ciprofloxacin) in preventing postcataract endophthalmitis, 0.06% versus 0.2%, $p = .001$ *(79)*.

There are few prospective randomized trials evaluating optimal prophylaxis for cataract surgery, since a large number of patients would need to be enrolled given the low incidence of postcataract endophthalmitis (0.1%). Recently, a prospective trial involving 24 eye clinics in 9 European countries (Austria, Belgium, Germany, Italy, Poland, Portugal, Spain, Turkey, and the United Kingdom) has been published *(80)*. This study by the European Society of Cataract & Refractive Surgeons (ESCRS) used a 2×2 design and placebo control to evaluate the efficacy of (a) intracameral injection of cefuroxime (1 mg in 0.1 ml normal saline) at the end of the cataract surgery, and/or (b) perioperative levofloxacin eyedrops. The study was started in September 2003 and stopped early, January 2006, due to interim analysis showing clear benefit from intracameral cefuroxime injection. The incidence of endophthalmitis in the control group (23 cases per 6,862 surgeries, 0.34%) was nearly five times higher than in the group that received intracameral cefuroxime (5 cases in 6,836 surgeries, 0.07%), and this difference was significant ($p = .002$). This includes both culture-positive and culture-negative cases; the difference was even greater if only culture-positive cases were considered. Of note, the incidence of endophthalmitis in the control group was higher than most previously published studies. The use of perioperative levofloxacin eye drops was associated with a small reduction in risk, but this was not statistically significant.

Environmental controls should include standard operating room environmental air controls (i.e., at least 15 air exchanges per hour with at least 3 air changes per hour being fresh air, air filtered through filters of at least 90% efficiency). All operative equipment and irrigating fluids should be sterile prior to use, and the use of multiple dose dispensers should be avoided or limited.

Scleral Buckle Infections

Retinal detachments occur with an incidence of 18 per 100,000 persons in the United States (81). One method used to reattach the retina is a scleral buckling procedure, a procedure popularized over 50 years ago. In this surgery, a single long silicone sponge or solid band of silicone is placed around the eyeball encircling it like a cinch, or segments of silicone sponges are sutured to the episclera. In each case, the underlying sclera is pressed inward against the detached retina, allowing reattachment. Silicone is the primary material used for scleral buckles. Hydrogel implants were also available between 1979 and 1994 but then were removed from the market by the manufacturer; late orbital complications years later due to continued swelling of the material have been described *(82)*.

Healthcare-associated scleral buckle infections often occur acutely. Patients typically present with signs of orbital cellulitis, with eye pain, chemosis, and proptosis. Vision may be decreased due to sympathetic vitreous inflammation. The vitreous is usually sterile, although in severe cases endophthalmitis may also be present. The incidence of acute scleral buckle infections is 0.4% to 0.8%, and was 0.6% in one large retrospective study *(83)*. In this study of 4,480 scleral buckle procedures, 15 patients developed severe infections 4 to 47 days postoperatively. The main pathogens were *S. aureus* (58% of the 12 culture-positive cases) and *S. epidermidis* (25%). Staphylococci are the major pathogens in other studies as well *(84)*. Atopic dermatitis may increase the risk of postoperative *S. aureus* scleral buckle infections. In a study from Japan of 293 eyes with scleral buckles placed between 1995 and 1997, 7 developed acute infections and all were due to methicillin-resistant *S. aureus* (MRSA). Six of these seven patients had atopic dermatitis, giving an infection rate of 19% in patients with atopic dermatitis, but only 0.4% in those without this condition *(85)*.

Scleral buckle infections may also present subacutely, typically with scleral buckle extrusion through the conjunctiva months to years postoperatively *(86)*. In many cases of extrusion, mechanical erosion occurred first and the exposed buckle became secondarily infected. In some cases, however, an indolent infection of the buckle is responsible for extrusion. It may be difficult to determine whether infection played a primary or secondary role in these subacute and chronic cases.

Two recent retrospective series of explanted scleral buckles, one from India and the other from Wisconsin, unfortunately do not report the interval from surgical placement to time of removal *(87,88)*. In the study from India of 66 patients who underwent scleral buckle removal for infection, 83% of buckles were culture positive. Although *S. epidermidis* was the most common isolate, similar to other studies, fungi were isolated in 15%, a much higher rate than other studies.

Prophylactic preoperative intravenous antibiotics are not routinely used in scleral buckle surgery, and there are

no studies evaluating the efficacy of systemic antibiotic prophylaxis. Scleral buckles are often soaked in antibiotics just prior to placement intraoperatively, based on the results of a 1974–1981 prospective study *(89)*. In this study, half of the patients received Silastic sponges ("soft" scleral buckles) that had been soaked for 30 minutes in penicillin plus gentamicin solution, and half received unsoaked sponges. More patients who received unsoaked sponges than soaked sponges developed acute infections (1/450 vs. 9/471, $p = .01$). This study has not been repeated. A retrospective study of patients who received a scleral buckle that either had (389 cases) or had not (735 cases) been soaked in a gentamicin solution for 30 minutes preoperatively found no cases of acute infection in either group *(90)*.

Infections after Intravitreal Injections

Injections of medicines directly into the vitreous are increasingly used to treat retinal diseases. Two such diseases are AMD and diabetic retinopathy. Both diseases are major causes of blindness, particularly in Western nations. Monthly injections of the anti-VEGF (vascular endothelial growth factor) drug ranibizumab (Lucentis) into the vitreous prevent visual loss in "wet" AMD and actually improve vision in some patients. The less expensive parent anti-VEGF drug, bevacizumab (Avastin), may be equally effective. Ranibizumab injections plus laser photocoagulation were recently found to be very effective in halting vision loss in diabetic patients with macular edema. Typically, topical povidone-iodine drops are applied to the eye prior to injection and a sterile lid speculum is used. The incidence of endophthalmitis following an intravitreal injection is approximately 0.02% to 0.1% (*91*,92).

Infections after Vitrectomy

Vitrectomy, or surgical removal of the vitreous humor, is performed for a number of indications. A retinal detachment may be repaired by removal of the vitreous by vitrectomy, followed by instillation of a gas bubble or silicone oil. Vitrectomy is also used to remove vitreous hemorrhage, commonly caused by diabetic retinopathy. Endophthalmitis following vitrectomy is rare. One multicenter study of over 12,000 vitrectomy surgeries found 18 postoperative endophthalmitis cases, for an incidence of 0.07% *(93)*. Coagulase-negative staphylococci caused seven of these cases. Another study of a single center over 20 years found 6 cases in over 15,000 surgeries (0.04%), with the 5 culture-positive cases due to *S. aureus* (3 cases), *Proteus*, and *Pseudomonas (94)*.

HEALTHCARE-ASSOCIATED OCULAR INFECTIONS NOT RELATED TO SURGERY

Conjunctivitis

Conjunctivitis is a common condition worldwide. It is characterized by conjunctival injection ("pink eye"), discharge, and a sensation of eye irritation or pruritis. However, true eye pain is not present unless there is also involvement of the cornea, or "keratoconjunctivitis." Vision is normal, unless the cornea is also involved. A watery conjunctival discharge suggests a viral or allergic etiology, while a purulent discharge suggests a bacterial process. Hyperacute conjunctivitis, due to *N. gonorrhoeae* or *N. meningitis*, is rare but is characterized by such a copious discharge that reappears as soon as it is wiped away.

Healthcare-associated conjunctivitis falls into two major groups: ophthalmia neonatorum (also known as conjunctivitis of the newborn), and healthcare-associated viral conjunctivitis.

Ophthalmia Neonatorum

Ophthalmia neonatorum refers to conjunctivitis that develops during the first month of life. According to the World Health Organization, this includes both microbial and chemical causes *(95)*. However, the most important causes are *N. gonorrhoeae* and *C. trachomatis*, and the term "ophthalmia neonatorum" is often used to refer specifically to these infections, so "conjunctivitis of the newborn" is a more inclusive term. Other causes of conjunctivitis of the newborn include bacterial microbes, herpes simplex, and chemical conjunctivitis due to the instillation of silver nitrate into the newborn's eye. The relative importance of each of these etiologic agents around the world depends on the prevalence of *C. trachomatis* and *N. gonorrhoeae* genital infections in women giving birth and whether silver nitrate prophylaxis is used. Silver nitrate 1% solution causes some chemical conjunctivitis, although much less than Crede's original 2% solution *(95)*. The United States has used erythromycin ointment for years both because of the concern for chemical conjunctivitis from silver nitrate and because the latter is not active against Chlamydia. Chemical conjunctivitis following prophylaxis with tetracycline or erythromycin is rare. Silver nitrate ophthalmic solution is no longer available in the United States.

Clinical Features of Infection *N. gonorrhoeae* causes hyperacute conjunctivitis with marked purulent exudate, chemosis, and injection. Severe complications include corneal ulceration and perforation, which may lead to visual loss. Inadequate prophylaxis may delay the onset of disease or minimize its severity. *C. trachomatis* conjunctivitis is characterized by mild unilateral or bilateral purulence, lid edema, conjunctival injection, and profuse exudate. Onset of conjunctivitis is typically 5 to 12 days after birth. Newborns lack lymphoid tissue and fail to develop an acute follicular conjunctivitis, which is typical of the adult infection. Chlamydial conjunctivitis may be associated with pneumonia, which has a subacute presentation, with onset usually between 1 and 3 months after birth.

Prophylaxis The latest CDC comprehensive guidelines for treatment and prevention of sexually transmitted diseases in the United States were published in 2006 *(96)*. These guidelines recommended applying either erythromycin ophthalmic ointment 0.5% or tetracycline ophthalmic ointment 1% (single application each eye) for prophylaxis against gonococcal ophthalmia neonatorum. The application should be given as soon as possible after delivery, preferably in the delivery room. Infants born by caesarian section should also receive prophylaxis, as infection may occur by the ascending route as well. Tetracycline ophthalmic ointment became unavailable in the United States after publication of the 2006 CDC guidelines,

so currently only erythromycin ophthalmic ointment 0.5% is recommended by the CDC. This is well tolerated by the infant. There was a shortage of this product in 2009, and the CDC recommended azithromycin ophthalmic solution 1% during this shortage *(97)*. The CDC initially (August 31, 2009 letter) recommended that if neither erythromycin ophthalmic ointment nor azithromycin ophthalmic solution were available, then either gentamicin ophthalmic ointment 0.3% or tobramycin ophthalmic ointment 0.3% could be used *(97)*. The Food and Drug Administration (FDA) and CDC subsequently received reports of eyelid swelling and dermatitis from gentamicin ophthalmic ointment (no other adverse effects were seen in the eye or orbit), and by October 21, 2009, the CDC advised limiting the contact exposure of gentamicin ophthalmic ointment on the skin. The update of March 4, 2010 by the CDC notes that there is no longer a shortage of erythromycin ophthalmic ointment 0.5%, so other methods of prophylaxis recommended during the shortage should no longer be used.

Silver nitrate 1% solution is not used in the United States but may be used in other parts of the world for prophylaxis against ophthalmia neonatorum. This solution often causes a chemical conjunctivitis in the newborn, however, and is expensive. Expense is a major consideration worldwide. A World Health Organization 2001 publication listed costs of the following in the developing world: 5 mL of povidone-iodine $0.10, tetracycline $0.31, erythromycin $0.74, and one dose of silver nitrate $7.30 *(95)*. Povidone-iodine 2.5% is very effective against both *N. gonorrhoeae* and *C. trachomatis* conjunctivitis, and causes less chemical conjunctivitis than silver nitrate. It does cause a burning sensation, so recent studies have looked at a 1.25% solution of povidone-iodine, which appears to be very well tolerated *(98)*. The CDC does not recommend povidone-iodine due to concern that the detergent-containing formulation will be mistakenly used.

Screening of pregnant women for gonorrhea and *Chlamydia* infections is recommended to prevent ophthalmia neonatorum. Topical erythromycin ophthalmic ointment 0.5% and silver nitrate prevent gonococcal conjunctivitis in the newborn but do not prevent transmission of *C. trachomatis* from mother to infant. Infants with conjunctivitis during the first 30 days of life should have testing for chlamydial infection, and if present, treatment with 2 weeks of oral erythromycin *(96)*. Early diagnosis and adequate therapy of ophthalmia neonatorum, especially gonococcal infections, can prevent corneal ulceration and blindness. Infants born to women with untreated gonococcal infections should receive one dose of parenteral ceftriaxone. Infants who have gonococcal ophthalmia should be hospitalized.

Epidemic Keratoconjunctivitis

Viral conjunctivitis may be caused by several different viruses. Acute hemorrhagic conjunctivitis is caused by enterovirus type 70 and coxsackievirus type A 24. Pharyngoconjunctival fever, an acute and highly infectious illness, is characterized by fever, pharyngitis, and acute follicular conjunctivitis. It is caused by adenoviruses, most commonly types 3, 4, and 7, but has also been associated with types 1, 5, 6, and 14. Epidemic keratoconjunctivitis (EKC) is the most serious of the adenoviral eye infections, because it typically involves the cornea (keratitis) as well as the conjunctiva, and consequently can lead to corneal scarring. The cornea has many nerve fibers, so EKC is typically painful. As the name implies, EKC is associated with healthcare-associated outbreaks. Infection control measures are important in preventing such outbreaks: the virus has been shown to be very hardy, surviving for up to 2 months on door handles that have not been properly disinfected.

EKC has been most commonly associated with adenovirus types 8 and 19, but also has been reported with other serotypes, including types 2 to 4, 7 to 11, 14, 16, 29, 37. All types produce a similar clinical picture, but types 8 and 19 are much more likely to be involved in large epidemics.

Attack Rates and Symptoms The prevalence and incidence of EKC are unknown *(99)*. During outbreaks in medical facilities, attack rates as high as 25% have been reported (Table 26-2). More cases are reported in the fall and winter months. The incubation period is approximately 8 days, and disease is unilateral initially, although most cases become bilateral via self-contamination. In patients who progress to bilateral disease, the second eye becomes involved in 4 to 5 days. Ford et al. *(99)* have summarized the symptoms and signs of EKC reported in the literature. Ocular symptoms included a foreign body sensation (43%), photophobia (15%), lacrimation (99%), and eye redness (98%). Extraocular symptoms included fever/malaise (1–33%), upper respiratory tract symptoms (1–63%), diarrhea (2–3%), nausea/vomiting (2–14%), and myalgias (2–12%). Ocular signs include conjunctival hypertrophy (95–96%), chemosis (26–50%), pseudomembranes (1–38%), focal epithelial keratitis (55–65%), diffuse epithelial keratitis (42%), stromal edema (18–47%), anterior uveitis (11%), preauricular adenopathy (15–94%), and decreased visual acuity (17–78%). Keratitis often begins 3 to 4 days after the onset of corneal opacities (infiltrates). Usually, these infiltrates resolve within several months and do not result in permanent loss of vision.

Transmission Large outbreaks of EKC have occurred in medical facilities *(100–129)* (Table 26-2). The major modes of transmission are person to person via the hands of medical caregivers and ophthalmic instruments (e.g., tonometers, slit lamps) or ophthalmic solutions (e.g., wash stations, topical anesthetic solutions). Infected healthcare workers may serve as both a reservoir for infection and a means of transmission of infection to other patients. In more than half of the outbreaks summarized in Table 26-2, a healthcare worker became infected. The direct cost of a single outbreak was calculated as approximately $30,000 *(124)*.

Adenovirus type 8 is extremely hardy when deposited on environmental surfaces, and this accounts for the fact that fomites play a significant role in healthcare-associated transmission. Gloves should be worn for contact with patients infected with adenovirus for two reasons. First, hand washing with soap has been shown to be ineffective in eliminating infectious virus *(113)*. Second, adenovirus can be recovered from the hands of approximately 50% of patients with adenoviral conjunctivitis *(130)*. Adenovirus can be recovered from plastic and metal surfaces for more than 30 days *(131)*.

TABLE 26-2

Selected Outbreaks of Epidemic Keratoconjunctivitis in Medical Facilities, 1970–2010

Reference	*Year of Outbreak*	*Site*	*Number of Infections*	*Attack Rate (%)*	*Risk Factors/ Environmental Sources*
CDC (*100*)	1974	Hospital ward and eye clinic	20	—	Tonometer
Vastine et al. (*101*)	1974–1975	Eye infirmary	52	—	—
Tullo and Higgins (*102*)	1977–1978	Eye hospital	17	—	—
Keenylside et al. (*103*)	1977–1978	Ophthalmologist's office	83	—	—
D'Angelo et al. (*104*)	1977–1978	Ophthalmologist's office	86	29.4	Ophthalmic procedures (e.g., tonometry) Ophthalmic solutions Physician contact
		Nursing home	16	2.5	—
		Nursing home	6	25.0	—
Darougar et al. (*105*)	—	Eye hospital	13	—	Minor surgical procedures
Nagington et al. (*106*)	1979	Eye department	14	—	—
Richmond et al. (*107*)	1981	Emergency room	200	—	—
Buehler et al. (*108*)	1981	Ophthalmologist's office	39	1.8	Contact with specific caregivers[a] Invasive procedures[a] Tonometry[a] Foreign-body removal[a]
Reilly et al. (*109*)	1984	Eye infirmary	186	—	—
Warren et al. (*110*)	1985–1986	Eye infirmary	110	0.47	Pneumotonometry[a]
Takeughi et al. (*111*)	1985	Hospital	30	—	—
Insler and Kern (*112*)	1986	Ophthalmologist's office	24	—	—
Jernigan et al. (*113*)	1986	Eye clinic	126	7.3	Pneumotonometry[a] Multiple clinic visits[a] Contact with infected physician[a]
Colon (*114*)	1986	Hospital eye clinic	132	—	Pneumotonometer
Koo et al. (*115*)	1987–1988	Eye clinic	102	16.7	Pneumotonometry[a] Contact with specific caregiver[a]
Buffington et al. (*116*)	1990	Nursing home	47	49.5	—
Birenbaum et al. (*117*)	—	Hospital	7	—	—
Ankers et al. (*118*)	1991	Eye hospital	23	—	Contact with infected physician
Tabery (*119*)	1993	Eye clinic	33	—	Contact with infected physician Multidose dropper bottle
Curtis et al. (*120*)	—	Eye department	22	—	—
Montessori et al. (*121*)	1994	Hospital eye clinic	39	—	Contact with specific caregiver Diagnostic lens applied to eye
Chaberny et al. (*122*)	1998	Hospital (NICU*)	12	—	contact with specific caregiver
Cheung et al. (*123*)	1999	Hospital eye clinic	19	—	Invasive procedures
Piednoir et al. (*124*)	2000	Long-term care facility	41	50.8	Person-to-person via indirect contact
Percivalle et al. *(125)*	2000	Hospital (NICU*)	47	—	Ophthalmologic instruments
Engelmann et al. *(126)*	2005	Ophthalmologist's office	12	—	—
Viney et al. *(127)*	2005–2006	Eye clinic	68	8%	Multidose eyedrops, tonometers, specific caregiver
Kim et al. *(128)*	2007	Hospital	46	—	—
Hamada et al. *(129)*	2007	Hospital ward and eye clinic	27	—	Multidose eyedrops, contaminated surfaces

[a]Risk factor statistically significant ($p < .05$).
*NICU, neonatal intensive care unit.

Effective Disinfectants Recently, Rutala, Weber and colleagues published results of an experimental study to evaluate 21 different germicides for their ability to sterilize adenovirus 8 from fomites (132). Virus was allowed to dry on metal discs, then various germicides were added. After 1-minute and 5-minute contact times and using various suspending media, the virus-germicide mixture was assayed for viable virus. A 3-$\log_{10}$ reduction in virus was considered effective. Only seven germicides were effective after 1-minute contact time when using the most challenging conditions (hard water plus 5% fetal calf serum). These included a 1:10 dilution of Clorox (6,000 ppm chlorine), Clorox Cleanup (1,900 ppm chlorine), Cidex (2.4% glutaraldehyde), 2.65% glutaraldehyde (Wavicide-01), Cidex OPA (0.55% orthophthalaldehyde), Steris 20 sterilant (0.2% peracetic acid), and Lysol disinfectant spray (79.6% ethanol with 0.1% quarternary ammonium compound). All of these also produced a 3-$\log_{10}$ reduction at 5 minutes except for 1:10 Clorox dilution (6,000 ppm chlorine), which only produced a 1.5-$\log_{10}$ reduction. This is surprising considering that Clorox Cleanup, which has one-third the concentration of chlorine (1,900 ppm chlorine), was effective at both 1 and 5 minutes. Two additional disinfectants produced 3-$\log_{10}$ reduction at 5 minutes under the most challenging conditions, but these failed at 1 minute: 70% ethanol and 65% ethanol with 0.63% quarternary ammonium compound (Clorox disinfectant spray). Not all disinfectants are safe to use on ophthalmologic equipment such as tonometer tips. The CDC previously recommended using one of four germicides to disinfect tonometer tips, but the Rutala study found that two of these, 70% isopropyl alcohol and 3% hydrogen peroxide, were not effective against adenovirus 8.

Tonometer Tip Disinfection Goldmann applanation tonometry is considered to the most accurate way of measuring intraocular pressure. A "tip" containing a prism is placed on the ocular surface to measure pressure. Disposable tips are available but costly to a busy practice. Reusable tips are standard and cost approximately $100 each. The CDC recommends that these tonometer tips be cleaned with soap and water (or an alternative agent suggested by the manufacturer) and disinfected by soaking for 5 to 10 minutes in a solution containing a 1:10 dilution of bleach (Dakin's solution, or approximately 5,000 ppm chlorine), or in 70% ethyl alcohol, providing compatibility with the manufacturer's recommendations *(133)*:

> *"Wipe clean tonometer tips and then disinfect them by immersing for 5 to 10 minutes in either 5,000 ppm chlorine or 70% ethyl alcohol. None of these listed disinfectant products are FDA-cleared high-level disinfectants. Category II."*

After disinfection, the device should be thoroughly rinsed in tap water and dried before use. Prior to the study discussed above by Rutala et al., only limited data were available on the efficacy of different methods for disinfection of tonometers. Threlkeld et al. *(134)* demonstrated that a tonometer tip contaminated with adenovirus type 8 could be disinfected by wiping or soaking for 5 minutes with isopropyl alcohol, hydrogen peroxide, or an iodophor. However, alcohol swabs have been shown ineffective in eliminating adenovirus type 5 from experimentally contaminated eyelid speculums *(135)*. Two studies have found that disinfection of tonometer tips between patients with a 70% isopropyl alcohol wipe contributed to an outbreak of EKC *(113,115)*. These wipes are still widely used, and the American Academy of Ophthalmology includes wiping with "an alcohol sponge" as one of the acceptable methods for cleaning tonometer tips *(136)*. However, they also may be ineffective against other pathogens in addition to adenovirus. One experimental study found that 5-second isopropyl alcohol wipes were ineffective in eliminating hepatitis C virus from tonometer tips *(137)*.

We are aware of anecdotal reports and personal experience that deterioration of Goldmann-type tonometer tips has been observed with soaking in 5,000 ppm chlorine (1:10 solution of bleach). Since 2,000 ppm of chlorine has been demonstrated to be effective in inactivating adenovirus 8 on tonometer tips (132), this lower concentration likely would successfully disinfect the tonometer and might produce less damage to the tonometer. This issue warrants investigation by the manufacturer.

Infection Control Because of the highly contagious nature of EKC, the CDC recommends the following work restrictions for healthcare workers with conjunctivitis: "Restrict personnel with EKC or purulent conjunctivitis caused by other microorganisms from patient care and the patient's environment for the duration of symptoms" *(138)* (Table 26-3). It is recommended that if symptoms persist longer than 5 to 7 days, the healthcare worker be evaluated by an ophthalmologist before return to work.

In an evaluation of effectiveness of an infection control program to control EKC, Gottsch et al. *(139)* reviewed the experience of EKC in a large teaching eye institute from 1984 to 1997. Following the implementation of an infection control program, the number of annual outbreaks fell from 3.89 to 0.543 ($p < .005$) and the number of affected patients from 54.09 per 100,000 visits to 5.66 per 100,000 patient visits ($p < .0005$). The infection control program included patient screening and isolation, hand hygiene, instrument disinfection, medication distribution, and furlough of infected employees.

Conjunctivitis Due to Other Microbes

Community-acquired conjunctivitis is most commonly due to *S. aureus*, *S. pneumoniae,* and *H. influenzae*. Both endemic and epidemic HAIs may be caused by these pathogens. Healthcare-associated outbreaks have been most commonly associated with neonatal intensive care units (NICUs) and nursing homes. In NICUs, outbreaks due to MRSA and gram-negative bacilli, including *Pseudomonas*, have been described *(140–143)*. The problem of antibiotic-resistant conjunctivitis in NICUs has increased. In a CDC study of 149 NICUs over 10 years (1995–2004), "late-onset" (after 3 days of age) infections due to MRSA increased 300% over the time period, and 17% of cases were MRSA conjunctivitis *(140)*. In most reported healthcare-associated conjunctivitis outbreaks, usual person-to-person transmission has been suspected. However, intrinsic contamination of a triclosan-containing soap with *S. marcescens* led to an outbreak of conjunctivitis in one newborn nursery *(144)*.

TABLE 26-3

Guidelines for the Prevention of Epidemic Keratoconjunctivitis

- Evaluate all medical personnel with conjunctivitis for EKC
- Furlough all medical personnel with clinically diagnosed EKC for the duration of their illness (~2 wk)
- All patients with known or suspected EKC should be seen in a separate area of any outpatient facility. The room, including all surfaces (e.g., doorknobs), should be disinfected after use
- All hospital personnel should wear disposable gloves when examining and caring for patients with known or suspected EKC; careful hand washing with an antimicrobial agent should precede and follow all patient contacts
- All equipment that comes into contact with the mucous membranes of the eye should be sterilized or undergo disinfection between patient uses. Appropriate disinfection methods include immersion for 5–10 min in 5,000 ppm chlorine (Dakin's solution = 1:10 dilution of Clorox) or 70% ethyl alcohol. After disinfection, the device should be thoroughly rinsed in tap water and dried before use
- Only single-use vials of ophthalmic solutions should be used when examining patients with EKC
- All persons with EKC should be cautioned against sharing towels, face cloths, glasses, goggles, or any other item that might come into direct contact with the eyes of another individual
- All hospitalized patients with EKC should be placed on Contact Precautions; EKC should be considered potentially contagious for 10–14 d

In nursing homes, outbreaks of MRSA conjunctivitis and nontypeable *H. influenzae* have been described *(145,146)*. Because resistant microorganisms may be present, it is important to obtain a Gram stain and culture of conjunctival discharge in healthcare-associated cases of conjunctivitis.

Keratitis

Keratitis means infection of the cornea. Because the cornea, with overlying tear film, accounts for 75% of the refractive power of the eye, keratitis often causes decreased vision. It also usually causes severe pain, since the cornea has many nerve fibers (although no blood vessels). Patients who have had a corneal transplant, or patients with repeated episodes of herpetic keratitis, may have decreased corneal sensation so may present with keratitis late. Symptoms of keratitis include a unilateral red eye with moderate to severe pain, photophobia, tearing, and decreased vision.

Keratitis may be caused by viruses, bacteria, fungi, and the parasite *Acanthamoeba*. Healthcare-associated adenovirus outbreaks have been discussed above (see "Epidemic Keratoconjunctivitis"). HSV keratitis is the most common cause of keratitis in the United States, with 500,000 people affected annually and 20,000 new cases per year. Nearly all cases are due to reactivation of previously acquired HSV type 1 infection, however, and almost none are healthcare associated. Contact lens wear is the number one risk factor for keratitis due to nonviral pathogens, and ocular surface disease is the second most important risk factor *(147)*. *Pseudomonas* is the most common cause of contact lens–related keratitis; *Pseudomonas* present in tap water may colonize contact lens storage cases.

Outbreaks Related to Contact Lens Cleaning Solutions There have been worldwide outbreaks related to contact lens cleaning solutions. Keratitis due to molds, such as *Aspergillus* and *Fusarium*, is rare in nontropical regions of the world, but there was a worldwide outbreak of *Fusarium* keratitis related to a particular contact lens-cleaning solution (Bausch and Lomb's ReNu with MoistureLoc, withdrawn from market 2006) between 2004 and 2006 (*148*,149). An outbreak of *Acanthamoeba* keratitis in contact lens wearers was seen in 2007, and was also associated with a particular type of lens-cleaning solution (Advanced Medical Optics Complete Moisture Plus, withdrawn from market 2007) that apparently had inadequate anti-*Acanathamoeba* activity *(150)*.

Keratitis in Intensive Care Units Healthcare-associated keratitis occurs most often in sedated, mechanically ventilated patients in the intensive care unit (ICU). Exposure keratopathy in such patients is common, occurring in 20% to 40% of patients, and ocular surface abnormalities are a major risk factor for keratitis (*147*,151). Colonization of the ocular surface with gram-negative bacteria in ICUs is also common and may lead to secondary bacterial keratitis. One study from Greece found that 77% of ICU patients who were mechanically ventilated and sedated for at least 7 days developed conjunctival colonization with bacteria other than normal flora within 7 to 42 days; pathogens included *Pseudomonas* and *Acinetobacter (152)*. The most common pathogen reported in critically ill patients has been *P. aeruginosa (153,154)*. The respiratory tract is the usual source. Measures to prevent exposure keratopathy are essential in preventing keratitis in sedated patients. The two most common methods, lubrication of the eyes and moisture chambers (e.g., polyethylene eye covers or goggles), are both effective (151).

Healthcare-Associated Keratitis from Contaminated Eye Drops Contamination of eye drop bottles may occur during use in the home or healthcare setting *(155–158)*. Recent studies have reported that bacteria can be cultured from 6% to 8% of in-use eye drops bottles *(156–158)*. Microorganisms vary, but include *S. aureus*, *Pseudomonas*, *Klebsiella*, *Enterobacter*, *Serratia*, *Bacillus*, and *Proteus*. A particular microorganism may be prevalent in a given healthcare facility. In one long-term care facility, 8% of 123 multiple dose solutions were contaminated with bacteria, with 80% due to *Proteus mirabilis (157)*. Multidose vials of ophthalmic solutions are frequently used in healthcare settings. The

same vial of dilating eye drops, for example, may be used for multiple patients in an eye clinic. Contamination of the vial may occur if healthcare workers touch a patient's eyelashes or ocular surface with the bottle tip, but use the same bottle for the next patient. Reports of keratitis developing from use of contaminated ophthalmic solutions are surprisingly rare. Keratitis with *P. aeruginosa (159)* and *S. marcescens (160)* has been reported from use of contaminated eye drops. A recent report from India described five patients who developed secondary *Pseudomonas* keratitis while using natamycin, an antifungal agent, to treat their *Fusarium* keratitis *(161)*. The cultures from the natamycin eye drop bottles being used by all five patients grew *Pseudomonas*. All had poor visual outcomes, with three requiring corneal transplants and one requiring evisceration for panophthalmitis.

Endogenous Endophthalmitis

Endophthalmitis means bacterial or fungal infection within the eye, including infection of the vitreous and/or aqueous humors. Most cases of endophthalmitis are exogenous, with infection introduced from "outside" the eye either from surgery, penetrating trauma, or extension of keratitis. Nearly all healthcare-associated cases of endophthalmitis are postsurgical and are discussed above (see "Postsurgical Eye Infections"). Endogenous endophthalmitis refers to bacteremia or fungemic seeding of the eye. Cases of endogenous endophthalmitis are considered healthcare-associated when the underlying bacteremia or fungemia is an HAI. Note that bloodstream infections may seed the eye, but the reverse does not occur: the infected eye never serves as a source of bacteremia or fungemia.

The most common sources of bacteremia in most series of endogenous endophthalmitis are community acquired rather than healthcare associated. These sources include endocarditis, urinary tract infections, meningitis, intravenous drug use, intra-abdominal abscesses (162,*163*,*164*). In Taiwan and other East Asian countries, liver abscesses due to *Klebsiella pneumoniae* are frequently associated with secondary endogenous *Klebsiella* endophthalmitis, particularly in older diabetic patients *(165,166)*. Community-acquired endogenous endophthalmitis due to molds, such as *Aspergillus* and *Fusarium*, are usually seen in intravenous drug users, or in severely immunocompromised patients (e.g., organ transplant recipients) who have invasive fungal infections, usually involving the lungs *(167,168)*.

Healthcare-Associated Endogenous Endophthalmitis

Healthcare-associated cases of endogenous endophthalmitis usually develop either after procedures that can produce transient bacteremia, such as endoscopy (162), or from infections related to indwelling central venous catheters. One of the most common nonsurgical healthcare-associated intraocular infections is ocular candidiasis. Ocular candidiasis is usually secondary to central line–related candidemia. The term "ocular candidiasis" includes both *Candida* chorioretinitis, characterized by clear vitreous but white "fluff balls" seen on the fundus, and endophthalmitis, in which there is also significant inflammation in the vitreous. The distinction is not always made in the literature, however, with both being described as endophthalmitis. *Candida* chorioretinitis or endophthalmitis is often asymptomatic, so patients with candidemia should have funduscopic examinations to look for intraocular seeding of fungus. In a prospective multicenter study of 118 hospitalized patients with candidemia, 9% were found to have chorioretinitis yet almost none had eye symptoms *(169)*. Candidemia may be clinically silent, transient, and undiagnosed during a hospitalization or rehabilitation stay, yet could have seeded the eye. Undiagnosed chorioretinitis may progress to endophthalmitis, which usually presents as a gradual and painless decrease in vision. Diagnosis is often delayed because symptoms may occur weeks or months after a hospitalization, and after an indwelling central venous catheter has been removed. A 10-year retrospective study of 15 patients with endogenous *Candida* endophthalmitis, 11 of whom had an indwelling central venous catheter, found that the average time from onset of symptoms to treatment of endophthalmitis was 2 months (170). Most cases of *Candida* chorioretinitis resolve with systemic antifungal treatment alone, but treatment of *Candida* endophthalmitis requires vitrectomy plus intravitreal amphotericin B injection in addition to systemic antifungal therapy.

CONCLUSION

Many healthcare-associated eye infections are due to surgical procedures. Such infections are likely to increase in the coming years with the increase in new surgical procedures, such as LASIK, lamellar keratoplasty, implantable plastic devices to treat glaucoma (e.g., Ahmed valve) and corneal blindness (e.g., KPro). The use of monthly intravitreal injections of anti-VEGF medications to treat macular degeneration and diabetic retinopathy may also lead to an increase in HAIs. Examples of healthcare-associated eye infections that are unrelated to surgical procedures include ophthalmia neonatorum, EKC, and keratitis in sedated, intubated patients in ICUs. Meticulous care in following infection control protocols can prevent most HAIs in ophthalmology, as in all fields of medicine.

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CHAPTER 27

Healthcare-Associated Central Nervous System Infections

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Healthcare-associated infections related to the central nervous system (CNS) are a relatively infrequent but important category of hospital-acquired infections. These infections span a spectrum from superficial wound infections, to ventricular shunt infections, to deep-seated abscesses of the brain parenchyma. The patient populations affected are equally diverse, involving neonates, children, and adults, with occurrence on nearly all medical and surgical services.

Healthcare-associated infections of the CNS are usually serious, if not life threatening, and are frequently associated with a poor outcome (*1–4*,5,*6–13*). These healthcare-associated infections present many challenges in diagnosis, and many controversies exist regarding effective prophylaxis and proper management. In addition, the identification of a particular infection as healthcare-associated may not be clear-cut; thus, overlaps and ambiguities concerning acquisition are unavoidable. Fortunately, a heightened awareness has fostered declining rates of infection. In spite of improving techniques and new preventive strategies, the threat is constant, and the stakes remain painfully high. The first part of this chapter focuses on the clinical and epidemiologic aspects of infections related directly to neurosurgical and neuroinvasive procedures as well as infectious processes that invade the CNS secondarily from other sites. The second part of this chapter discusses prevention and control of these infections.

RISK FACTORS

General Risk Factors

Not surprisingly, the patients at greatest risk for acquiring healthcare-associated CNS infections are neurosurgical patients. Patients with surgical site infections (SSIs) are drawn almost entirely from this population. These patients are subjected to procedures that traverse the scalp, violate meningeal coverings, impinge upon the paranasal sinuses, implant foreign bodies, and expose tissues to hematogenous sources of infection. Infection in this setting is often facilitated by the presence of a cerebrospinal fluid (CSF) leak that occurs when the dura is disrupted and the subarachnoid space communicates with the skin, nasal cavity, paranasal sinuses, or middle ear *(14–19)*. This group includes adult and pediatric patients undergoing common neurosurgical and neuroinvasive procedures such as craniotomy, spinal fusion, laminectomy, insertion of halo pins, burr hole placement, and implantation of ventricular shunts and reservoirs. Less common procedures include stereotactic brain biopsy, hypophysectomy, paranasal sinus surgery, acoustic neuroma resection, temporary ventricular drainage, placement of intracranial monitoring devices, nerve stimulator placement, lumbar puncture, spinal anesthesia, myelography, and skull/spinal fixation.

Patients who have suffered accidental head trauma are another population at increased risk to develop meningitis. These individuals have sustained trauma or fractures to the basilar skull and facial bones, facilitating the formation of a CSF fistula. This posttraumatic condition substantially increases the likelihood of CNS infection, particularly bacterial meningitis *(20–22)*. In one series, a CSF leak was a predisposing factor in approximately 9% of cases of healthcare-associated bacterial meningitis (5).

The majority of healthcare-associated CNS infections reported from the National Nosocomial Infections Surveillance (NNIS) system at the Centers for Disease Control and Prevention (CDC) occurred in newborn nurseries and on surgical services (Table 27-1). All other hospital services account for a small but still substantial number of cases. Patients from this smaller population generally have a parameningeal source of infection that is either contiguous (e.g., sinusitis) or occult (e.g., unsuspected CSF leak), reactivation of latent infection, or an infection that has hematogenously seeded the CNS from a distant site. Patients with malignancies (especially lymphoma and leukemia), organ transplants, and other immunocompromised hosts frequently fall into this last category.

Risk factors for SSIs can be classified into host factors and surgical factors. Examples of host factors include age, sex, American Society of Anesthesiologists (ASA) physical status classification, underlying diseases such as diabetes mellitus, nutritional status, presence of other remote infections, and duration of preoperative stay. Surgical factors include whether the procedure was emergent or elective, hair removal technique, surgeon, use of perioperative antibiotics, duration of surgery, type of operation, site of surgery, and whether gloves were punctured *(23)* (see Chapter 21 on SSIs.) One study showed that when

TABLE 27-1

Healthcare-Associated CNS Infections by Hospital Service in NNIS Hospitals 1986 to 1992

	Percentage of Total Infections		
Service	*Meningitis*	*Intracranial*	*Spinal Abscess*
Neurosurgery	43	60	14
High-risk nursery	23	13	0
Well-baby nursery	10	2	0
Medicine	7	6	29
Pediatrics	5	2	14
Surgery	3	6	14
Bum/trauma	3	4	0
Oncology	2	6	0
Orthopedics	1	0	0
OB/GYN	1	0	14
Cardiac surgery	<1	0	14
Total	100	100	100

NNIS, National Nosocomial Infections Surveillance system. (*Source:* Centers for Disease Control and Prevention/NNIS.)

patients underwent a neurosurgical procedure, the presence of a postoperative CSF leak was associated with a 13-fold increase in the infection risk *(24)*. Also, a non-CNS concurrent infection increased the infection risk six times, whereas use of perioperative antibiotics was associated with a decrease in the infection rate of about 20%. Three other risk factors—paranasal sinus entry, placement of a foreign body, and use of postoperative drains—were associated with an increased risk of infection, although these associations were not statistically significant. Factors not associated with an increased risk of infection included obesity, surgical reexploration, use of the operative microscope, steroid administration, and acute therapy for seizures. Length of surgery was also not a factor associated with an increased risk of infection. A prospective study of postoperative neurosurgical infections demonstrated a validated five-category classification system for neurosurgical infections based on specific definitions. It found that infection rates were highest for contaminated cases (contamination known to occur, 9.7%), followed by dirty cases (established sepsis at the time of surgery, 9.1%), clean-contaminated (risk of contamination of operative site during surgery, 6.8%), clean with temporary or permanent foreign body (6.0%), and clean (no identifiable risk factors present, 2.6%). In this study, surgery lasting longer than 4 hours was associated with an infection rate of 13.4% *(25)*.

In addition to neonates (see Chapter 52) and patients undergoing neurosurgery, patients undergoing invasive diagnostic or therapeutic procedures that penetrate the CNS are at risk for developing a healthcare-associated CNS infection (see Section VIII). A subgroup of neurosurgery patients at high risk for healthcare-associated CNS infections includes those with ventricular shunts. Since most shunt infections (70%) have an onset within 2 months of surgery, it is likely that the infecting microorganism is introduced during surgery or in the postoperative period *(10)*. Risk factors for shunt infections are discussed in Chapters 49 and 65. The rate of infection varies with the neurosurgeon *(26,27)*. The efficacy of prophylactic antibiotics in preventing shunt infection is controversial and is discussed below (see Prevention). Patients undergoing diagnostic or therapeutic procedures that penetrate the CNS, such as the installation of dyes or drugs, are more likely to develop healthcare-associated meningitis *(28)*. Although such infections occur infrequently in the present era, they should be considered in the appropriate setting.

Device-Related Risk Factors

Infection is a well-recognized complication of ventriculostomy catheters used for monitoring and drainage *(29)*. Aucoin et al. *(30)* noted that the rate of infection was associated with the type of monitor used. The lowest infection rate was associated with the subarachnoid screw (7.5%), followed by a rate of 14.9% for the subdural cup catheter and a 21.9% rate for the ventriculostomy catheter. An intracranial monitoring technique, the Camino intraparenchymal fiberoptic catheter system, is associated with an infection rate of 2.5% *(31)*. The method of ventriculostomy insertion using the tunneled technique has been associated with the lowest rates of infection *(29)*. Use of prophylactic antibiotics did not reduce significantly the risk of infection. In a study by Mayhall et al. *(9)* of ventriculostomy-related infections, risk factors significantly associated with infection included an intracerebral hemorrhage with intraventricular hemorrhage, a neurosurgical operation, ICP of 20 mm Hg or higher, ventricular catheterization for longer than 5 days, and irrigation of the system. The incidence of infection was not related to insertion location when the intensive care unit was compared with the operating room. Infection rates were also not reduced by the use of nafcillin prophylaxis. Several additional studies have confirmed the direct relationship between the duration of ventricular catheters and infection risk *(32–36)*. Additional risk factors associated with ventriculitis include sepsis, pneumonia, urinary tract infection, depressed skull fracture requiring surgery, craniotomy, CSF leakage around the device, drain blockage, reinsertion related to catheter malfunction, and intraventricular hemorrhage. To reduce the risk of ICP monitor–related infections, it is recommended that the device be inserted using aseptic technique, that the device be removed as soon as possible and preferably before 5 days, and that a closed system be maintained. A randomized, controlled trial of external ventricular drain-associated infection compared regular exchange of the drain every 5 days with clinically indicated exchanges and found no difference in the rate of infection between these groups *(37)*. The use of prophylactic catheter exchange and extending the duration of catheterization to 10 days has been proposed, but more data are needed *(29)*. The type of ICP monitor device used influences the rate of infection, with epidural tunneled monitors having the lowest rates.

SOURCES OF INFECTION

Sources of Infecting Microorganisms

Nonsurgical Infections Healthcare-associated CNS infections can be classified into those infections unrelated to surgery and postsurgical infections. In patients with

nonsurgical-related infections, the microorganisms can compose a patient's endogenous flora, such as coagulase-negative staphylococci (CoNS), or arise from an exogenous source, such as from a contaminated solution or device *(28)*. Gram-negative bacilli are usually responsible for infections related to contaminated solutions or devices *(38)*. Microorganisms can gain access to the CSF by hematogenous spreading of an infectious agent, spread to the CSF from contiguous foci, such as an infected sinus, or via a communication of the CSF with the flora of the skin, sinuses, or other mucosal surfaces *(39,40)*. CSF leakage can be obvious in a patient with rhinorrhea or otorrhea, or occult if the subarachnoid space communicates with a paranasal sinus. Rarely, neoplasms erode into the subarachnoid space and produce a fistula. Microorganisms can also gain access to the CSF by direct inoculation of the agent in a patient having a lumbar puncture, especially if a substance is injected. Microorganisms acquired in this manner are usually gram-negative rods *(41,42)*. It is extremely unusual to develop meningitis following a lumbar puncture unless a solution is injected into the CSF.

Infection is a well-recognized complication of chronic epidural catheters and intracerebroventricular devices *(43)* used for control of pain in patients with AIDS or malignancy *(44)* (see Chapter 60). Hayek et al. studied patients with noncancer pain and found a higher infection rate (5.51 infections per 1,000 catheter-days) among patients using tunneled epidural catheters (TECs) for neuropathic pain compared to those with TECs used to treat somatic pain (2.43 infections per 1,000 catheter-days) *(45)*. Staphylococci accounted for 11 of 23 positive epidural space or catheter tip cultures, supporting the hypothesis that most of the TEC infections were due to skin flora migration and colonization of these catheters. Other complications include meningitis and epidural abscess, but prolonged surgery during catheter placement has been found to be the only factor associated with catheter infection *(46)*. Infection may also complicate the use of an Ommaya reservoir *(47)*. Repeated access of these devices may permit colonizing skin flora such as *Staphylococcus aureus, S. epidermidis,* or diphtheroids to produce ventriculitis and meningitis. The source of the infecting microorganisms may also be the hands of the hospital personnel accessing the device, although powder contamination from gloves has also been implicated *(48)*.

Neurosurgical Infections Although many sources of contamination of a neurosurgical operation have been described, it is usually impossible to document with certainty the source for a given SSI. Probably most infections occur at the time of surgery from either direct inoculation of residual flora of the patient's skin or from contiguous spread from infected host tissue. Direct inoculation of microorganisms can also occur occasionally from the hands of surgical team members via a tear in a glove. Rarely, the source of infection is traced to contaminated surgical material such as a solution, device, or instrument. In two neurosurgical patients with postoperative *Bacillus cereus* meningitis, the source of the microorganisms was found to be heavily contaminated linen *(49)*. Occasionally, during the postoperative period, an SSI results from direct inoculation of microorganisms. Airborne contamination at the time of surgery, either from the patient or from operating room personnel, accounts for some neurosurgical infections *(1,50)*. Lastly, a postoperative infection rarely results from hematogenous seeding of a wound from an infected intravenous line or other remote infection.

Outbreaks of neurosurgical infections occur infrequently today, and when they have been described, they have occurred mainly in hospitalized neonates *(51–53)*.

INCIDENCE AND DISTRIBUTION

Healthcare-associated infections of the CNS (excluding wound or SSIs) are relatively uncommon, accounting for approximately 0.4% of all healthcare-associated infections (R. Gaynes, personal communication to Nelson Gantz). Meningitis accounts for 91% of these infections, followed by intracranial suppurations (8%) and isolated spinal abscess (1%) (R. Gaynes, personal communication to Nelson Gantz). When infection rates are examined using data reported from 163 hospitals participating in the NNIS system, 0.56 CNS infections per 10,000 hospital discharges occurred from 1986 through early 1993 (R. Gaynes, personal communication to Nelson Gantz). Comparable rates over the past 25 years have shown a slow decline from approximately one infection per 10,000 hospital discharges to the present lower rate *(54)*. While these numbers are relatively small, it must be noted that CNS infections directly related to neurosurgical procedures (SSIs) are not reflected in these numbers. The majority of healthcare-associated CNS infections occurring in this setting are designated under the larger category of SSIs (22% of all healthcare-associated infections) by the CDC National Healthcare Safety Network (NHSN) system surveillance criteria (see below) *(401)*. Certain healthcare-associated CNS infections may represent a greater proportion of specific types of infection. For example, a retrospective study of acute bacterial meningitis in adults over a 27-year period at the Massachusetts General Hospital found 40% of 493 total episodes to be healthcare-associated in origin (5).

Healthcare-associated surgical site and CSF infections among neurosurgical patients are a primary focus of this chapter. Table 27-2 shows the distribution of SSIs complicating neurosurgical procedures and illustrates the significant proportion of deep infections that occur in relation to the surgical site; these data are derived from the NNIS reporting period 1986–1992. Infection rates as reported in the general neurosurgical literature are often difficult to interpret and compare for a variety of reasons, including differences in definitions, methodology, reporting techniques, and use of prophylactic antibiotics. Not uncommonly, postoperative infections unrelated to the surgical site or CNS are included in the rate calculation *(2)*. An overview of infection rates associated with neurosurgery from some of the more rigorously performed (although nonstandardized) studies over the last 30 years is shown in Table 27-3. Taking into account some of the problems mentioned above, most hospital series report infection rates of <5%. When individual neurosurgical procedures are compared, differences in infection rate become more apparent. The incidence of all CNS infection following typically clean craniotomy may vary from <1% to nearly 9%,

TABLE 27-2

Surgical Site Infections Following Neurosurgical Procedures

		Surgical Site								
Procedure	*Men*	*SA*	*SSI*	*DSI*	*IC*	*IAB*	*Bone*	*Disc*	*Other*	*Total*
Craniotomy ($n = 191$)[a]	22%	—	60%	2%	12%	—	—	—	4%	100%
Laminectomy ($n = 615$)	1%	3%	75%	11%	—	—	4%	6%	—	100%
Ventricular shunt ($n = 93$)	76%	—	18%	—	—	4%	—	—	2%	100%
Head and neck ($n = 324$)	3%	—	77%	13%	—	—	2%	—	5%	100%
Miscellaneous ($n = 49$)	8%	2%	82%	—	—	8%	—	—	—	100%

Data from Refs. *(55–71).*
[a]Number of operations performed.
Men, meningitis; SA, spinal abscess; SSI, superficial surgical site infection; DSI, deep surgical site/soft tissue infection; IC, intracranial infection; IAB, intra-abdominal abscess; bone, osteomyelitis; disc, discitis.
(*Source:* CDC/NNIS.)

whereas the rates following laminectomy range from 0.6% to 5%. Postoperative meningitis after clean craniotomy has a reported incidence of 0.5% to 2% when perioperative antibiotics are given *(55,56,72–74)*. Without antibiotic prophylaxis, other studies have found rates ranging from 2% to 7% *(74–76)*. A more recent large prospective study of infections after craniotomy among 2,944 patients found an overall SSI rate of 4%, with meningitis representing approximately 48% of these infections (77).

Infection rates for selected neuroinvasive procedures are shown in Table 27-4. Again, differences in methodology, definition, and duration of follow-up greatly affect the reported rates. Analysis of infection rates following ventricular shunt surgery is particularly complex. Depending on the use of a case rate (occurrence per patient) or an operative rate (occurrence per procedure) of infection and the duration of follow-up, an extremely wide variation in incidence may be seen. Perhaps, when in 1916 Cushing *(107)* stated, "There has never been any infection, even of a stitch in the scalp, in something over 300 cranial operations in the writer's series," he underestimated the situation. A procedure-oriented risk factor analysis is covered in a later section, and additional details are discussed elsewhere in this text (see Chapters 49, 60, and 65).

TABLE 27-3

Infection Rates in Selected Neurosurgery Trials

Series (year)	*All Procedures*	*%*	*Laminectomy*	*%*	*Craniotomy*	*%*
Odum (1962)			3,774	0.6	2,342	1.3
Cairns (1963)					1,169	4.4
Wright (1966)			2,085	4.1	2,148	5.7
Green (1974)	1,770	2.3	529	2.3	692	2.6
Savitz (1974)	495	3.6	239	3.8	214	4.2
El-Gindi (1965)			650	0.8		
Madeja (1977)	1,129	3.8				
Quadery (1977)	357	4.8	40	5.0	144	5.7
Haines (1982)	1,663	1.7				
Lindholm (1982)			3,576	0.8		
Chan (1984)					338	4.7
Jomin (1984)					500	3.0
Puranen (1984)			1,100	0.7		
Blomstedt (1985)	1,039	5.7			622	8.0
Tenney (1985)	936	5.5			494	7.3
Savitz (1986)					872	0.2
Ingham (1988)					1,167	3.3
Cartmill (1989)	423	0.7				
Winston (1992)					312	0.3
Holloway (1996)	560	0.5				
Korinek (1997)					2,944	4.0
Zhu (2001)	180	2.8				
Whitby (2000)	780	6.9				

TABLE 27-4

Infection Rates in Selected Neuroinvasive Procedures

Procedure	*Infection Rate*
Ventricular shunt	
Operative	3–13%
Case	9–41%
Cerebrospinal fluid reservoir	4–23%
Ventriculostomy[a]	0–11%
Burr hole	1–5%
Spinal anesthesia	<0.5%
Lumbar puncture	<2%
Epidural catheter	0–4%
Stereotactic biopsy	<1%
Myelography	Rare

(Data from Refs. *9,10,30,44,60,62,78–106,409.*)
[a]Includes external drainage and intracranial pressure monitoring devices.

Examination of SSIs reported from NNIS system hospitals between 1992 and 2004 shows infection rates in uncomplicated procedures with minimum risk factors to be 0.91/100 operations for craniotomies, 1.04/100 operations for spinal fusion, 0.88/100 operations for laminectomies, and 4.42/100 operations for ventricular shunts (108) The last rate is the third highest among all operative procedures (108). These surveillance rates, by definition, include both superficial and deep infections related to the operative site (109,*110*). The addition of one or more complications (surgical risk factors) will increase most of the figures to varying degrees *(111)*.

The incidence of both community- and hospital-acquired CNS infections in immunocompromised hosts has been estimated to range from <1% to over 10%, depending on the host population *(112–115)*. Classic studies at the Memorial Sloan-Kettering Cancer Center in the early 1970s revealed an incidence of CNS infections approximating 0.02% of total hospitalizations *(116)*. These infections occurred most commonly in lymphoma patients (33%), followed by neurosurgical patients (30%) and leukemic patients (20%). Overall, meningitis accounted for the majority of infections (71%), followed by brain abscess (27%) and encephalitis (2%). Of note, intracerebral abscess in leukemic patients was responsible for 70% of CNS infections in this group. It has been postulated that conventional incidence figures may significantly underestimate the actual magnitude of CNS infections in this population *(112)*. Other studies have shown similar patterns in cancer patients, with perhaps a higher incidence of CNS infection in transplant recipients estimated at 5% to 12% *(114,115)*. One retrospective study of bone marrow transplant recipients found symptomatic neurologic complications, predominantly infectious (23% of complications), among 16% of patients *(117)*. CNS infections were more common among allogeneic compared to autologous transplants and included cerebral toxoplasmosis, viral encephalitis, and fungal infections. Brain abscess was found to be a common complication in one study of heart and heart–lung transplant recipients, accounting for 35% to 44% of CNS infections *(113,118)*. These abscesses are often caused by fungi, particularly *Aspergillus* species, among liver transplant recipients *(119)*. Bacterial meningitis in the febrile neutropenic patient is often indolent in presentation and masked by the early use of broad-spectrum antibiotics. Disseminated fungal infections are not uncommon in the compromised host and are frequently difficult to diagnose; *Candida* is reported to involve the CNS in up to 50% of cases *(120,121)*. Although the absolute number of healthcare-associated infections in this population cannot easily be determined, the proportion is likely to be high, as many occur after multiple or prolonged hospitalizations and are caused by typical healthcare-associated pathogens.

TYPES OF HEALTHCARE-ASSOCIATED CENTRAL NERVOUS SYSTEM INFECTIONS

Healthcare-associated infections related to the CNS may be broadly divided into two major categories (Table 27-5): postsurgical infections and nonsurgical infections, including those related to neuroinvasive or neurodiagnostic procedures. The first category consists of SSIs (109). Infections of this type may occur following craniotomy, ventriculostomy, and spinal column surgery. Rarely, SSIs complicate other neurosurgical operations, such as peripheral nerve surgery and carotid endarterectomy. SSIs are further classified as superficial or deep incisional SSIs, using the fascial plane as divider. Deep surgical infections unrelated to soft tissues are classified as organ/space SSIs by the aforementioned CDC criteria (109). These infections may present as a local and/or diffuse infectious process. Local suppurative infections complicating neurosurgical procedures include the following: parenchymal brain abscess, subdural empyema, epidural abscess,

TABLE 27-5

Healthcare-Associated CNS Infections

Postsurgical	*Nonsurgical*
Surgical site infections	Contiguous focus or hematogenous
Superficial incisional	Epidural abscess
Deep incisional	Subdural empyema
Organ/space infections	Brain abscess
Local suppurative infections	Meningitis
Osteomyelitis	Meningoencephalitis
Discitis	
Subgaleal collection	
Epidural abscess	
Subdural empyema	
Brain abscess	
Diffuse infections	
Meningitis	
Ventriculitis	
Meningoencephalitis	

discitis, subgaleal collection, and osteomyelitis of the cranium or spine. Diffuse infection of the subarachnoid space defines meningitis or ventriculitis if the process is related to a prior ventriculostomy and essentially remains localized. This latter distinction is somewhat arbitrary. Meningoencephalitis is an infrequent diffuse healthcare-associated CNS infection generally due to prions or viruses transferred during neuroinvasive procedures or via organ transplantation *(122–128)*.

Nonsurgical infections constitute a smaller, but equally important, class of healthcare-associated CNS infections. These infections are acquired by a variety of routes that include spread from a contiguous focus, posttraumatic/CSF leak, and neuroinvasive procedures, as well as hematogenous spread. Meningitis, brain abscess, subdural empyema, and epidural abscess all may occur in this setting.

DEFINITIONS, DIAGNOSTIC CRITERIA, AND CLINICAL PRESENTATION

It is essential for the purposes of identification, surveillance, and management that healthcare-associated infections be defined and diagnosed with as much sensitivity and specificity as possible. Unfortunately, factors such as colonization and aseptic inflammation prevent the establishment of gold standards and place many conditions within a spectrum of disease. Recognition of an infection as healthcare associated is often not straightforward, and CNS infections are no exception. Doubt over hospital versus community acquisition of an infection is a constant problem compounded by the ubiquity of the major pathogens. The time course that defines specific healthcare-associated infections is neither consistently defined, easy to determine, nor universally accepted. Although the CDC outlines strict definitions and diagnostic criteria, the length of hospitalization prior to an infection being classified as healthcare associated is not specified, with the exception that such infections should not be considered HAIs if they are present or incubating at the time of admission to the acute care setting (109). For SSIs related to implantable devices, healthcare-associated infection may be diagnosed up to 1 year after surgery, according to CDC criteria (109). Some experts consider 60 days a more reasonable length of time for healthcare-associated ventricular shunt infections, as the majority of infections occur within this period (129). In addition, the diagnosis of infection ultimately may be left to the discretion of the attending physician and is inherently subjective. A prospective study by Taylor et al. *(130)* demonstrated that 40% of neurosurgical wound infections were diagnosed using nonstandardized criteria by the surgeon. The potential effect on infection rates is obvious. Ventricular shunt infections illustrate several of these problems. CSF profiles may be nondiagnostic, the microorganism involved may be from the normal flora, and the infection may become evident weeks after hospital discharge. This section integrates the CDC definitions with additional clinical criteria to facilitate proper identification and diagnosis of healthcare-associated infections related to the CNS. The CDC surveillance definitions for healthcare-associated surgical site and specific CNS infections have been previously published (109).

Surgical Site and Related Surgical Infections

Studies dealing with SSIs in neurosurgical patients have used a variety of both strict and less stringent diagnostic criteria for identification *(2,4,12,25,57,58,131–136)*. Commonly, these infections are classified in the surgical literature as either superficial or deep. Superficial neurosurgical infections are considered to be limited by the cranial or lumbodorsal fascia. Deep wound infections encompass soft tissue infections below the fascia, including discitis, osteomyelitis, and bone flap infections. However, infections below the dura (ventriculitis, meningitis, brain abscess) have been included under this heading as well *(24,56,131)*. To improve surveillance and clarify potential overlap in reporting, the CDC definitions include the category of organ/space SSI to cover additional sites adjacent to the operative site. Specific organ/space SSIs related to neurosurgery include the following: meningitis, ventriculitis, disc space infection, osteomyelitis, intracranial abscess, and spinal abscess (109). With the exception of infections related to implantable devices, infection occurs within 30 days of the operative procedure. Since the organ/space SSI category includes several non–soft tissue infections, the definitions are relatively liberal. Diagnosis of some of these infections is covered in subsequent sections, as they also occur unrelated to surgical procedures. More detail on SSIs in general may be found elsewhere in the text (Chapter 21).

Incisional Surgical Site Infections

From a practical point of view, the diagnosis of incisional SSIs is usually made clinically. Neurosurgical site infections must be promptly identified because of the propensity to spread to deeper spaces *(137)*. Superficial incisional SSIs tend to be diagnosed at an early stage, usually within the first postoperative week *(59,138,139)*. Generally, the area is swollen and erythematous with local tenderness. Purulent discharge and/or microorganisms isolated from drainage or a wound aspirate complete the picture. Temperature and the white blood count (WBC) are not uniformly elevated; the erythrocyte sedimentation rate (ESR) and CRP may be increased *(2,136)*. Deep incisional SSIs present later postoperatively with a course that may be insidious or progressive. The average time between surgery and the diagnosis of a deep infection in spinal surgery may vary from 10 to 15 days, with the range extending several weeks *(136,140)*. A relatively normal appearance of the overlying surgical site contributes to this delay in many cases *(140)*. Elevations of temperature, WBC, ESR, and CRP, as well as the presence of fever/chills or hyperglycemia in diabetic patients, while clearly nonspecific signs, are not infrequently seen *(136,138,140)*. Patients often complain of increased pain at the surgical site *(141)*.

Infections of bone flaps following craniotomy are well described and account for up to one half of infections following this procedure *(1,56,60,142)*, though a more recent large series described bone flap osteitis in 12% of postcraniotomy SSIs (77) By definition, infection involves either the free (devitalized) or the osteoplastic bone flap following a supratentorial craniotomy. These infections may be obviously symptomatic with high fever, scalp tenderness, and suppuration *(4,143)* or more indolent with a persistent fistula *(2)*. In one series, 12 of 13 bone flap

infections were diagnosed within 30 days of surgery *(139)*; Korinek found a median time to diagnosis of bone flap osteitis of 27 days (77). Sequential nuclear scanning with technetium 99 may have enhanced diagnostic accuracy for cranial flap osteomyelitis, especially to rule out this infection *(143)*. Indium 111–labeled leukocyte scanning is a useful technique *(144,145)*. Plain skull radiographs are helpful, if positive, but lack sufficient sensitivity to be useful routinely *(60)*. The use of magnetic resonance imaging (MRI) is invaluable in establishing a diagnosis, while CT findings are nonspecific and may not help establish a diagnosis of infection (146). In general, a cranial bone flap infection is diagnosed clinically with either radiographic or microbiologic confirmation *(4)*. A subgaleal abscess occasionally occurs adjacent to a scalp surgical site. In this case, a localized collection forms in the space between the galea of the scalp and the pericranium. Scalp tenderness, erythema, fever, and regional adenopathy may be seen. Osteomyelitis or intracranial spread of infection can occur secondarily if the underlying skull integrity has been compromised. Diagnosis of most deep incisional SSIs may be established clinically, via culture of a deep aspirate, or, rarely, with the assistance of radiologic studies. Evaluation of a soft tissue fluid collection with sonography or CT scan can be helpful.

Organ/Space Surgical Site Infections

Discitis (infection of the intervertebral disc space) is a relatively uncommon but potentially serious postoperative complication of spinal surgery *(147–151)*. The fact that almost 20 years of surgery passed before this infection was recognized illustrates the difficulties encountered in diagnosis *(152)*. Patients typically present with worsening back pain and muscle cramping 1 to 8 weeks after surgery and initial improvement of preoperative symptoms *(58,61,153,154)*. In a series of 111 cases of discitis described by Iversen et al. *(155)*, back pain appeared at an average of 16 days postoperatively. Occasionally, overt infection occurs immediately after surgery *(61,156)*. Patient examination may disclose pain with lumbar range of motion, paraspinal muscle spasm, and/or an abnormal straight leg raising test *(58,61,151,157)*. Neurologic deficits are unusual and should raise suspicion for an epidural abscess. Fever is variably present, and the superficial surgical site frequently appears normal. Most notable is the severe and persistent low back pain out of proportion to the findings on physical examination. Routine laboratory studies such as the WBC are generally unremarkable, with the exception of the ESR *(61,155,157)*. Following spine surgery, the ESR rises rapidly (peak 90–110) and falls steadily to near-normal levels within several weeks *(158,159)*. A significantly elevated ESR more than 2 weeks postoperatively correlates positively with disc space infection *(62,158–160)*. Others have found this test less valuable, especially with early infections *(155)*. CRP, an acute-phase reactant, may be useful as a diagnostic tool when followed serially in patients postoperatively. A prospective study of 348 consecutive patients undergoing spinal surgery had CRP measured on days 1, 3, and 5 postoperatively; these values demonstrated a characteristic increase and fall in 96% of patients experiencing a benign clinical course, with mean values of 14.9, 15.4, and 7.9 mg/dL on days 1, 3, and 5, respectively *(161)*. However, 4.6% (16 patients) displayed an abnormal CRP response with a second increase, and five of these patients were ultimately diagnosed with a postoperative spinal infection, though none with diskitis. The sensitivity, specificity, positive, and negative predictive values for the abnormal CRP response in this patient population were 100%, 96.8%, 31.3%, and 100%, respectively.

Several radiographic modalities are helpful in establishing the diagnosis of discitis. Plain films are of little utility in the early weeks, as most decreases in disc height are expected postoperatively. More characteristic findings occur weeks to months later with blurring of the end plate and irregularity and lytic destruction of the subchondral surface *(162)*. Osteomyelitis of the adjacent vertebrae may occur in advanced cases. These findings are visualized in greater detail with CT scans *(163)*. Currently, MRI with gadolinium enhancement has become the procedure of choice for the so-called failed back syndrome following spinal surgery *(164)*. Early changes on MRI may distinguish disc space and vertebral body infection from the normal postoperative spine with a high degree of accuracy *(154,165–168)*. Nuclear imaging is of limited value because of the high level of background positivity *(62)*. Sequential technetium 99 and gallium 67 scans improve sensitivity but require at least 48 hours to complete *(169)*. Although somewhat controversial, diagnosis of infectious discitis should be confirmed by biopsy despite a consistent clinical and radiographic picture. Tissue sampling allows discrimination between septic and aseptic (chemical or avascular discitis) processes and facilitates directed antibiotic therapy. Peripheral blood cultures are rarely positive for the offending microorganism *(58,170)*. Percutaneous needle aspiration of the affected disc space under fluoroscopic or CT guidance is the method of choice. Ideally, antibiotics should be withheld until after the procedure is complete. The results of the Gram's stain and/or culture are diagnostic in up to 70% of cases, and histologic examination may indicate a septic picture in cases lacking positive microbiology *(157,160)*.

Isolated vertebral osteomyelitis is very uncommon following laminectomy and related procedures. When present, it is usually associated with progressive infection of the contiguous disc space (spondylodiscitis) *(154, 170–172)*. Clinical presentation and diagnosis are virtually the same as outlined above for discitis.

Meningitis

The diagnosis of healthcare-associated meningitis requires a high index of clinical suspicion and support from CSF analysis. Excluding ventricular shunt infections, most cases of meningitis following neurosurgery are diagnosed in the early postoperative period. Several series have shown that the majority of cases develop within 10 days of surgery, and virtually all are diagnosed within 28 days *(3,6,7,60,72,173)*. Healthcare-associated meningitis unrelated to surgical procedures has a more variable time course. Posttraumatic bacterial meningitis associated with a CSF leak may occur days to years after the initial injury *(21,174)*. Although some of these infections may develop in the hospital, acquisition of the infecting microorganism likely has occurred in the community environment *(21,22,175)*. Since the CDC definitions do not specify a period during or after hospitalization that distinguishes healthcare-associated

from community-acquired infection, evidence for hospital acquisition must be sought (109). In a review of 197 episodes (157 patients) of healthcare-associated meningitis by Durand et al. (5), 97% of patients were diagnosed more than 48 hours after admission or within 1 week of discharge (5). Interestingly, 41 episodes (10 patients) in this study were recurrent during the same hospitalization. Other studies indicate a similar pattern of presentation *(7,21)*. We consider it reasonable to view nonsurgical healthcare-associated meningitis as developing several days after hospitalization and unrelated to an obvious community-acquired infection. Unfortunately, these distinctions are not always easy to make.

The standard clinical signs and symptoms suggestive of meningitis are often of little help in diagnosing healthcare-associated infection. Fever appears to be the most ubiquitous finding in all healthcare-associated cases *(3,6,7,72,173)*. Neurosurgical patients commonly demonstrate an altered level of consciousness, neck stiffness, and headache reflecting some combination of their underlying disease and the surgical procedure itself in the absence of infection. These relatively nonspecific findings may become more useful if a change over time is noted or a new fever develops. Findings indicative of meningeal irritation are more useful in nonsurgical patients, especially when combined with fever and a change in mental status. Aseptic meningeal inflammation is a common postoperative condition that may further confound the diagnosis. Clinical parameters have been consistently unable to distinguish aseptic from bacterial meningitis *(176,177)*. The use of corticosteroids may blunt the signs and symptoms of inflammation in both surgical patients and compromised hosts *(114,178)*. Neutropenic hosts cannot mount an inflammatory response, and the resultant symptoms are often minimal *(178)*. Low-grade fever, lethargy, and/or headache may be the only clues in these patients *(115)*. Concurrent medical conditions or extremes of age often modify the typical clinical presentation *(6,179,180)*. Finally, the administration of perioperative antibiotics may alter the natural course of clinical responses and laboratory findings (see below).

The signs and symptoms of posttraumatic bacterial meningitis are often similar to those seen in acute bacterial meningitis *(181)*. However, as with the neurosurgical patient, clinical findings may be more difficult to interpret in the patient with considerable head trauma. CSF infection should be considered when there has been any change in neurologic status, or when fever or neck stiffness is noted that was not present initially *(21,182)*. For these patients at increased risk, it is important to establish evidence of CSF leakage when meningitis is a concern. In a retrospective study of 860 patients with moderate-to-severe head trauma, 12 (1.39%) developed meningitis, with 58% of these patients presenting with clinically apparent rhinorrhea (183). The most common signs of a CSF leak are rhinorrhea, otorrhea, hemotympanum, Battle's sign (mastoid ecchymosis), and cranial nerve palsies *(22,184)*. Detection of CSF rhinorrhea is critical and may be performed at the bedside using a glucose oxidase reagent strip to detect increased glucose in nasal secretions, with the caveat that blood, especially when visible in the nasal fluid, may produce a falsely positive test *(185)*. Unfortunately, a negative result does not rule out the presence of a fistula *(186)*. Identification of beta(2)-transferrin in nasal secretions using immunofixation or electrophoresis has shown promise as a useful indicator of CSF leakage (187,*402–404*). A fluorescein dye test can also be used to identify suspected cases of CSF otorrhea and localize the source *(188)*. Radiographic studies are the procedures of choice to document and localize CSF leakage. CT scanning and MRI are superior to plain films in diagnosing basilar skull fractures and identifying fistulae *(189,190)*. Radioisotope cisternography using ^{111}In- or technetium-99m-labeled diethylenetriamine pentaacetic acid (DTPA) is highly sensitive, but specificity is a problem and localization is poor (191,*406*). A combination of different imaging modalities may be required to accurately localize the site of a CSF leak *(405)*; high-resolution CT combined with a fluorescein injection study may offer the best characteristics currently (191). Considering the diagnostic subtleties associated with healthcare-associated meningitis, examination of the CSF assumes a critical role.

Analysis of CSF obtained from hospitalized patients at risk for developing meningitis is often difficult. Neurosurgical patients commonly have abnormal CSF profiles secondary to underlying disease (tumor), procedures, intracranial bleeding, and seizure activity. Perioperative antibiotics will influence the results of cultures of CSF. Nonsurgical patients are likely to be receiving concurrent antibiotics for other infections. Compromised patients may have blunted inflammatory reactions or abnormal CSF profiles from noninfectious processes (e.g., carcinomatous or leukemic meningitis). Despite these limitations, the results are often revealing, and examination of the CSF should be performed routinely in all suspected cases *(407)*.

The CDC definition for healthcare-associated meningitis does not specify abnormal values for routine CSF parameters. As with community-acquired bacterial meningitis, most cases of healthcare-associated meningitis are associated with an increased CSF white cell count, neutrophilic pleocytosis, elevated protein, and depressed glucose (*2*,*3*,5,*7*,*20*,*72*,*137*,*148*,*181*,*192*,193). Neurosurgical patients with culture-proven meningitis generally have more than 100 WBCs/mm^3 with over 50% neutrophilia *(7,72,137,173)*. In the series by Berk and McCabe *(173)*, all patients were noted to have over 100 WBCs/mm^3, with the majority having more than 1,000 cells/mm^3 (median 2,500). In 72 episodes of culture-negative healthcare-associated meningitis described by Durand et al. (5), 97% of patients had more than 300 WBCs/mm^3, and 96% had more than 50% neutrophils. Since an intracerebral bleed or a subarachnoid hemorrhage allows both WBCs and RBCs to enter the CSF, a correction formula may be used to better approximate the number of abnormal white blood cells *(194)*. A CSF protein level >100 mg/dL and a glucose level <40 mg/dL are present in the majority of healthcare-associated cases (5,*7*,*72*,*137*,*173*,*177*). Unfortunately, several studies have found no significant difference in cell counts and other CSF parameters in (early) postoperative patients with septic versus aseptic meningitis *(176,177)*. In these patients, a significantly lowered glucose level (<20 mg/dL) might be the best indicator of an infectious etiology in the absence of culture data (5). The administration of muronomonab (OKT3) to organ transplant recipients during rejection has been associated with the development of aseptic meningitis *(195,196)*.

Routinely, the CSF should be Gram-stained and set up for bacterial culture. In immunocompromised patients, fungal, mycobacterial, and viral studies may be indicated as well. The yield on Gram-stained CSF is lower than in community-acquired cases and approximates 50% overall (5,*78*). Although a positive culture remains the gold standard, it is impossible to make this requirement for healthcare-associated cases if the clinical data and CSF profile are otherwise supportive. In one large retrospective study, a positive culture was obtained in 83% of healthcare-associated cases and a comparable percentage of community-acquired cases (5). Since concurrently positive cultures are often obtained from sites outside the CNS, cultures from blood, adjacent wounds, and urine are suggestive in the appropriate setting *(3,7,60,63,72,137,173)*.

Clearly, the diagnostic value of CSF sampling, under any circumstance, can be greatly influenced by the administration of intravenous antibiotics. The effect of antibiotics prior to lumbar puncture is most marked on the Gram's stain and culture with little alteration of the other standard parameters *(197,198)*. A negative Gram's stain and culture will commonly occur after 24 hours of appropriate therapy *(199)*. The CSF glucose and white cell count usually remain abnormal for at least several days *(194)*. When combined with the baseline abnormal CSF of the craniotomy patient or the tempered inflammatory reaction of the neutropenic host, the effect of prior antibiotics on diagnosis is substantial, and second-line tests assume greater importance. Latex agglutination to detect the capsular polysaccharide of *Cryptococcus neoformans* is a highly efficacious test in immunocompromised patients *(115,178)*. Broad-range polymerase chain reaction (PCR) to amplify the 16S ribosomal RNA sequences specific to bacterial pathogens offers a promising avenue to supplement Gram's stain and bacterial culture, particularly in patients who have received antimicrobial therapy prior to CSF sampling *(200)*.

Final mention should be made concerning the role of neuroimaging in the diagnosis of bacterial meningitis. Although contrast enhancement of meninges may be seen on CT or MRI early in the course of illness, these findings are nonspecific and contribute little to establishing the diagnosis *(164)*. A better use of these modalities is to exclude other CNS pathology or to diagnose intracranial complications of meningitis *(201)*.

CEREBROSPINAL FLUID SHUNT INFECTIONS

A variety of temporary and permanent prosthetic devices are used to access, drain, divert, and monitor the CSF. These devices may be internalized for chronic use or externalized for use in the acute setting. Internalized devices consist of shunts (ventriculoperitoneal, ventriculoatrial, ventriculoureteral, lumboperitoneal), and reservoirs (lumbar, ventricular). Externalized devices facilitate drainage (ventriculostomy, lumbar drain, external shunt) or measure ICP when the device (intraventricular, epidural, subdural) is connected to a transducer. Insertion of a ventriculoperitoneal shunt is the most common surgical procedure performed for the long-term control of hydrocephalus. Infections complicating these devices may occur at any site or compartment traversed by the prosthesis. Proximal infections include meningitis, ventriculitis, empyema, abscess, and infection involving the surgical site (wound infection, cellulitis, osteomyelitis). Distal infections include tunnel infections along the catheter tract, bacteremia, pleuritis, peritonitis, and related intra-abdominal infections. Infections of temporary devices are almost always healthcare associated, because their insertion and use requires hospitalization. The current CDC guidelines define infection secondary to an implantable device as healthcare associated if it occurs within 1 year of the operative procedure and the two appear to be related (109). Such a designation must often be based subjectively on the type of infection, clinical setting, and responsible microorganism. Because of the clustering of shunt infections within 60 days of implantation (*10,64*,*79*,*80*,202,*203*), shorter periods have been suggested to designate a shunt infection as healthcare associated (129). Because of the considerable overlap among infections of different CNS prosthetic devices, this discussion can focus on the diagnosis of CSF shunt infections as the prototype for this group. Certain specific infections potentially related to CSF shunts have already been covered in detail earlier in this chapter (SSIs) or are covered in later sections (intracranial suppurations).

The most important risk factor for the development of CNS shunt infection is the level of training of the neurosurgeon, with neurosurgical trainees having a higher rate of infection *(27)*. Variables such as year of placement of the shunt, age of the patient, length and time of the operation, and exact placement of the distal drain do not increase the risk of infection (202,204). Additionally, elevated CSF protein content does not appear to increase the risk of shunt infection *(205)*.

The clinical manifestations of infections related to CSF shunts, reservoirs, and monitoring devices are quite variable and often nonspecific. Infections of the surgical site or subcutaneous tunnel in the early postoperative period are the most easily recognized, as purulent drainage, erythema, warmth, and tenderness are usually present *(10,79,81,206)*. As will be discussed, infections at these sites are intimately associated with the pathogenesis of deeper and more extensive infections. It has been suggested that CSF shunts be viewed as composed of a proximal and a distal segment with specific signs and symptoms of infection referable to each section *(207)*. Since infection of one shunt section may spread contiguously to involve the entire length of the prosthesis, a patient may present with any combination of signs and symptoms related to the proximal, distal, and intervening sections of the shunt *(82,208–211)*.

In general, fever appears to be the most constant feature of shunt infection (*212,213*,214). Several studies have shown that virtually all patients have a temperature >100°F with the majority febrile to 102°F or higher *(10,82,215,216)*. Unfortunately, the absence of fever cannot be used to rule out infection, as others have demonstrated a small but significant percentage of asymptomatic patients *(81)*. In a recent series examining shunt infections among adult patients (median age: 50, range: 12–80), fever was a presenting symptom in 78%, while neck stiffness (45%) and local signs of infection (49%) were less common (214). Proximal infection of shunts with a ventricular origin is usually associated with symptoms secondary to shunt obstruction

or malfunction *(10,79,81,217)*. Typical clinical manifestations include nausea, vomiting, seizure, malaise, lethargy, irritability, headache, and other indications of increased ICP *(10,13,81,212,213,216–218)*. Classic signs of meningeal irritation (meningismus, photophobia) are present in only one third of patients (*10*,*181*,214). This is due to the inability of CSF to pass into the subarachnoid space of patients with obstructive hydrocephalus or to eventual closure of the aqueduct of Sylvius in shunted patients with communicating hydrocephalus *(219)*. Meningeal signs are more frequently seen in patients with infected lumboperitoneal shunts *(82)*. Manifestations of distal shunt infection depend on the site of the terminal portion. Nearly one third of patients with infected ventriculoperitoneal shunts present primarily with abdominal symptoms in the absence of ventriculitis *(216,220,221)*. Early inflammation about the shunt catheter may result in impaired CSF absorption and loculation of fluid with formation of a peritoneal cyst *(222,223)*. This CSF-oma may present as a palpable mass in younger patients and may represent either a sterile process or an overt infection *(224)*. Multiloculated hydrocephalus, a complication of CNS shunt infection, is more commonly seen as a result of failure to clear a gram-negative bacillus shunt infection following external drainage *(225)*.

Progressive inflammation results in full-blown peritonitis with fever and abdominal tenderness *(212,213)*. An acute abdomen similar to appendicitis may be seen, and intestinal obstruction, bowel perforation, and intra-abdominal abscess have all been described in small numbers *(211,221,226–231)*. Infection complicating a ventriculopleural shunt can lead to the formation of an empyema *(232,233)*. In contrast, patients with vascular shunt (ventriculoatrial) infections tend to present subacutely with lethargy and fever *(10,79)*. The often-indolent presentation of a chronic low-grade vascular infection may delay the correct diagnosis several weeks or longer *(234)*. These patients are also more likely to manifest bacteremia, immune complex nephritis, hypocomplementemia, and thromboembolic complications *(235–237)*. Septicemia, not an uncommon complication in the early years of vascular shunting, is rarely seen today *(208,238)*. A syndrome of immune complex glomerulonephritis (shunt nephritis) is seen in a small number of patients with staphylococcal infections of vascular shunts *(10,239–241)*. Immunoglobulin G and immunoglobulin M antigen–antibody immune complexes are deposited along the basement membrane of renal glomeruli with activation and subsequent depletion of circulating complement *(242–245)*. The nephrotic syndrome may follow generally with mild to moderate impairment of renal function *(246,247)*. Clinically, the patient may have fever, hepatosplenomegaly, proteinuria, hematuria, and an increased ESR *(234,239,247)*. Resolution of the infection usually results in return of the renal function to normal *(234,240)*. Vascular shunt infections may also be accompanied by any of the proximal manifestations mentioned above.

Definitive diagnosis of CSF shunt infections depends on recovery of the etiologic agent from cultures of CSF. However, the physician must always strongly suspect such infection in any patient with fever or evidence of shunt malfunction, as CSF cultures may be negative, particularly if the patient has received prior antibiotic therapy *(248–250)*. As with the clinical presentation, the usefulness and yield of various diagnostic tests differ according to the type of shunt. A recommended diagnostic approach based on the clinical presentation is shown in Table 27-6. The peripheral WBC is generally elevated but may be below 10,000/mm^3 in 25% of patients *(9,10,213,250)*. In patients with ventriculoatrial shunts and chronic bacteremia, positive blood cultures may be obtained in 90% of patients who have not recently received antibiotics *(10,79,82,212,216)*. Conversely, ventriculoperitoneal shunts have a rate of blood culture positivity that approximates only 25% *(79,82,216)*. Urinalysis is indicated when shunt nephritis is suspected, and urine cultures may be useful in patients with ventriculoureteral or lumboureteral shunts. In the early postoperative period, cultures of an infected surgical site or of aspirate obtained from an erythematous subcutaneous tract are always indicated, but the correlation with more definitive CSF cultures is less than perfect. Aspiration of any fluid collection adjacent to the shunt apparatus is also helpful, as a communication with the CSF pathway often exists. Lumbar punctures in patients with ventriculoperitoneal shunts may not reveal evidence of more proximal infection *(207)*. Among 73 CSF specimens collected from adults patients with shunt infections, 66% yielded a positive bacterial culture, with

TABLE 27-6

Clinical Presentation of Shunt Infections and Suggested Diagnostic Steps

Condition	*Diagnostic Procedures*
Meningitis or ventriculitis	Shunt tap and lumbar puncture
Shunt malfunction	Check shunt function by pumping reservoir, shunt tap, contrast radiographic studies of shunt, computed tomography
Wound or shunt tract inflammation	Culture aspirate from inflamed area, shunt tap
Bacteremia (acute or chronic)	Blood cultures, shunt tap, evaluate for endocarditis
Thrombophlebitis or pulmonary embolism	Blood cultures, shunt tap, PE study (CT angiogram, etc.)
Cardiac complications (valve insufficiency, atrial perforation, tamponade)	Blood cultures, shunt tap, cardiac catheterization, echocardiography
Abdominal pain or mass	Culture aspirate from inflamed area along distal ventriculoperitoneal catheter, shunt tap, evaluate surgical abdomen clinically and radiographically
Glomerulonephritis	Blood cultures, shunt tap, urine sediment examination, evaluate for endocarditis

(From Gardner P, Leipzig T, Sadigh M. Infections of central nervous system shunts. *Topics Infect Dis* 1988;9:185–214, with permission.)

valve puncture (91%) and ventricular (70%) CSF specimens more commonly yielding a pathogen compared to lumbar (45%) CSF specimens (214). These limitations make direct sampling of the CSF from the shunt apparatus the most reliable diagnostic test (*10*,*207*,214,*216*,*248*,*249*).

Performing a shunt aspiration enables assessment of shunt function as well as a detailed fluid analysis. Sampling of lumber CSF is of little use, as cultures are often negative (214,*250*). Routine chemical tests are of little value, as an elevated protein or a depressed glucose level is a nonspecific and inconsistent finding *(212,248,249)*. The CSF WBC averages 75 to 150 cell/mm^3; >100 cell/mm^3 correlates with a subsequent positive culture in 90% of confirmed cases *(11,83,248)*. When the cell count is under 20 cell/mm^3, a positive culture is obtained in <50% of cases *(10,79,248)*. All CSF specimens should be immediately Gram-stained, cultured aerobically and anaerobically, and examined for fungus, especially if the host is immunocompromised. The yield of Gram's stain approaches 50% overall and markedly increases with a concurrently elevated CSF cell count or with gram-negative infection *(79,215)*. Although cultures of the CSF appear to be positive in 80% of patients later documented to have infected shunts after removal, the false-negative rate of this test has never been firmly established *(13,82)*. The predictive value of a negative CSF culture may also be substantially decreased in patients whose distal catheters are blocked *(252)*. Supplemental laboratory tests that have been used in diagnosing shunt infection include determination of antistaphylococcal antibody titers and CRP and detection of immune complexes in serum *(252–256)*. In general, the poor sensitivity and specificity of these studies severely limits any clinical utility *(13,252)*. Elevation of the CSF lactate has proven useful in diagnosing postneurosurgical meningitis, but it remains unclear if this readily available test can be used as part of the diagnostic algorithm for shunt infections. In the study by Conen et al., 81% of the patients with shunt infection had CSF lactate values >1.9 mmol/L (214). Neuroradiologic studies such as CT or MRI may give indirect evidence of infection by suggesting obstruction of CSF circulation.

Infection that is essentially restricted to the distal portion of a ventriculoperitoneal shunt is more difficult to diagnose. Peritoneal signs may be present with a normal functional assessment of the shunt and laboratory assessment of the CSF, especially if obtained proximally *(209,222)*. Diagnosis may necessitate a trial of externalization of the distal end with appropriate cultures and close observation for prompt clinical improvement *(203,221,226)*.

Infections of ICP monitoring devices present as proximal shunt infections do. Fever is the most frequent indication of infection, as signs of meningeal irritation are usually absent, and these patients often have an altered sensorium *(34,212,257)*. The most important risk factor for external drain infections is the duration of the device, with a sharp increase in infection rates after 5 days of monitoring in most studies *(14,33–36)*. Infection of the surgical insertion site, ventriculitis, or meningitis is the typical clinical presentation *(9,14,33–36,64,236)*.

In summary, an infection should be strongly suspected in any febrile patient with an indwelling CNS prosthesis. It is important to always consider occult infection as a potential cause of shunt dysfunction *(81)*. All available clinical and laboratory parameters must be utilized in an effort to make an accurate diagnosis. Blood cultures are usually positive in patients with ventriculoatrial shunts, and CSF cultures are positive in the majority of patients with ventriculoperitoneal shunts. Again, it should be emphasized that the CSF may be sterile in a significant number of documented infections. Antibiotic-coated catheters have been proposed as a mechanism to decrease shunt-related infections. A Cochrane meta-analysis examining the use of antibiotic-impregnated shunts (AIS) found that AIS reduced the risk of shunt infections (OR: 0.21, 95% CI: 0.08–0.55) (258). A recent review outlines an approach to treatment of shunt infections using decision analysis *(259)*. This report recommends use of both antibiotics plus shunt removal as the best method to cure shunt infections.

Meningoencephalitis

Meningoencephalitis implies a global CNS inflammation involving the meninges as well as the brain parenchyma. These uncommon healthcare-associated prion and viral infections have been reported following neurosurgical and neurodiagnostic procedures, corneal transplantation, and cadaveric dural grafting *(122–127,260)*. More details on these uncommon infections can be found elsewhere in this text (see Chapter 47), and only a brief overview is offered here.

Generally, meningoencephalitis is characterized by fever and early mental status changes that may later progress to obtundation or coma. The altered level of consciousness and impairment of cognitive functioning may be more impressive than typical meningitis. Focal neurologic features, including sensory disturbances and seizures, are universal findings. Patients with Creutzfeldt–Jakob disease (CJD) develop sensory dysfunction (i.e., ataxia), myoclonus, and cognitive and behavioral abnormalities that progress to overt dementia and finally coma over weeks to months *(261)*. The clinical manifestations of rabies virus have been previously reviewed *(262,263)*. A prodrome of nonspecific symptoms and fever is usually followed by an acute neurologic syndrome manifested by either hyperactivity or progressive paralysis *(263)*. Subsequent coma and death complete the classic picture. Incubation periods of 18 months for CJD and 5 weeks for rabies have been reported in the small number of transplant cases *(125,127)*.

Routine analysis of the CSF is not particularly helpful and usually reveals a nonspecific pleocytosis, elevated protein content, and normal glucose level. The diagnosis of rabies is made by isolation of the virus from saliva, CSF, or brain tissue, or by measurement of neutralizing antibodies in the serum or CSF *(262,264)*. Immunofluorescent staining for rabies antigen may be applied to corneal epithelial cells or to sensory nerves obtained from a full-thickness skin biopsy of the neck *(262,265)*. Histopathologic examination reveals pathognomonic Negri bodies in the majority of cases *(266)*. Patients with CJD exhibit markedly abnormal electroencephalogram results and evidence of cortical atrophy on CT scan *(267)*. Definitive diagnosis of CJD must ultimately be made from brain tissue. Demonstration of pathologic lesions of the cerebral cortex or identification of specific polypeptides (scrapie-associated protein) by immunostaining confirms the diagnosis *(268)*.

Identification of four abnormal proteins in the CSF by gel electrophoresis allows discrimination of CJD from other neurologic diseases *(269)*.

It should be noted that certain bacteria and fungi may cause meningoencephalitis in compromised hosts. The clinical presentation and approach to diagnosis in these patients is essentially the same as for meningitis.

Cranial Epidural Abscess

A CEA or empyema represents a rare infection that occurs between the dura mater and the overlying bone of the cranium. Signs and symptoms are largely based on mass effect, and as these infections often coexist with subdural infections, a composite clinical picture is frequently seen *(270–272)*. Conditions predisposing to the development of a CEA include head trauma, craniotomy, osteomyelitis, paranasal sinusitis, mastoiditis, otitis, and the application of skull tongs *(1,59,273–278)*. Few studies have estimated the number of total cases (as opposed to the incidence per procedure or per hospital admissions) that clearly qualify as healthcare-associated according to the CDC guidelines. However, the reported risk of these infections related to the most common neurosurgical and neuroinvasive procedures appears to be relatively small; most cases (60–90%) are related to paranasal sinus infections *(272)*, and acute sinusitis may be healthcare-associated, especially in the setting of nasogastric intubation.

Healthcare-associated CEA generally occurs as a complication of craniotomy or head trauma. Symptoms include fever, headache, altered mental status, local swelling, erythema, focal neurologic signs, and occasionally seizures *(271,278,279)*. Progression of the abscess is often accompanied by subdural extension and can lead to deterioration of neurologic status, increased ICP, and cerebral herniation *(280)*. The peripheral WBC and ESR are usually elevated, and the CSF profile (lumbar puncture may be contraindicated) reflects parameningeal infection *(270,281)*. The diagnosis is best established by CT, as contrast scanning will reveal a hypodense epidural collection with some degree of ring enhancement *(276,282)*. CEA collections can cross the midline and the underlying brain parenchyma typically appears normal, features that distinguish them from subdural abscesses *(283)*. MRI is likely to be an equally useful modality, but experience remains limited.

Spinal Epidural Abscess

Although hematogenous spread is possible, most healthcare-associated cases of SEA are more likely to be related to spinal procedures (e.g., laminectomy, anesthesia, epidural catheter, injection). In the largest review of published spinal epidural abscess (SEA) cases, 188 of 854 abscesses (22%) were associated with invasive procedures, the most common being epidural anesthesia, extraspinal operations, and spinal operations (284). By definition, healthcare-associated infection becomes evident within 30 days of the procedure, and this is certainly the typical time frame for postoperative cases *(84,285–287)*. However, infection might have been introduced at surgery weeks to months prior to presentation, blurring the distinction between healthcare and community acquisition *(288)*. Patients with SEA secondary to spinal anesthesia develop symptoms from 72 hours to 5 months after catheter placement *(289,290,412–414)* (see also Chapter 60).

The clinical evolution of an epidural abscess as described by Heusner *(291)* occurs in four progressive phases: spinal ache, nerve root pain, radicular weakness, and paralysis. This classic presentation has been well documented in many series, although the rates of neurologic deterioration have been quite variable (*84*,*281*,284,*287*,*288*,*292*,*411*). Backache (71%) and fever (66%) are the most common clinical findings, with one-fifth having local tenderness on exam (284). Other typical symptoms in approximate decreasing order of prevalence include motor weakness, paraparesis, bowel/bladder dysfunction, and sensory deficit (284). Fever, peripheral leukocytosis, and an increased ESR are present in the majority of cases (*84*,284,*287*,*288*,*293*). Rarely, sepsis dominates the clinical picture and the neurologic symptoms go unnoticed *(286)*. In hospitalized patients, initial manifestations may be subtle or difficult to detect because of concurrent conditions, and fever with persistent pain may be the only clue. A small series of postoperative SEAs found a notable absence of fever and peripheral leukocytosis and a paucity of neurologic features *(285)*. Pain and tenderness localized to the surgical site was uniformly present by the second postoperative week *(285)*. Clinical presentations of SEA have also been classified as acute and chronic based on the presence of symptoms for less than or more than 2 weeks, respectively *(84,288)*. Acute cases are likely to be hematogenous in origin, whereas chronic cases are usually related to a contiguous focus of infection *(162,410)*. Although the possibility of an SEA might be considered earlier in healthcare-associated cases, most studies indicate that this is uncommonly the initial diagnosis (284,*287*).

In patients with SEA, CSF analysis usually reflects a parameningeal process with a pleocytosis and elevated protein (*281*,284,*288*,*293*). It might be expected that this profile would overlap considerably with CSF sampling from a relatively early postoperative spinal surgery patient. The CSF white cell count seems to vary inversely with the duration of symptoms *(287)*. Gram's stain and culture of the CSF rarely are revealing; blood cultures are often positive *(287,288)*. Intraoperative cultures are usually positive *(288,293)*.

The diagnosis of an SEA is best confirmed by a neuroradiographic examination showing displacement of intrathecal contrast and/or direct visualization of the abscess. Myelography remains a highly sensitive tool but suffers from the inability to delineate the full extent of the abscess and can cause complications. CT scanning with intrathecal contrast is both highly sensitive and relatively specific but is accompanied by some element of risk *(293–295)*. In selected cases of presumed SEA, CT-guided needle aspiration is useful diagnostically and perhaps therapeutically *(296,297)*. MRI with gadolinium-DTPA contrast is currently the initial examination of choice in patients with suspected spinal infection *(164,166,298)*. MRI is highly sensitive and essentially noninvasive and allows accurate visualization of the full length of an epidural abscess in addition to any contiguous infectious processes *(293,299–301)*. Plain films and radionuclide scans are low-yield nonspecific studies that offer little diagnostic utility. In conclusion, any clinical suspicion should always prompt an imaging study, as rapid neurologic deterioration of the patient may ensue.

Subdural Empyema

Subdural empyema refers to a collection of pus in the space between the dura and the arachnoid. Infection can progress rapidly, as there is little anatomic barrier to spread in this space *(276)*. As with CEAs, most cranial subdural empyemas (CSEs) are related to paranasal sinusitis, otitis media, trauma, and neurosurgical procedures *(302)*. CSEs may be found in conjunction with an osteomyelitis or epidural abscess in 50% of cases. Mortality, near 100% before effective antibiotic therapy, has declined to 9% in one series *(303)*. Clinically, patients present with rapid onset of altered sensorium, meningismus, seizures, focal neurologic findings, and signs of increased ICP following a period characterized by headache and fever *(276,278,303–306)*. A more subacute presentation of CSE has been described in postoperative infections *(307)*. Peripheral leukocytosis and a neutrophilic pleocytosis in the CSF are usually present *(304,305)*. Differentiation from a brain abscess may be difficult on clinical grounds alone. CT scanning or MRI is currently the procedure of choice for diagnosis of CSE, although false negatives may occur *(298,308–312)*. A contrast study will show a crescent-shaped hypodense area with intense enhancement at the brain periphery *(267,309)*.

Spinal subdural empyema is extremely rare; the few cases (61 cases, summarized in reference 297) reported in the literature have been associated with distant sources of infection *(276,313,314,415)*. Presentation is similar to that of SEA except that spinal tenderness on examination may be absent *(314)*. The diagnosis is best made by MRI with gadolinium contrast *(315)*.

Intracranial Septic Thrombophlebitis

Any intracranial suppuration may be associated with septic thrombophlebitis or thrombosis affecting the dura, lateral, sagittal, or cavernous sinuses. Subdural empyema may be complicated by septic venous thrombosis, which can result in brain abscess and infarction. Cortical vein thrombosis has been observed in approximately 25% to 30% of cases and is often associated with a poor outcome *(304,306,415)*. Clinical presentation may resemble parenchymal brain abscess with focal neurologic signs often related to the cranial nerves *(316)*. Similarly, the compressive effects of an SEA may result in thrombosis, thrombophlebitis, and congestion of the epidural venous system *(84,270)*. Again, CT and MRI are the diagnostic methods of choice *(164,267)*.

Brain Abscess

A brain abscess is a focal suppurative process confined to the brain parenchyma. The most common conditions associated with brain abscess include contiguous sources of infection, such as sinusitis, otitis, mastoiditis, dental infection, and cranial trauma (surgical or accidental), or metastatic infection, as in endocarditis or cyanotic heart disease (*64,271,277*,317,*318–320*). Healthcare-associated brain abscess is an unusual complication of routine neurosurgical procedures, paranasal sinus infection, sinus surgery, and transient bacteremia, but may occur following penetrating craniocerebral trauma and in immunocompromised patients *(60,115,321–323)*. In a retrospective study of postneurosurgical brain abscesses, Yang et al. describe 31 patients (0.17% of neurosurgical procedures over a 19-year period) with this condition *(324)*. The period from procedure to diagnosis ranged from 8 to 35 days (mean: 20 days), and there was a male predominance (24 males, 7 females) *(324)*. Gunshot injuries to the head associated with retained bone fragments constitute a particularly high-risk condition *(325)*. Brain abscesses have also rarely complicated the application of cranial tongs and halo fixation devices *(326,327)*. Finally, a brain abscess may follow cranial wound infections, meningitis, shunt infections, or any of the previously discussed CNS-related healthcare-associated infections.

The clinical presentation of a healthcare-associated brain abscess may vary from a relatively acute postcraniotomy suppuration to a more subacute or chronic infection developing secondary to a gunshot wound or indwelling ventricular shunt. Although published data are few, most of these infections appear to present within several weeks of a neuroinvasive procedure. As expected, the healthcare-associated etiology of these infections is often difficult to determine, and supportive evidence is derived from the clinical setting and available microbiology. The presenting features of a brain abscess depend on the size, location, virulence of the microorganism, and condition of the host. Abscesses that evolve secondarily by direct intracranial extension are usually solitary and typically found in the frontal and temporal lobes *(318,319,328–331)*. Infections related to cranial surgery or trauma generally occur in close proximity to the wound (or foreign body), whereas hematogenously spread infection may cause multiple lesions predominantly in a middle cerebral artery distribution *(325,328,332)*. Fever, headache, and focal neurologic findings (the classic triad) are the most common clinical manifestations, seen in approximately 50% of all cases *(329,332,333)*. In the Yang et al. series, fever was present in 17 (54.8%), headache in 11 (35.5%), and motor deficits in 10 (32.3%) *(324)*. Nausea, vomiting, papilledema, seizures, and meningismus are seen in 25% to 50% of patients *(328,332,333)*. Unfortunately, most of these signs and symptoms are difficult to interpret in the neurosurgical patient. The differential diagnosis includes a variety of underlying conditions (e.g., tumor, hydrocephalus, hemorrhage, infarction, thrombosis, and other CNS infections). Any unexpected alteration in mental status or change in the neurologic examination, especially if combined with fever, should prompt a more detailed evaluation (see below). In immunocompromised patients, the abscess must be strongly suspected, as the onset of symptoms may be indolent and the diagnostic clues often are subtle. In these patients, a careful physical examination might disclose purulent drainage or a black eschar on the nasopharyngeal mucosa suggestive of rhinocerebral mucormycosis *(334)*. Proptosis, periorbital cellulitis, ophthalmoplegia, and, ultimately, coma make up the classic rhinocerebral syndrome *(178)*. The spectrum of *Aspergillus* species infections include cellulitis, sinusitis, and pneumonia that may extend to the CNS directly or, more commonly, hematogenously *(335)*. Because of the angiotropic nature of this pathogen, cerebral hemorrhage, thrombosis, or seizure are not uncommon with *Aspergillus* species invasion of the CNS *(114)*.

Peripheral blood studies are rarely useful in the diagnosis of a brain abscess. The WBC may vary from normal to moderately increased, the ESR is nonspecifically elevated in

most cases, and blood cultures are nearly always negative *(332,336)*. Lumbar puncture is generally contraindicated in any patient suspected of having a CNS mass lesion because of the high risk and low yield. When obtained, CSF fluid analysis reveals a mild pleocytosis, elevated protein, and normal glucose consistent with a parameningeal focus of infection (317,*332*,*336*). Cultures are rarely positive unless there is a concurrent meningitis or ventricular rupture has occurred *(337)*. Rapid clinical deterioration and death (presumably from tentorial or brainstem herniation) may occur when CSF is sampled in the presence of a brain abscess, further substantiating the poor risk/benefit ratio of this procedure *(328,329,336)*.

The best approach for the early diagnosis and subsequent management of a brain abscess is provided by radiographic imaging. Previously utilized radionuclide brain scanning with technetium 99 remains a highly sensitive technique (especially in the early cerebritis phase) but has essentially been replaced by newer studies *(267,338)*. The advent of CT scanning has provided a rapid, sensitive, and relatively specific method for diagnosing this intracranial infection. The early phases of cerebritis are characterized by a low-density region on noncontrast scans representing the necrotic center of the abscess. Ring enhancement with contrast occurs variably but may become apparent if delayed images are obtained *(323)*. With formation of a collagen capsule, ring enhancement with contrast is seen in early images surrounding a hypodense center *(323)*. Both edema and contrast enhancement may be attenuated by corticosteroids with minimal effect on a mature lesion *(339)*. Although the sensitivity of CT scans exceeds 95%, the typical findings mentioned above are not pathognomonic and may be seen with neoplasm, infarction, resolving hematoma, and radiation necrosis *(295,339,340)*. Features favoring the diagnosis of abscess include intraparenchymal gas, ependymal or leptomeningeal enhancement, corticomedullary location, multiloculation, ring thickness, and homogeneous capsular enhancement *(323,340)*.

MRI may be the most accurate imaging technique for the diagnosis of brain abscess *(164,312)*. Subtle edema and cerebritis may be detected at an earlier stage on gadolinium-enhanced T2-weighted MRI images than on a corresponding CT scan *(341–343)*. Other potential advantages of MRI over CT include the use of nonionizing radiation, minimal artifact from bone, better delineation of the posterior fossa, and increased ability to differentiate edema from liquefaction necrosis *(341)*. Although the sensitivity of MRI is impressive, the clinical superiority of MRI over CT has not been established *(333)*.

Despite the proper clinical setting and suggestive radiology, an interventional procedure is frequently required to establish the diagnosis, define the etiology, and assist therapeutically. The initial procedure of choice is currently a CT-guided stereotactic aspiration. This highly efficacious technique has an overall diagnostic accuracy exceeding 90% with a reported complication rate (e.g., hematoma, infection, seizure) of approximately 1% *(85,344,345)*. Specific indications for this procedure include (a) the presence of multiple lesions, (b) deep-seated lesions, (c) evaluation for noninfectious etiologies, and (d) the need for external drainage *(344,345)*. Significant coagulopathy is the most common contraindication *(346,347)*. Laboratory evaluation of aspirated material should include histologic examination, Gram's stain, cultures for aerobic and anaerobic bacteria, wet mount, fungal cultures, and viral studies if appropriate. The application of stereotactic biopsy has largely circumvented the use of completely empiric antibiotics as well as the need for a craniotomy.

ETIOLOGY OF HEALTHCARE-ASSOCIATED CENTRAL NERVOUS SYSTEM INFECTIONS

The etiologic agents involved in healthcare-associated CNS infections may be viewed from several perspectives. CoNS, *S. aureus,* and gram-negative aerobic bacilli account for nearly 70% of infections collected through the NNIS system from 1986 to 1992. Table 27-7 displays the distribution of pathogens isolated from neurological SSIs during the period from 2006 to 2007, based on data collected by the NHSN /CDC. Unfortunately, since many healthcare-associated CNS infections are classified as SSIs, only part of the overall picture is reflected in these data. *Propionibacterium acnes,* a gram-positive anaerobic rod, continues to be an increasingly recognized pathogen in craniotomy infections (348). Organ/space SSIs may include meningitis, discitis, and intracranial or spinal abscess. Gram-negative aerobic bacilli are major pathogens in this group, often with significant resistance to antibiotic regimens. Table 27-7 also displays the percentiles of antimicrobial resistance for each respective pathogen. Note that greater than half of the *S. aureus* isolates are methicillin resistant, one-fifth of the *E. coli* isolates are fluoroquinolone resistant, >10% of the *P. aeruginosa* isolates are carbapenem resistant, and nearly one-third of the *A. baumannii* isolates are carbapenem resistant. Yeast (mostly *Candida albicans*) and filamentous fungi (mostly *Aspergillus* species) are involved in an increasing number of CSF shunt infections as the number of susceptible hosts becomes larger. Although the use of rigorous standards makes the NHSN/CDC data extremely useful, further examination of the pathogens responsible for specific healthcare-associated CNS infections, and in specific host populations, is worthwhile. The pathogens in certain infections can be observed to change with the host population (e.g., oncology patients), a particular device, or the duration of follow-up (e.g., CSF shunts). With a few exceptions, the experience with most healthcare-associated infections in the literature correlates well with NHSN/CDC surveillance data.

To a great extent, the pathogens responsible for skin and soft tissue infections following neurosurgery are similar to those found in other surgical infections (see Chapter 21). The close proximity to and often open communication with the CNS underscores the importance of these infections. As will be discussed in the next section, there is a strong association between microorganisms cultured from neurosurgical wounds and isolates obtained from the CSF. *S. aureus* is generally the most common isolate from superficial and deep wound infections following both craniotomy and laminectomy procedures (*1*,*4*,*24*,*56*,*60*,77, *133*,*136*,*347*,*349*). Several studies have identified gram-negative bacilli among the top three isolates; Aucoin et al. *(30)* found these

TABLE 27-7

Healthcare-Associated Pathogens in Neurological Surgical Site Infections 2006–2007, NHSN/CDC Report 2008

Microorganism	*Neurological SSI Percentile*	*Percentile Resistant (Antimicrobial Type)*
Gram-positive pathogens		
Coagulase-negative staphylococci	16.2	
Staphylococcus aureus	50.9	49.2(Oxa)
Enterococcus faecalis	1.2	4.7(Van); 4.1(Amp)
Enterococcus faecium	0.1	56.5(Van); 71(Amp)
Enterococci NOS	1.7	6.7(Van); 10.9(Amp)
Gram-negative pathogens		
Escherichia coli	3.7	22.7(FQ); 2.5 (CARB); 5.3 (CTR or TAZ)
Pseudomonas aeruginosa	4.2	15.9(FQ); 7.9(PTZ); 2.0(AMK); 11.8(CARB); 7.3(TAZ); 5.7(CPM)
Klebsiella pneumoniae	1.8	14.8(CTR or TAZ); 5.2(CARB)
Klebsiella oxytoca	0.4	8.1(CTR or TAZ)
Acinetobacter baumannii	0.8	30.6(CARB)
Enterobacter spp.	4.6	
Fungal pathogens		
Candida albicans	0.4	
Other Candida spp. or NOS	0.0	

(Data adapted from CDC/NHSN Annual Update. *Infect Control Hosp Epidemiol* 2008;29:996–1011.)
Oxa, oxacillin; Van, vancomycin; Amp, ampicillin; CARB, carbapenem; CTR, ceftriaxone; TAZ, ceftazidime; FQ, fluoroquinolone; PTZ, piperacillin-tazobactam; AMK, amikacin; CPM, cefepime; NOS, not otherwise specified.

microorganisms to be the most common isolates from ventriculostomy-related wound infections. Other important microorganisms in decreasing frequency of occurrence include *S. epidermidis,* streptococci, diphtheroids (including *P. acnes*), and *Clostridium* species (*1*,*24*,*30*,*56*,*60*,77,*131*,*133*).

As discussed previously, meningitis is responsible for over 90% of all healthcare-associated CNS infections. The largest single institutional study of bacterial meningitis in adults was published by Durand et al. (5) at the Massachusetts General Hospital. They identified 197 episodes of healthcare-associated meningitis in 151 patients over a 27-year period. The majority of patients had had recent neurosurgery or a neurosurgical device (65%), evidence of immune system compromise (20%), or a CSF leak (9%). The most common healthcare-associated pathogens included gram-negative bacilli (33%), *S. aureus* (9%), CoNS (9%), *Streptococcus* species (9%), *H. influenzae* (4%), *Listeria monocytogenes* (3%), and *Enterococcus* species (3%). The relatively lower incidence of gram-positive infections in this series may reflect changing epidemiologic trends, the increased number of procedures, and improving culture techniques inherent in a long study period. Of note, 41 episodes of recurrent meningitis occurred in this group and were caused primarily by gram-negative bacilli (46%).

Studies examining meningitis following neurosurgery have repeatedly implicated gram-negative bacilli as the predominant pathogen responsible for up to 69% of cases *(3,7,72,173)*. In a series of 23 cases of neurosurgical meningitis reported by Buckwold et al. *(3)*, 19 cases were due to gram-negative bacilli and four cases to *S. epidermidis (3). Enterobacter* species and *Klebsiella* species were the most common microorganisms. In a large prospective single institution study of postcraniotomy meningitis over 6 years (1997–2003), 28 of 86 pathogens isolated (32.6%) were Enterobacteriaceae, 20 (23.3%) were CoNS, and 13 (15.1%) were *S. aureus* (350). Looking at the entity of gram-negative meningitis as a whole, approximately 50% of cases are related to neurosurgery *(7,72,173). Klebsiella* spp, *Enterobacter* spp., *Escherichia coli, Pseudomonas aeruginosa,* and *Acinetobacter baumannii* are the most frequent isolates. So-called diphtheroids (*Corynebacterium, Bacillus* species, and *P. acnes*) are also important pathogens in neurosurgical patients (see below). Wound infection due to *P. acnes,* with and without meningitis, has been reported after neurosurgical procedures (348,*351–353*).

In studies similar to those yielding the NHSN/CDC system data in Table 27-7, staphylococcal species are isolated from approximately 60% to 80% of CSF shunt infections in large series, whereas gram-negative bacilli are found in 5% to 27% of cases *(10,13,79,81,82,181,212,213,216,250,354, 355)*. CoNS (mostly *S. epidermidis*) are isolated in 50% to 75% of cases followed by *S. aureus* in 10% to 25% of cases *(82,86,354)*, although McGirt et al. *(250)* reported that a hospital stay of >3 days at the time of shunt insertion and a prior *S. aureus* shunt infection independently predicted that *S. aureus* was the causal pathogen. There appears to be little difference in the pathogens involved in early versus late shunt infections, although one study suggested that gram-negative pathogens, especially *H. influenza,* may be more common in late infections *(79,250)*. Conen et al. found that late shunt infections were polymicrobial in six of eight adult patients (214). Similarly, the location of the distal end of the shunt catheter does not seem to significantly affect the distribution of pathogens unless intestinal perforation has occurred *(216,356)*. Other commonly encountered pathogens include streptococcal species and

diphtheroids. *P. acnes* is particularly important, as it has been reported to be the second most common pathogen in some series *(357,358)*. Whether the incidence of this pathogen is truly increasing or underestimation occurs secondary to inadequate anaerobic culturing remains unclear *(359)*. *Bacillus* species have also been implicated in shunt infections *(360)*. Anaerobic bacterial and fungal shunt infections have been reported but are seen much less frequently.

The microbiology of infections complicating other CNS prosthetic devices closely parallels the profile seen with ventricular shunts. Gram-positive cocci account for the majority (70–75%) of infections complicating the placement of CSF reservoirs, with the remainder caused primarily by gram-negative microorganisms and diphtheroids *(36,87)*. Ohrstrom et al. *(361)* found gram-positive cocci in almost 90% of 27 ventriculostomy-associated CSF infections. In a large prospective study of ventriculostomy-related infections, Mayhall et al. *(9)* described nearly equal numbers of gram-positive (47%) and gram-negative (53%) pathogens. CoNS were the predominant species, accounting for 32% of isolates. Aucoin et al. *(30)* noted an increase in gram-negative ventriculomeningitis (~75%) in patients with ICP monitors compared with craniotomy alone. A more recent study of ventriculostomy infections by Arabi et al. found gram-negative bacilli in 50% of cases, with gram-positive cocci in 29% *(35)*. *B. cereus* meningitis was reported in two patients with external ventricular drainage and could be traced to contaminated linen used during surgery *(49)*.

The infectious agents responsible for deep CNS and neurosurgical infections (organ/space infections) have generally been well described in the literature. Unfortunately, although significant numbers of these cases are healthcare associated, information relating specific pathogens to healthcare-associated cases is relatively limited. Most healthcare-associated cases of CEA and CSE occur in the setting of trauma, surgery, or paranasal sinus infection *(270,303)*. Infections originating from the sinuses or mastoids are usually caused by anaerobes, streptococci, enterococci, or *S. aureus (303,304,362,363)*. Postsurgical and posttraumatic suppurations are usually due to *S. aureus,* streptococci, or gram-negative bacilli *(304,364)*. Khan and Griebel *(365)* found that most cases of postsurgical and posttraumatic subdural empyemas were caused by *S. epidermidis* or *S. aureus*. A large review of 699 cases of CSE found viridans group streptococci (*S. milleri*, *S. haemolyticus*) in nearly 25% of patients and gram-negative bacilli in 14% (366). Spinal epidural abscess is caused by *S. aureus* in 50% to 65% of cases, followed in frequency by streptococci (9–14%), gram-negative bacilli (8–16%), and *S. epidermidis* (3–9%) *(84,274,287,288,292,362)*. Again, although varying numbers of these infections were healthcare associated, correlation to specific pathogens was not performed. However, a small series of iatrogenic cases of spinal epidural abscess reported by Ericsson et al. *(286)* describes a distribution of pathogens quite similar to the studies cited above. In the largest analysis of SEA cases to date, Reihsaus et al. reported *S. aureus* in 73% of the cases (551 of 753 pathogens isolated) (284). Disc space infection in adults is usually a postsurgical complication, although hematogenous spread occurs as well *(162)*. *S. aureus* is the most common pathogen followed by *E. coli, S. epidermidis,* and other gram-negative microorganisms *(58,61,151,157)*.

Healthcare-associated brain abscess is an uncommon infection that usually occurs in association with neurosurgical procedures or penetrating head trauma *(60,271,323–325,332)*. A smaller number of cases may occur in the setting of sinus infection or generalized bacteremia *(328)*. If present, the abscess is usually related to the surgical site, and staphylococci are usually isolated *(182,332,333,367)*, commonly as part of a polymicrobial infection *(324)*. Other prevalent pathogens in this setting include streptococci, gram-negative aerobic bacilli, and *Clostridium* spp. *(320,324,368)*. Anaerobes, streptococci, and, less commonly, *S. aureus* and gram-negative microorganisms are involved when a paranasal sinus or a mastoid source of infection is present *(329,332,367)*. Hematogenous seeding of the brain may occur during the course of staphylococcal endocarditis and with gram-negative bacterial or fungal dissemination in immunocompromised hosts (see below) *(115,178)*.

In the hospital setting, immunocompromised patients are at risk for a somewhat different spectrum of CNS infectious agents than their counterparts with normal immune function. It is important to recognize the close relationship between the duration and type of specific immune defect and the infections to which the host is susceptible. Table 27-8 illustrates the association between host immune status, typical CNS pathogens, and the clinical syndromes they cause. Several important pathogens (e.g., *Cryptococcus, Toxoplasma, Nocardia*) in this group are not included, as hospital acquisition would be unusual. Studies by Chernik et al. *(116)* identified the pathogens responsible for CNS infections among patients at a large cancer hospital. Of potential healthcare-associated pathogens, gram-negative bacilli (50% *P. aeruginosa*) were the most frequent cause of meningitis, followed by *L. monocytogenes,* streptococci, and, rarely, fungi. Various gram-negative bacilli were also responsible for three quarters of the brain abscesses, although *Aspergillus* was the most common isolate *(112)*. The majority of cases developed during the course of hospitalization. In a follow-up to their initial studies, the same authors noted a high incidence of fungal CNS involvement on postmortem examination alone *(112)*. Other reports have also described an increase in CNS candidiasis with systemic involvement, suggesting a higher-than-expected prevalence of this pathogen *(121,369)*. *Aspergillus* invasion of the CNS is often cited as the most common intracranial infection in cardiac and renal transplant patients *(370)*. Needless to say, these patients are also at risk for the common healthcare-associated pathogens that may complicate neuroinvasive procedures.

OUTCOME

The considerable morbidity and mortality associated with infections involving the CNS place them among the most serious of healthcare-associated infections. Morbidity may be manifested by varying degrees of neurologic deficit, ranging from paresthesia to permanent paralysis. Intellectual impairment can be a particularly devastating consequence. Mortality due to CNS infection is

TABLE 27-8

Healthcare-Associated CNS Infections in Immunocompromised Patients

Defect/Patients	*Pathogens*	*Clinical Syndromes*
Cell mediated		
Chronic steroids	*Listeria*	Meningitis, encephalitis
Lymphoma	*Aspergillus*	Brain abscess
Hodgkin's disease	Mucorales	Brain abscess
Solid organ transplant and AIDS	Mycobacterial	Brain abscess
Neutrophils		
Aplastic anemia	*Pseudomonas*	Meningitis
Acute leukemia	Enterobacteriaceae	Meningitis, brain abscess Meningoencephalitis
Chemotherapy	*Candida*	Meningitis, brain abscess
Radiation therapy	*Aspergillus*	Brain abscess
	Mucorales	Brain abscess
	Pseudallescheria boydii	Brain abscess
Mixed		
Bone marrow transplant	Enterobacteriaceae[a]	Meningitis, brain abscess Meningoencephalitis
	Candida	Meningitis, brain abscess
	Aspergillus	Brain abscess

[a]During the period of neutropenia in the early posttransplant period (0–30 days).

frequently difficult to establish with certainty in critically ill patients with other significant medical problems. These patients may have died for reasons apart from healthcare-associated CNS infections, severely limiting the usefulness of most mortality data. Hospitals reporting through the NHNS system determine (subjectively) whether healthcare-associated infections were a contributing factor in patient death. For the period 1988 to 1993, healthcare-associated CNS infections were deemed to be related to death in 49 of 53 patients (92%) who died with a diagnosed healthcare-associated CNS infection (R. Gaynes, personal communication to Nelson Gantz). This finding suggests that healthcare-associated CNS infections may contribute significantly to mortality. In addition, the economic costs of healthcare-associated CNS infections are often substantial and are associated with the need for extended hospitalization, intravenous antibiotics, sophisticated imaging, and multiple surgical procedures.

Superficial SSIs in neurosurgery, although often prolonging hospitalization, are rarely associated with any mortality by themselves *(131)*. The majority of bone flap infections resolve with antibiotics and/or debridement, and a small number develop chronic persistent drainage *(4,143)*. The real danger of these infections lies in intradural extension leading to increasing complications and deaths *(1)*.

The reported mortality related to healthcare-associated meningitis (not associated with prosthetic devices) ranges from 20% to 67% (*3*,5,*6*,*7*,*72*,*173*). Durand et al. (5) found the mortality rate to be 35% for healthcare-associated cases, compared with 25% for community-acquired infections. The complication rate (i.e., seizures) is also high and may be up to 50% in some series *(7)*. However, Baltas et al. found no mortality associated with posttraumatic meningitis and reported the development of hydrocephalus in two (of 12 patients with meningitis) patients who also happened to receive intrathecal amikacin as part of their therapeutic regimen (183). Given the fact that these patients sustained injuries in the community setting, it is unclear whether their favorable outcomes can be translated to those who acquire healthcare-associated pathogens postoperatively. As discussed above, many of these cases involve gram-negative bacilli, and some authors have demonstrated that increased mortality occurs with these microorganisms *(3)*.

Of all infectious complications related to neurosurgery, CSF shunt infections are probably responsible for the largest volume of morbidity and mortality. Walters et al. *(82)* found patients with infected shunts required three times the number of surgical procedures as non-infected patients, and had greatly prolonged hospitalizations and double the case fatality rate. Schoenbaum et al. *(10)* found long-term mortality to approach 40% in patients with infected shunts as compared to 17% in shunted patients without infection. Yogev *(371)* performed an extensive review of success rates in treatment of CSF shunt infections by compiling multiple studies over a 25-year period. Cure rates were directly related to the therapeutic modality as follows: (a) 36% for antibiotics alone; (b) 65% for antibiotics and immediate shunt replacement; and (c) 96% with antibiotics, shunt removal, and external drainage or repeated ventricular aspirates. In a similar analysis by Kaufman and McLone *(207)*, cure rates were nearly identical in each category, with mortality rates decreasing from approximately 24% with intravenous antibiotics alone to <10% with antibiotics plus externalization. One potential drawback of the latter method is secondary

contamination of the ventriculostomy and complications related to a new infection. Retrospective studies have shown that shunt infections are associated with deterioration of intelligence quotient (IQ) scores *(372)*. Infections related to other CNS prosthetic devices are also associated with significant mortality, especially in the setting of gram-negative involvement *(9,30,111)*. Mayhall et al. *(9)* found no untreated patient survived a ventriculostomy-related infection; Smith and Alksne *(88)* found 100% mortality when *P. aeruginosa* was the pathogen.

Unfortunately, the precise relationship between most healthcare-associated organ/space CNS infections and outcome cannot easily be determined from reviewing the literature. Therefore, and because of the low incidence of these infections, only general trends can be examined. Spinal epidural abscess is an infection in which significant neurologic deficit is probably the most common complication. Mortality ranges from 5% to 33%, and persistent neurologic abnormalities (weakness, paraparesis, paralysis) can be seen in 10% to nearly 50% of cases *(84,286–288,292)*. Two large series found paralysis or death in 23% of patients *(287,288)*. In their large meta-analysis, Reihsaus et al. found that SEA mortality improved from 34% during the period from 1954 to 1960 to 15% during the period from 1991 to 1997'. Cranial subdural empyema carries a mortality rate of 15% to 35% with a high incidence of seizures and disabling neurologic sequelae *(268,304,306,365,373,374)*. Kaufman et al. *(304)* described four cases of postoperative subdural empyema in which two patients died and another suffered a permanent neurologic deficit. In a retrospective review of subdural empyema, Dill et al. *(303)* reported an overall mortality of 9%, but 55% had neurologic deficiency at time of hospital discharge. In their review of 699 cases of intracranial subdural empyema, Nathoo et al. report a mortality rate of 12% and a morbidity rate of 25.9%, including 14.7% of 509 patients with clinic follow-up who experienced postoperative seizures (366). The prognosis of a healthcare-associated brain abscess is particularly difficult to estimate because of the low frequency of occurrence and the often-concurrent existence of another serious intracranial infection *(60,323)*. In general, advances in diagnosis and treatment have resulted in a current overall mortality rate of approximately 10% to 32% *(320,375,376)*. Adverse prognostic factors include delay in diagnosis, ventricular rupture, depressed mental status at the time of diagnosis, large and/or multiple lesions, extremes of age, and specific gram-negative or fungal etiology *(328,329,332,336,337,377)*. Since most patients with healthcare-associated brain abscess have one or more of these risk factors, morbidity and mortality can be expected to be high in this population. Even successfully treated brain abscesses can result in appreciable long-term neurologic complications. Chronic seizure disorders and persistent focal neurologic deficits can develop in up to 50% of patients *(328,336,337–379)*. Neurologic outcome is most influenced by location of the abscess and the age of the patient *(378)*. Cognitive and behavioral function may be permanently impaired, especially in younger patients *(377,380)*. In a more recent study, Yang et al. found a mortality rate of 16% (5 of 31 cases) for healthcare-associated brain abscesses in patients after neurosurgical interventions, with death occurring as a result of brain edema and herniation in all five *(324)*. Three of 31 case patients in this series experienced a relapse of brain abscess. Of the 26 survivors, 3 were in a persistent vegetative state, 15 had moderate-to-severe residual neurodeficits, and 8 were able to resume normal activities with little or no deficits. Lastly, postoperative disc space infection (usually healthcare associated) is rarely associated with mortality but may cause significant morbidity. Chronic pain unrelated to the primary problem occurs in many; 39% to 88% of patients are able to return to work after treatment *(58,62,381)*.

The consequences of infection from pathogens of even low virulence are frequently devastating in the immunocompromised patient. CNS infections are often caused by gram-negative bacteria and fungi; eradication of these microorganisms from the CNS is difficult enough in immunocompetent hosts. Chernik et al. *(112,116)* found mortality from CNS infections to be related primarily to the microorganism and the underlying disease of the patient. The highest overall mortality for intracranial infections was seen in leukemic patients (90%), followed by lymphoma patients (77%) and patients with head and spine tumors (59%). Survival was lowest with gram-negative bacterial infection (10–22%) and highest with infections caused by *L. monocytogenes* (63%) and *S. aureus* (76%). Notably, no patient with noncryptococcal fungal infection of the CNS survived in their series. Other series have also described overall mortality rates exceeding 50% from CNS infections in immunocompromised patients *(114,382)*. Darras-Joly et al. describe three cases of cerebral aspergillosis in immunocompromised patients that developed after neurosurgical operations; two of these patients survived after combined surgical debridement, high-dose amphotericin B, 5-flucytosine, and itraconazole *(383)*. These authors reasonably conclude that cerebral aspergillosis should be treated aggressively with a combination of medical and surgical therapy in order to improve an extremely high baseline mortality rate. Subsequent reports in organ transplant patients have documented rare survival with intracerebral aspergillosis *(384)*. Rhinocerebral infection with Mucorales can be cured in over 50% of cases with aggressive medical-surgical therapy and control of acidosis in diabetic patients *(334)*.

PREVENTION

Prevention of Craniotomy Infections

Prior to the 1980s, use of prophylactic antibiotics in neurosurgery was based mainly on data from uncontrolled trials. In the 1980s and 1990s, data from prospective randomized placebo-controlled trials demonstrated the efficacy of antibiotic prophylaxis in patients having clean neurosurgery. A meta-analysis of 2,075 patients evaluating antibiotic prophylaxis prior to neurosurgery found a fourfold reduction in wound infection rate when antibiotic prophylaxis was given *(416)*. Table 27-9 demonstrates at least a three- to fourfold reduction in the incidence of infection after craniotomy using an antistaphylococcal antibiotic such as cefazolin or vancomycin. Some studies have also added gentamicin to the antistaphylococcal antibiotic. Antibiotic prophylaxis is usually administered for 24 hours. Some of the studies

TABLE 27-9

Randomized Trials of Antibiotic Prophylaxis in Neurosurgical Procedures

First Author	*Year*	*Comparator 1 (Infection Rate %)*	*Comparator 2 (Infection Rate %)*
Savitz	1976	Clindamycin (1.2)	None (10.9)
Shapiro	1986	Van/gent (2.8)	None (11.7)
Young	1987	CFZ/gent (1.0)	None (3.8)
Blomstedt	1988	Van (1.8)	None (7.3)
Bullock	1988	Pip (2.1)	None (5.9)
Van Ek	1988	Clox (3.3)	None (10.3)
Djindjian	1990	Oxa (0.6)	None (4.9)
Whitby	2000	CFT (2.5)	TMP-SMX (2.3)
Zhu	2001	Amp-Sul (2.3)	CTX (3.3)

(Data from Refs. *74,385–392*.)
Van, vancomycin; gent, Gentamicin; CFZ, cefazolin; Pip, piperacillin; Clox, cloxacillin; Oxa, oxacillin; CTX, ceftriaxone; TMP-SMX, trimethoprim–sulfamethoxazole; Amp-Sul, ampicillin–sulbactam; CFT, cefotaxime.

used, in addition to the parenteral antibiotics, a bacitracin irrigation solution. In a study of 356 patients given oxacillin or placebo for prolonged clean neurosurgery, there was an eightfold reduction in the incidence of infection in those given parenteral oxacillin compared with the placebo group *(385)*. Use of an antibiotic irrigating solution in that study was not mentioned.

In an uncontrolled study to assess the efficacy of intravenous cloxacillin prophylaxis in patients undergoing craniotomy, the infection rate was 4% *(393)*. Patients with a penicillin allergy received erythromycin. Antibiotics were given for 24 hours. In operations ($n = 17$) when prophylactic antibiotics were inadvertently omitted, the infection rate was 27%. The authors concluded that an antistaphylococcal penicillin such as cloxacillin was effective in reducing the incidence of craniotomy infections to less that 5% compared with the usual rates of 5% to 15% without additional prophylaxis. Whitby et al. performed an open randomized trial comparing cefotaxime with trimethoprim–sulfamethoxazole (TMP-SMX) prophylaxis in patients undergoing neurosurgical procedures (craniotomy, shunt surgery, stereotactic surgery) and did not find a difference in the postoperative infection rate between these groups (2.5% cefotaxime, 2.3% TMP-SMX) *(386)*. Similarly, Zhu et al. performed a randomized, double-blind study comparing ceftriaxone with ampicillin–sulbactam (AMP-SUL) for prophylaxis of neurosurgical SSIs and found no difference between these groups (SSI rates: 2.3% AMP-SUL, 3.3% ceftriaxone) *(387)*. Finally, a recent meta-analysis of randomized trials examining antimicrobial prophylaxis for postcraniotomy meningitis found a significant reduction (pooled OR: 0.43, 95%CI: 0.2–0.92) in this complication when antimicrobial prophylaxis is employed (394).

The American Society of Health-System Pharmacists (ASHP) 1999 guidelines on surgical prophylaxis, currently being updated in collaboration with the Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America, recommend cefazolin 1gm iv given at induction of anesthesia for elective craniotomy (395).

Prevention of Cerebrospinal Fluid Shunt Infections

The majority of neurosurgical shunt infections occur within 2 months of surgery. Most infections result from the direct inoculation of bacteria during surgery and in the perioperative period. Antibiotic prophylaxis is usually directed against CoNS, the most frequent cause of shunt infections. Numerous studies have been undertaken to determine if antibiotic prophylaxis is effective in decreasing the number of infections that complicate the implantation of CSF shunts *(110,396)*. These studies have yielded conflicting results. In a meta-analysis of 12 controlled randomized trials (1,359 patients), antibiotic prophylaxis at the time of CSF shunt placement decreased the rate of infection by 50% *(397)*. However, only a single trial of these 12 studies achieved statistical significance *(60)*. Most of the studies were performed in a pediatric population and are discussed in Chapters 49 and 65. In the one study including adult patients, oxacillin reduced the infection rate from 20% in the control group to 3.3% in the treated group ($p < 0.05$) *(385)*. Various antimicrobial agents were used in these trials, including cloxacillin, trimethoprim–sulfamethoxazole, cephalosporins such as cephalothin, vancomycin, and gentamicin *(398)*. The duration of prophylaxis ranges from <24 hours to up to 48 hours after surgery. The ideal agent to prevent CSF shunt infections is unknown, since comparative studies are unavailable. Based on the results of susceptibility testing, vancomycin might be the preferred drug, but in one trial a histamine-like rash was noted in 35% of patients, despite being infused over 1 hour *(79)*. Despite the suggested benefit from antibiotic prophylaxis in the meta-analysis of the 12 studies, infection rates in the treated group still averaged 6.8%, with a range of 1.9% to 17% *(397)*. Infection rates in the control groups for these studies averaged 13%, with a range of 5.5% to 24% *(397)*. Such high rates in the groups that received prophylaxis for clean surgery suggest the need for other approaches to prevent infection such as the use of shunts with antimicrobial or antiadherence properties. A 2006 Cochrane

meta-analysis of antimicrobial-impregnated shunts (AIS) concluded that the use of these shunts is associated with a reduced risk of shunt infection (OR: 0.21, 95%CI: 0.08–0.55) but suggested that more evidence be sought via more well-designed trials (258,*408*).

Prevention of Infections After Spinal Surgery

In a classic retrospective study, prophylactic antibiotics reduced the infection rate in patients undergoing a laminectomy for lumbar disc disease *(133)*. However, infection rarely occurs after spinal surgery such as a lumbar discectomy, and antibiotics are usually not given. However, in spinal procedures involving fusion or for operations that are prolonged, antibiotics are often used, although randomized prospective controlled trials are lacking. In addition, spinal procedures in immunocompromised hosts or procedures involving implantation of hardware are usually given antibiotic prophylaxis, although controlled data are lacking. A 2002 meta-analysis of prospective randomized trials and/or trial subgroups that studied antimicrobial prophylaxis in patients undergoing spinal surgery demonstrated a significant benefit favoring antimicrobial prophylaxis (pooled OR: 0.37, 95%CI: 0.17–0.78), despite the failure of any individual trial to find such a benefit (399). No recommendation can be made for a specific antimicrobial based on the currently available clinical trial data; use of a first- or second-generation cephalosporin is suggested.

Prevention of Infection with a Cerebrospinal Fluid Leak

The value of antimicrobial prophylaxis in any patient with a CSF leak remains unclear. Definitive studies to resolve this issue are lacking, and at present their use cannot be recommended *(400)*.

ACKNOWLEDGMENT

We would like to acknowledge the tremendous amount of work done by our predecessor, Dr. Nelson Gantz, in preparing, writing, and editing the prior editions of this chapter.

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SECTION V
Epidemiology and Prevention of Healthcare-Associated Infections Caused by Specific Pathogens

PART A. Bacterial Infections

CHAPTER 28

Staphylococcus aureus

Joseph F. John, Jr. and Sanjay K. Shukla

The carrier is the archetypal stranger, both embodying the danger of microbial invasion …and transforming it into the possibility for rejuvenation and growth.

Priscilla Wald *in Contagious*

Staphylococcus aureus throughout history has been the preeminent scourge of *Homo sapiens*. Though not a requirement for homeostasis, its ready integration into the flora of the anterior nares and other moist or hairy bodily areas in over 20% of healthy people suggests that *S. aureus* may function symbiotically at those sites. Yet nasal carriage is the constant element of pathogenesis, the major risk factor for subsequent infection *(1–3)*. After years of tedious delineation of its multiple virulence factors, publications of the whole genomes from heterogeneous strains and new functional studies on regulation and pathogenesis are providing new insights into the mechanisms for invasion of the skin, endovasculature, and solid organs by *S. aureus (4–6)*. Over the last three decades, methicillin-resistant *S. aureus* (MRSA), because of its relative increase, has overshadowed studies of its relative nonresistant counterpart, methicillin-susceptible *S. aureus* (MSSA) *(7)*. Yet, MSSA continues to be a major healthcare-associated problem with the risk of MSSA infection in hospital wards three times that of patients who are not carriers *(3,8)*. Much of the phenotypic identity of MRSA comes from the presence of a staphylococcal chromosomal cassette (SCC*mec*) that with its *mec*A gene, encodes a new penicillin-binding protein PBP2a, which is necessary for expression of resistance to most beta-lactam antibiotics. Studies of specific genes such as *mec*A *(9)* have revealed the complexity of gene expression in pathogenic strains of *S. aureus* (need new reference). Since the expression of other virulence genes in MSSA and MRSA such as those involving surface adherence is highly regulated like *mec*, many years of additional study will likely be required to understand pathogenesis in order to design new antimicrobials and vaccines to reduce invasive healthcare-associated infections due to both entities *(10–12)*.

S. aureus as a community pathogen is best known for its ability to produce furuncles and infect soft tissue. A community MRSA known as USA 300 has recently produced a global pandemic, primarily consisting of severe skin and soft tissue infections *(13)*. Along with traditional (USA 200, USA 400) and emerging healthcare-associated strains, USA 300 now threatens hospitalized patients *(14,15)*. The emergence of new healthcare-associated strains comes as no surprise since, historically, healthcare-associated infections were almost exclusively caused by *S. aureus* until the 1960s, when the prevalence of infections due to gram-negative bacilli increased noticeably *(16)*. That ascent of gram-negative bacteria as the new threat in hospitals lulled hospital physicians into thinking that their old nemesis—*S. aureus*—would remain of historical interest only. Yet by the early 1990s, data from the National Nosocomial Infections Surveillance (NNIS) system at the Centers for Disease Control and

Prevention (CDC) indicated that *S. aureus* was again increasing in incidence as a healthcare-associated pathogen *(17)*, a trend that only until recently has leveled off *(18)*. With broadening resistance to newer antimicrobials and disinfectants, MRSA along with MSSA has become the dominant healthcare-associated pathogen in hospitals worldwide *(19)*. Additional new strategies are needed to limit healthcare-associated spread and consequent morbidity due to MSSA *(20)*. This chapter reviews the role that MSSA continues to play in healthcare-associated infections and serves as an introduction to Chapter 29, dedicated to MRSA.

HISTORICAL PERSPECTIVE

There are several early biblical descriptions of staphylococcal infection. Of the 10 plagues brought by Yahweh onto the Egyptian Pharaoh, the sixth cast boils or sores upon man and beast (Exodus 9:8–12) *(21)*. The boils arose after Moses took ashes and sprinkled them aloft, filling the air over Egypt with dust that induced outbreaks of boils on man and beast, sores that were wretched in their appearance but not fatal. In another biblical passage, Job is stricken by Satan with boils (or ulcers) that made his body turn black (Job 2:7). There is little information about furunculosis during the next millennium, though it must have remained a major problem. The so-called high Middle Ages has been described as a period that was remarkably disease free, though, ironically, it was followed by centuries of epidemics of plague with little attention to other bacterial infections *(22)*. With the advent of Pasteur's techniques to culture bacteria, the coagulase-positive *Staphylococcus* was isolated and assigned a species name in the 1880s *(23)*. Since that time, the number of species of the genus has grown to over 36 *(24)*. Using automated techniques, any clinical laboratory is able to distinguish among the growing number of other species capable of infecting humans *(25–27)*.

Not until the 20th century was a connection made between colonization by specific bacteria and subsequent healthcare-associated infection. The increasing importance of *S. aureus* as a cause of hospital sepsis resounds from the documentary writing of Dr. Wesley Spink *(28)*. In the preantibiotic era, mortality due to staphylococcal sepsis secondary to pneumonia, osteomyelitis, and cellulitis was as high as 82% *(29)*. Osteomyelitis due to *S. aureus*, especially infection of the long bones, was often disabling, although mortality due to staphylococcal sepsis was lower in patients with osteomyelitis. The use of sulfonamides from 1937 to 1942, strangely, was not much better than maggots in the treatment of local or osseous staphylococcal infection *(28)*. The miracle of penicillin became available in 1942 and quickly reduced the mortality rate of invasive staphylococcal infection from 80% to 35%. Penicillin resistance, however, developed rapidly in *S. aureus*, and in hospitals where penicillin was heavily used there were frequent epidemics caused by strains of penicillin-resistant *S. aureus (28,30)*. Multiple advisory groups in the late 1940s, therefore, were assembled to make recommendations for control of staphylococcal epidemics. Pharmaceutical companies, spurred on by the early success of penicillin, mobilized to develop new antistaphylococcal agents *(30a)*.

By the 1950s, Spink et al. established the connection between the carriage in the nasopharynx of hospital employees and the frequent contamination of wounds *(31)*. After penicillin resistance became widespread, Spink's Minnesota group showed again that the reservoir of *S. aureus* was hospitalized patients and hospital personnel. Spink stated that the rise in mortality due to penicillin-resistant *S. aureus* was due to cross-infection of "traumatic and surgical wounds transmitted by healthy hospital carriers or from other patients with sepsis. Patients and hospital personnel were found to be heavily parasitized by highly resistant strains of pathogenic staphylococci primarily within bacteriophage type Group III" *(31)*. Indeed, the problem of staphylococcal sepsis in US hospitals during the early 1950s was the major stimulus for development of infection control committees *(16)*. Such committees, eventually under the direction of hospital epidemiologists, created strict isolation units that, over the next several years, reduced the number of infections at the University of Minnesota and other hospitals. Despite early successes in infection control of staphylococcal infection, Spink's prescient, cautious words resonate today: *"The skin and respiratory tract will remain as the major portals of entry, and staphylococcal sepsis will continue to challenge medical practice."*

Sixty years later, we should remember the intensity of infection control measures that were required for containment of staphylococcal sepsis in the 1950s. Assuredly, during the 1960s and 1970s, newer antibiotics, particularly the semisynthetic penicillins, did reduce the risk of healthcare-associated staphylococcal infection. Extensive use of these agents over the next three decades, however, ushered in international healthcare-associated epidemics due to related MRSA strains *(16)*. In a study comparing the rates of *S. aureus* infection in a tertiary care hospital from the periods 1971 to 1976 and 1989 to 1992, all but one of the MRSA strains from the later period were acquired in the hospital or in a nursing home, whereas about 80% of the infections due to MSSA were community-acquired (D. Musher, personal communication). Since the third edition of this text was published, the problems of healthcare-associated MRSA and more regularly recognized MSSA with the resultant medical literature have clearly burgeoned worldwide. Over the last 10 years, there have been 8,771 MRSA infections references and 695 MSSA infections references in PubMed, respectively.

MICROBIOLOGY OF *STAPHYLOCOCCUS AUREUS*

Species Characteristics

Species Identification *S. aureus* has traditionally been defined by phenotypic traits that distinguish it from micrococci and other staphylococci *(26)*. *S. aureus* is a catalase-negative, coagulase-positive, nonmotile coccus that appears as bluish-black clusters or tetrads after Gram staining. *S. aureus* grows by 3 days as 6- to 8-mm colonies that are usually hemolytic on blood agar and salt tolerant; they become gold-pigmented after 24 to 48 hours of incubation. Laboratory identification can be aided by observing anaerobic acid production from glucose, production of

acid from glycerol in the presence of 0.4 μg/mL erythromycin, and mannitol fermentation, as well as by susceptibility to lysostaphin and furazolidone and resistance to bacitracin *(25)*. *S. aureus* also produces a thermonuclease that is useful in identifying the species *(32)*. Salt tolerance is probably due to the stability of the *S. aureus* cell wall derived from the *N*-acetyl glucosamine residues cross-linked with glycine pentapeptide. Ribitol teichoic acid polymers also link the peptidoglycan *(4)*. Alterations in this structure can actually reduce the minimum inhibitory concentration (MIC) to antistaphylococcal penicillins *(33)*. *S. aureus* has other survival genes including those to respond to low pH and high salinity, and some of these genes are regulated by sigma factors like σ *(34–36)*.

Staphylococci can be identified by both conventional and rapid laboratory methods. Several marketed kits allow rapid species identification with 70% to over 90% accuracy in detecting as few as 10 CFU/mL *(37)*. Mannitol salt agar has traditionally been the selective culture method of choice for isolation of *S. aureus*. Newer chromogenic media designed to recover and rapidly identify *S. aureus* and MRSA appear superior to mannitol salt agar *(38)*. Methods such as restriction fragment length polymorphism (RFLP) of RNA genes (ribotype) and detection of the *S. aureus nuclease* gene by polymerase chain reaction (PCR) or fluorescein tagging are available commercially to differentiate *S. aureus* from other species when specialized tracking is required *(39)*. In the future, other methods like MALDI may also become very useful for rapid surveillance of *S. aureus* healthcare-associated infection/colonization (infra vide).

There are several commercially available PCR assays for use in detecting either *S. aureus* or MRSA from nasal surveillance swabs. While significantly more expensive than conventional culture methods, several of these PCR assays can be performed on the day of admission to enable colonized patients to be isolated more quickly from the general patient population, thus decreasing the risk of healthcare-associated transmission. In addition, patients undergoing orthopedic or cardiothoracic surgery are often tested for the presence of *S. aureus* and/or MRSA and decolonized prior to surgery.

S. aureus can be identified directly from positive blood culture bottles by peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) or by PCR; the latter method can distinguish MSSA and MRSA. Thus, the healthcare epidemiologist has a growing armamentarium of laboratory methods to expand clinical and epidemiologic investigations.

Strain Identification The healthcare epidemiologist may find it necessary to distinguish among multiple endemic versus epidemic strains of *S. aureus* for purposes of tracing the source of the infecting isolate, identifying reservoirs of antibiotic-resistant *S. aureus*, monitoring the colonization of patients or personnel, and, possibly, identifying virulent subtypes. Identification of epidemiologically related microorganisms at the subspecies level may help determine whether the observed clustering of isolates represents distinct strains or several isolates of the same strain that are causing an outbreak. A typing system is adequate if there is a high probability that two random isolates that are epidemiologically unrelated are indeed different. An ideal typing system would generate about 20 groups with even distribution of random isolates. A high proportion of isolates must be typeable, and the method must be reproducible, easy to perform, and inexpensive, and it must avoid the necessity of a second typing system to provide further discrimination. Because of the increasing need to relate strains of *S. aureus* epidemiologically, methods for typing strains have increased over the last 10 years. Nonmolecular and molecular methods of typing *S. aureus* are shown in Table 28-1.

TABLE 28-1

Nonmolecular and Molecular Methods of Typing *S. aureus*

Molecular Methods	*Nonmolecular Methods*
Plasmid content	Antibiotic susceptibility
Chromosomal REA	Phage typing
Serotyping	
Plasmid REA	Capsule typing
RFLP	Alloenzyme patterns
Gene polymorphism	Immunoblotting
Random PCR	
Repetitive element PCR	Multilocus enzyme focusing
PFGE	SDS-PAGE
MLST	
Whole genome analysis	
Microarray analysis	
SCC*mec* type	

MLST, multilocus sequence typing; PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis; REA, restriction endonuclease analysis; RFLP, restriction fragment length polymorphism; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis.

Nonmolecular Methods of Typing

Typing systems have been based on differences in antigenic structure, phage susceptibility, antibiotic susceptibility, biochemical profiles, and DNA composition. One antigenic typing method uses antibodies to the 11 known capsular polysaccharides. Healthcare-associated isolates, however, are predominately composed of only two types, 5 and 8 *(40)*, though 24% of strains remain untypeable by this system.

One antigenic system is based on 30 soluble protein or carbohydrate determinants *(41)*. Antigen expression by specific strains depends on the selected growth media, which may be why the antibodies necessary for these systems are not available commercially.

Phage typing has been in use since 1952 and is a laborious method that is performed only by a few reference laboratories. The international set of typing phages, seldom employed but of practical significance, is shown in Table 28-2 *(16,42)*. The phage reactions are relatively stable; lysis is graded from weak to strong, and if no lysis develops at 100 times routine test dilution, the strain is considered untypeable. Strains are considered different if the phage pattern differs by two or more phage reactions that show strong lysis. Yet, the same lysis pattern does not necessarily equal epidemiologic relatedness. Phage-typing methods are further limited, because many strains—particularly MRSA—are not lysed by the available phages and are therefore untypeable *(42)*. Phage-typing patterns can change when *in vitro* selected vancomycin-resistant strains are compared to their vancomycin-susceptible parents *(43)*.

TABLE 28-2

Phages and Phage Groups of *S. aureus*

Phage Group	*Standard Phages that Lyse*
I	29, 52, 52a, 79, 80
II	3a, 3c, 55, 77
III	6, 42e, 47a, 53, 54, 75, 83a, 84, 85
IV	Bovine strains
V	94, 96
Miscellaneous	81, 95

Although pulsed-field gel electrophoresis (PFGE) patterns between susceptible parents and resistant selectants remained the same, phage types frequently changed or selectants became nontypeable.

An elegant antigenic typing method, termed immunoblotting, uses pooled human sera for detecting various antigens among *S. aureus* strains by Western blotting *(44)*. Immunoblotting identified eight patterns using different batches of pooled sera that correlated with phage typing. The method was more discriminating than plasmid profiles, but between 2% and 28% of immunotypes were discrepant on repeat testing. The method was capable of identifying strains that were clinically and epidemiologically related. Immunoblotting combined with antibiograms has been used to discriminate a new outbreak strain from an endemic strain of MRSA (45). Applied in another study, immunoblotting could differentiate 43 strains into only two major groups, making it only as good as endonuclease digestion of plasmid DNA *(46)*.

Antibiograms can be useful when a unique resistance pattern prevails. A given resistance phenotype, however, may result from different arrangements of multiply resistant genes, thus not ensuring DNA sequence identity. Furthermore, resistance (R) plasmids mediating traits such as antibiotic resistance are not always stable. The loss of R plasmids would allow otherwise identical parent strains to be typed as different using antibiograms. A clever way to circumvent this problem is through the use of multiplex PCR that will simultaneously generate multiple amplicons signifying the presence or absence of specific resistance determinants like *mec*A, aacA, tetM, and so on *(47)*. Multiplex PCR is the current extension of "resistotype" identification suggested by Elek et al. 40 years ago *(48)*.

Biochemical typing (biotyping) is based on enzyme activities, including the commercial methods of such companies as API and Vitek. Color changes are based on acid production from carbohydrates. Although such typing is relatively inexpensive and easy to perform, the traits may vary over time and geographic areas. They are not highly discriminating and need to be combined with other typing methods. Differences in single enzymes, such as esterase, have been used in typing but are also not discriminatory when used alone *(49,50)*.

Multilocus enzyme electrophoresis (MLEE) is based on small differences in electrophoretic mobility of chromosomally encoded metabolic enzymes. Proponents of MLEE feel that each pattern of enzymes determines a clone. MLEE has identified 11 types of *S. aureus*, though the predominance of type 15 in healthcare-associated outbreaks may limit its usefulness to the healthcare epidemiologist *(51)*. Because it is technically difficult to perform *(52)*, MLEE is also not ideal for hospital outbreaks. Another method analyzes differences in the cell wall peptidoglycan. This method, termed peptidoglycan fingerprinting, separates cell wall components by thin-layer chromatography. Unfortunately, this method is difficult to perform and yields an insufficient number of bands for discriminating among endemic and epidemic strains *(53)*.

In the last 3 years, mass spectrometry has burst onto the clinical microbiology scene as a fast and accurate method for identifying pathogens at a species and even a subspecies level *(54)*. Using one application called matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), species can be obtained quickly in around 90% of instances. Of course, a mass spectrometry instrument is required for local application, so the initial outlay in startup costs is expensive. Nevertheless, recent studies suggest that MALDI-TOF compares to spa typing (infra vide) for rapid and accurate identification of *S. aureus* clonal complexes *(55)*.

Molecular Typing Techniques

Rapid advances in commercially available DNA manipulation kits, high-throughput sequencing, sophisticated imaging, newer molecular biology instrumentations, etc. have made the molecular genotyping of bacteria feasible in small to advanced clinical microbiology laboratories. DNA-based analysis can differentiate bacterial strains that are similar in phenotypic traits but similar or dissimilar in their genotypes *(56)*. A select number of genotypic methods are described below.

Plasmid Analysis. One of the earliest genotypic methods to distinguish clinical strains of *S. aureus* was plasmid analysis. Plasmid analysis by either visualization of individual intact plasmid bands in an agarose gel or after digestion with an appropriate restriction enzyme has been a classic genotypic method for more than 20 years. But it has major limitations. First, unlike coagulase-negative staphylococci, *S. aureus* seldom has more than three plasmids, so there is little chance of generating a complex fingerprint, thus limiting discrimination. Second, as with other bacteria, *S. aureus* strains may lose plasmids and/or gain or lose antibiotic-resistant genes within a desired plasmid, thus limiting the reproducibility of the method. Third, many strains lack plasmids and are, therefore, untypeable by this method. Fourth, very large plasmids that migrate near the top of the gel may be difficult to differentiate; therefore, precise comparisons between strains with large plasmids would be difficult. In case of large plasmids, inclusion of restriction enzyme digestion steps to digest the plasmid DNA enhances the reproducibility and discriminatory power, though this method is seldom used in clinical microbiological laboratories *(57)*.

Pulsed-Field Gel Electrophoresis. Methods for analyzing chromosomal DNA instead of plasmids overcame many of the limitations of plasmid analysis. PFGE has become one of the most popular methods to genotype *S. aureus*, particularly MRSA in recent years. In PFGE, chromosomal DNA from

S. aureus is digested preferably with *Sma*I (*51,53*,58). *Sma*I digests have been optimized for and shown to be stable in *S. aureus* strains even after repeated subculture. Since *Sma*I fragments are too large to permit electrophoresis with a conventional electrophoresis apparatus, a new system has been developed *(59)*. PFGE requires a relatively expensive, specialized apparatus (e.g., CHEF DR II system, BioRad) to resolve the restricted fragments. In PFGE, high molecular weight DNA is extracted *in situ* from agarose-embedded *S. aureus* cells using lysostaphin and proteinase K to minimize the shearing of DNA. The *in situ* DNA (in agarose plugs) is then digested with *Sma*I, and the digested fragments are resolved in a 1% high-quality agarose gel. During electrophoresis, the direction of the electrical field is alternated to allow the large molecules to be reoriented *(60)*. The alternate or the abrupted electric field enhances the resolution of large DNA molecules (>200 kb and up to 10 MB) by allowing them to snake through the agarose. For *S. aureus*, the number of *Sma*I restricted DNA fragments resolved by this method is <20. The similarity and dissimilarity in the fingerprints of two strains are determined by combining genetic relatedness criteria and the Dice Coefficient *(61,62)*: The equation appears as

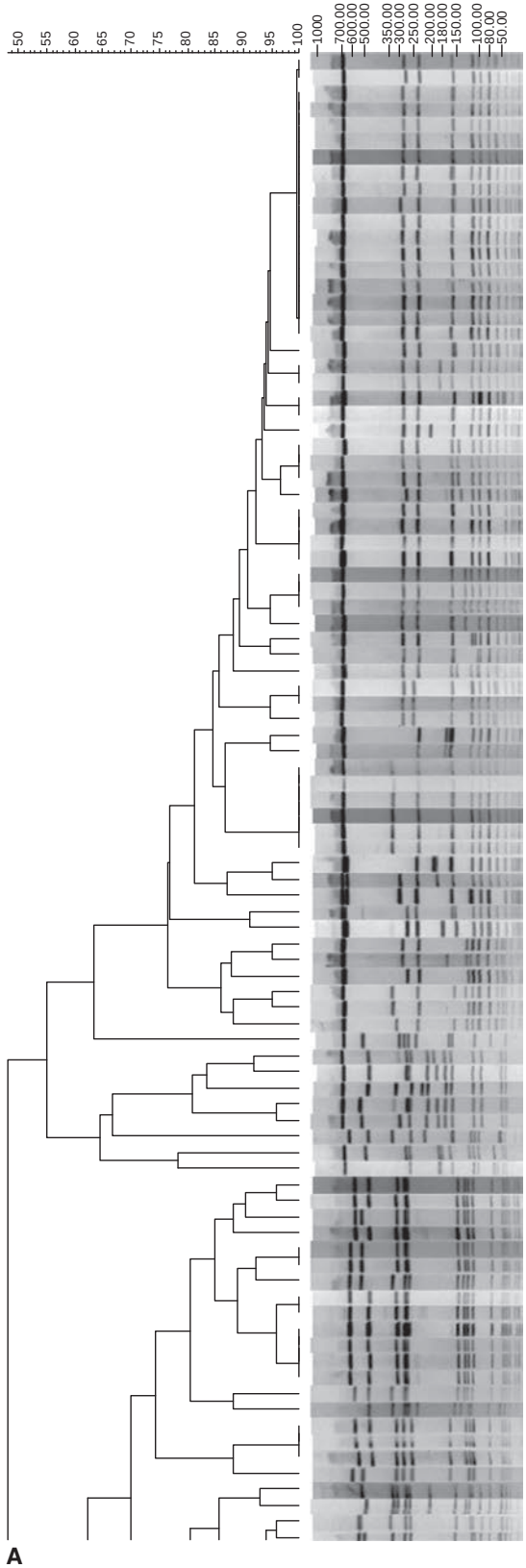
$$\mathrm{Sd} = \{2N \times 100\}/F,$$

where the Dice coefficient, Sd equals twice *N*, the number of shared restriction fragments times 100 divided by F, the total number of restriction fragments generated by enzyme digestion *(62)*. Computer software such as Bionumerics is used to establish a DNA similarity matrix based on the Dice coefficient and band tolerance (*63,64*). The simplicity in interpretation of PFGE results has led it to be the "gold standard" for bacterial genotyping methods. Indeed, PFGE has been extensively used over the last 15 years to describe MRSA outbreaks and their changing epidemiology (58,*61,63,65–67*). Although PFGE is highly discriminatory and reproducible within a laboratory, methods and technician experience differ among various laboratories and lead to differences that may arise in gel appearance and difficulties when comparing results from different laboratories. Matching of PFGE types through gel images from different sources to implicate spread from one source to another has its limitations. In addition, PFGE is time consuming and takes up to 48 hours to complete the experiment (Fig. 28-1).

Multilocus Sequence Typing. A DNA sequence-based method termed multilocus sequence typing (MLST) has been used for analyzing large collections of bacterial strains from several genera (Table 28-3). This method overcomes the problems with reproducibility and interpretation created by gel-based DNA typing systems. In this method for typing *S. aureus*, approximately 450-bp long internal fragments of both strands of seven housekeeping genes (carbamate kinase [*arcC*], shikimate dehydrogenase [*aroE*], glycerol kinase [*glp*], guanylate kinase [*gmk*], phosphate acetyltransferase [*pta*], triosephosphate isomerase [*tpi*], and acetyl coenzyme A acetyltransferase [*yqiL*] are amplified and then sequenced to determine their allelic differences (Table 28-3) *(68)*. The sequence is submitted to the MLST Web site (www.mlst.net) for comparison to known allelic variants to obtain the MLST allelic profile of an isolate. Based on the gene sequence of each of the seven alleles, a sequence type (ST) is determined. Further comparisons between STs can be performed using one of several algorithms. eBURST (electronic Based Upon Related Sequence Types) is one such algorithm. Clonal complexes consisting of related groups or STs are thus generated. This strategy has been used to show marked similarities among a highly diverse collection of MRSA and MSSA *(70)*, reflecting the population and the evolutionary genetics because of the large number of possible STs that can potentially exist. Other advantages of the MLST include its portability between laboratories and availability of a large, freely available, constantly updated MLST database (www.mlst.org/). Unfortunately, the ability to perform PCR and rapid DNA sequencing has limited this method to research laboratories. It should be possible for commercial or university laboratories to adopt the methods and rapidly sequence PCR products generated from epidemiologically important isolates *(69)*. combined the MLST technique with RFLP for tracking genomic islands that may insert into different genetic backgrounds to elegantly show the evolution of MRSA strains from ancestral MSSA strains.

Spa Typing. It was mainly developed to overcome the need of sequencing multiple genes in MLST. *Spa* typing is based on the polymorphic 21- to 24-bp variable-number tandem repeat (VNTR) within the 3′ coding region of the polymorphic X region of *S. aureus*-specific staphylococcal protein A. In the *spa* gene, the in-frame, short-sequence repeats are degenerative, variable in number, and variable in the order in which trinucleotide repeats are organized *(70)*. In this approach, both rapid (microvariation) and slow (macrovariation) genetic variations in the *spa* gene are indexed. Indexing two types of variations makes it useful in both local and global epidemiologic studies. The sequencing of the polymorphic region allows one to identify the 21- or the 24-bp repeats designated by a letter code (A–Z, A2, B2, etc.), and the profile of these repeats (Y-1-H1-G1-F1-M1-B1-Q1-B1-L1-O1) gives a *spa* type. A publicly available large database of *spa* types exists (*http://www.egenomics.com/* and Ridom Staphtype software) where one can compare their *spa* sequence profile to obtain the *spa* type. The advantages of *spa* typing are in its lower cost and labor, ease of analysis, and the ever-growing *spa* database. The disadvantages are that 0.1% of *S. aureus* strains are non–*spa* typeable and there is a lack of a strong evolutionary perspective for phylogenetic analysis. Nevertheless, to overcome this shortcoming, BURP (Based Upon Repeat Pattern) has been developed to determine the *spa*-based clonal complexes (*spa*CC). The BURP allows the determination of the founder *spa* types, *spa*CC, and unrelated types as singletons *(71)*.

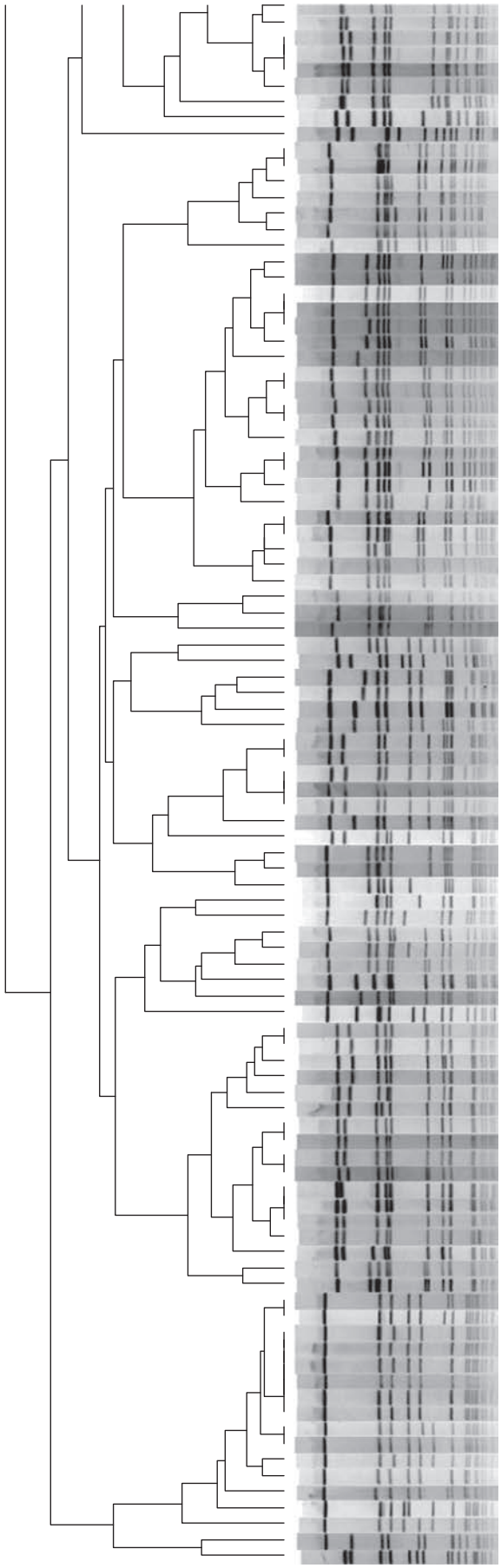
Each of the three methods, PFGE, MLST, and *spa* typing has its own advantages and disadvantages. An investigator needs to know which approach will be most useful for a particular investigation. In general, disease outbreaks investigations are preferably done by the PFGE and now also by *spa* typing. MLST is the preferred method to study the population structure of the *S. aureus* and global epidemiology. PFGE has been found to be more discriminatory than MLST and in most cases *spa* typing as well. One of the main advantages of the PFGE approach is the characterization of major US MRSA clones described as USA100, USA200, USA300 (CA-MRSA), USA400 (CA-MRSA), … USA1200. These USA reference strains are available from the NARSA database (*http://www.narsa.net/*).



Strain	PT	CG	ST	*spa*	CC
UWL-94-S	B1	B	t018	30	30
WSLH-43-S	B1	B	t363	30	30
MC-146-S	B1	B	t018	30	30
MC-133-S	B1	B	t012	30	30
MC-116-S	B1	B	t840	30	30
MC-151-S	B1	B	t1333	543	30
UWL-13-S	B1	B	t275	30	30
UWL-32-S	B1	B	t012	30	30
UWL-79-S	B1	B	t046	30	30
UWL-87-S	B2	B	t2920	30	30
WSLH-9-S	B1	B	t017	30	30
WSLH-19-S	B1	B	t2926	30	30
WSLH-10-S	B1	B	t021	30	30
WSLH-11-S	B1	B	t871	1101	30
WSLH-16-S	B1	B	t122	30	30
WSLH-30-S	B1	B	t1522	1103	30
WSLH-31-S	B1	B	t2923	30	30
WSLH-39-S	B1	B	t1642	30	30
UWL-39-S	B3	B	t012	30	30
MC-145-S	B5	B	t012	30	30
UWL-20-S	B5	B	t012	30	30
MNDH-107-S	B4	B	t2917	992	30
MC-140-S	B4	B	t012	30	30
USA200 (NRS383)			t018	36	
UWL-45-S	B7	B	t021	243	30
WSLH-1-S	B7	B	t1306	30	30
WSLH-22-S	B7	B	t012	30	30
WSLH-15-S	B6	B	t2910	30	30
UWL-89-S	B9	B	t012	30	30
WSLH-14-S	B9	B	t012	30	30
WSLH-34-S	B9	B	t338	1104	30
WSLH-38-S	B9	B	t018	30	30
UWL-9-S	B10	B	t012	30	30
UWL-23-S	B10	B	t019	30	30
UWL-93-S	B10	B	t012	30	30
UWL-16-S	B11	B	t012	30	30
MC-108-S	B12	B	t012	1107	30
UWL-76-S	B13	B	t021	30	30
WSLH-33-S	B8	B	t021	30	30
MNDH-106-S	B14	B	t012	30	30
UWL-72-S	B14	B	t021	1001	30
MNDH-101-S	B15	B	t012	30	30
MNDH-112-S	B16	B	t012	30	30
UWL-19-S	B17	B	t018	30	30
MC-144-S	B18	B	t274	30	30
MNDH-37-S	B18	B	t012	30	30
MNDH-47-S	B18	B	t1152	30	30
UWL-12-S	B18	B	t021	30	30
UWL-66-S	B18	B	t338	30	30
UWL-80-S	B18	B	t018	30	30
MNDH-124-S	B19	B	t2959	39	30
WSLH-29-S	B20	B	t2643	39	30
WSLH-7-S	B21	B	t2924	39	30
MC-106-S	B23	B	t2918	30	30
USA1100 (NRS484)				30	
MNDH-105-S	L1	L	t136	991	30
WSLH-23-S	L2	L	t166	1102	30
MNDH-108-S	L3	L	t136	989	30
MNDH-120-S	L4	L	t2917	989	30
MNDH-122-S	L5	L	t2917	989	30
MNDH-121-S	L6	L	t2917	989	30
MNDH-98-S	R1	R	t1960	1021	1021
MNDH-62-S	J3	J	t159	51	121
WSLH-20-S	J4	J	t159	51	121
MNDH-84-S	Y1	Y	t1961	51	121
MNDH-32-S	J1	J	t159	51	121
MNDH-60-S	J2	J	t2155	121	121
UWL-102-S	Z1	Z	t518	50	50
UWL-69-S	zz1	zz	t375	1000	509
UWL-91-S	yy1	yy	t1977	22	22
UWL-11-S	C5	C	t084	15	15
WSLH-36-S	C6	C	t346	15	15
UWL-84-S	C7	C	t335	15	15
WSLH-25-S	C8	C	t094	15	15
UWL-5-S	C3	C	t084	15	15
UWL-28-S	C3	C	t2925	15	15
MC-109-S	C4	C	t3027	15	15
MNDH-99-S	C2	C	t346	802	15
MC-101-S	C2	C	t084	15	15
MNDH-43-S	C1	C	t084	1143	15
UWL-26-S	C1	C	t084	15	15
UWL-74-S	C1	C	t774	15	15
UWL-88-S	C1	C	t2914	1003	15
UWL-24-S	C9	C	t084	15	15
UWL-95-S	C10	C	t316	59	15
MC-124-S	P1	P	t1164	9	9
UWL-50-S	P1	P	t2921	9	9
WSLH-21-S	P1	P	t193	9	9
MNDH-29-S	P2	P	t100	27	9
MC-132-S	G5	G	t216	59	59
WSLH-40-S	G6	G	t216	87	59
UWL-18-S	G2	G	t216	59	59
UWL-49-S	G3	G	t216	59	59

A

FIGURE 28-1 PFGE dendrogram of *S. aureus* strains collected over 19 years from Wisconsin and Minnesota. The collection was composed of three groups, including nasal isolates of MSSA, clinical isolates of MSSA, and clinical isolates of community MRSA. Each pulsotype (PT) is also characterized by corresponding PFGE-based clonal group (CG), *spa* type, and MLST-based sequence type (ST), and clonal complex (CC). Note also the inclusion of PFGE-based USA genotypes that were included as reference strains. The dendrogram was made using 1.25% tolerance, the Dice similarity coefficient, and unweighted-pair group method using arithmetic averages. Strains were considered related if they had ≥80% genetic similarity. (Reproduced from Shukla SK, Karow ME, Brady JM, et al. Virulence genes and genotypic associations in community-associated methicillin-resistant and susceptible *Staphylococcus aureus*. *J Clin Microbiol* 2010;48:3582–3592, with permission.)



Strain	PT	CG	ST	*spa*	CC
UWL-18-S	G2	G	t216	59	59
UWL-49-S	G3	G	t216	59	59
UWL-30-S	G1	G	t216	59	59
UWL-77-S	G1	G	t316	59	59
WSLH-24-S	G1	G	t216	59	59
UWL-25-S	G4	G	t216	1108	59
MNDH-110-S	G7	G	t216	1110	59
USA1000 (NRS483)				59	
UWL-55-S	ww1	ww	t937	1112	398
MNDH-35-S	F4	F	t2909	1144	25
MNDH-94-S	F1	F	t078	25	25
MNDH-102-S	F2	F	t078	25	25
MNDH-103-S	F3	F	t078	25	25
MC-125-S	F6	F	t078	25	25
UWL-56-S	F5	F	t258	25	25
MNDH-115-S	F7	F	t660	1146	25
169-R	A5	A	t128	1	1
272-R	A2	A	t175	1	1
USA400 (MW2)			t125	1	1
34-R	A1	A	t128	1	1
88-R	A1	A	t128	1	1
397-R	A3	A	t128	1	1
33-R	A6	A	t128	1	1
MNDH-77-S	A7	A	t128	1	1
WSLH-6-S	A7	A	t558	1	1
MC-112-S	A8	A	t591	1	1
WSLH-32-S	A8	A	t922	1	1
MC-118-S	A9	A	t2915	1113	1
UWL-57-S	A16	A	t1178	1	1
UWL-83-S	A16	A	t922	1	1
WSLH-35-S	A17	A	t922	1	1
MNDH-97-S	A18	A	t160	1142	1
MC-127-S	A12	A	t2297	97	1
MNDH-125-S	A12	A	t189	97	1
UWL-35-S	A13	A	t267	97	1
UWL-92-S	A14	A	t359	97	1
MNDH-31-S	A15	A	t1965	987	1
MC-139-S	Q1	Q	t189	188	1
UWL-100-S	Q2	Q	t189	188	1
UWL-10-S	Q3	Q	t189	1106	1
WSLH-8-S	V1	V	t2913	1148	1148
WSLH-12-S	V2	V	t082	395	395
MNDH-36-S	M2	M	t2919	20	20
MNDH-25-S	M1	M	t164	20	20
WSLH-17-S	M3	M	t164	20	20
MC-177-S	M4	M	t164	20	20
MC-126-S	K2	K	t209	109	9
MC-167-S	K2	K	t209	109	9
MNDH-54-S	K1	K	t2922	1141	9
MC-131-S	K1	K	t209	109	9
UWL-41-S	K1	K	t209	109	9
WSLH-5-S	K3	K	t2700	144	9
USA100 (NRS382)			t002	5	
MNDH-90-S	S1	S	t2703	990	8
UWL-86-S	S2	S	t148	72	8
USA700 (NRS386)			t126	72	
USA800 (NRS387)			t088	5	
USA300 (NRS384)			t008	8	
MC-117-S	H2	H	t008	1150	8
UWL-78-S	H1	H	t404	30	30
MC-104-S	H4	H	t008	1105	8
UWL-37-S	H6	H	t622	8	8
UWL-99-S	H5	H	t334	8	8
USA500 (NRS385)			t064	8	
MC-115-S	D1	D	t067	5	5
UWL-33-S	D1	D	t179	5	5
UWL-81-S	D2	D	t062	5	5
UWL-85-S	D5	D	t179	5	5
MNDH-33-S	D3	D	t002	148	5
UWL-82-S	D6	D	t002	5	5
UWL-68-S	D7	D	t2916	5	5
UWL-4-S	D7	D	t548	5	5
MNDH-92-S	D8	D	t002	5	5
UWL-96-S	D8	D	t045	5	5
MNDH-46-S	D9	D	t688	148	5
MNDH-86-S	D9	D	t179	5	5
MNDH-85-S	D9	D	t067	5	5
MC-158-S	D10	D	t002	148	5
MNDH-69-S	D11	D	t002	5	5
MNDH-87-S	D13	D	t548	5	5
MNDH-113-S	D14	D	t548	5	5
UWL-27-S	E2	E	t015	45	45
UWL-67-S	E3	E	t065	45	45
MNDH-123-S	E1	E	t1549	45	45
MC-105-S	E1	E	t061	256	45
MC-138-S	E1	E	t2143	45	45
MC-174-S	E1	E	t2911	45	45
MNDH-82-S	E1	E	t1964	256	45
UWL-90-S	E1	E	t715	794	45
MC-128-S	E4	E	t004	45	45
MNDH-61-S	E4	E	t1826	45	45
MC-184-S	E5	E	t917	45	45
MNDH-70-S	E6	E	t1962	45	45
UWL-70-S	E7	E	t050	508	45
USA600 (NRS22)			t204	45	
UWL-36-S	E8	E	t330	45	45
MC-113-S	U1	U	t2912	395	395
WSLH-18-S	U2	U	t2927	395	395

B

TABLE 28-3

Housekeeping Genes Amplified by MLST Primers

arc	Carbamate kinase
aro	Shikimate dehydrogenase
glp	Glycerol kinase
gmk	Guanylate kinase
pta	Phosphate acetyltransferase
tpi	Triosephosphate isomerase
yqi	Acetyl coenzyme A acetyltransferase

Multiple-Locus Variable-Number Tandem-Repeat Assay (MLVA). This PCR-based assay exploits the VNTRs in the *clfA*, *clfB*, *sdrCDE*, *spa*, and *sspA* loci to obtain PCR amplicon banding pattern that can be used to investigate MRSA outbreaks. (*72*,73). It is comparable to PFGE if >75% relatedness for MLVA criteria is used.

Amplified Fragment Length Polymorphism. Amplified fragment length polymorphism (AFLP), which utilizes a combination of selective PCR amplification of restriction fragments from a total digest of genomic DNA, has also been used to study the population structure of *S. aureus* (74,75). In one study a large collection of *S. aureus* isolates (n = 1,056), AFLP revealed the presence of three major and two minor phylogenetic branches. The above grouping, however, was not able to distinguish virulent strains from the nonvirulent strains as expected suggesting that any *S. aureus* genotype could cause a serious infection although some lineages appear to be more virulent than others *(75)*.

Whole Genome Sequencing. Genome sequencing remains the last resort to conclusively genotype a pathogenic strain. Despite the steadily decreasing cost of sequencing, cost is still prohibitive due to personnel time needed in annotation and characterization of novel open reading frames. Yet, with literally hundreds of *S. aureus* genome-sequencing projects in progress, its pan genome features are emerging. The innovative combined approaches of PCR and sequencing will likely spawn a new genechip-based technology that can not only identify different lineages but also distinguish virulent strains from the nonvirulent ones. Host specificity and susceptibility play major roles in the genesis and persistence of staphylococcal infection. This coming decade of investigation should identify the susceptibility markers for *S. aureus* infection *(75a)*.

Microarray Analysis. A microarray-based approach was published recently that was based on the genome sequence of seven *S. aureus* genomes and their MLST types. The array was able to identify core genes common to all *S. aureus* strains besides 10 dominant lineages, although substantial variations were observed in their mobile genetic elements and associated virulence genes *(76)*. These studies did not find any evidence to show that certain *S. aureus* lineages are associated with invasive isolates in community settings but showed the importance of hypercolonizing strains *(77)*.

Optical Mapping. Optical mapping is a newer tool that relies on the creation of a high-resolution restriction map of a bacterial genome (optical maps) and then comparing with the other optically mapped strains (78). While this is a very powerful technique to visualize major genomic changes with reference to the index or reference genome strains, it is not widely available in clinical microbiology laboratories. It is also limited by the small-sized database of the optical maps.

Optical Fingerprinting by Raman Spectroscopy. Other genotypic tools have been developed in the last few years but are not yet widely available. One novel method has been developed to identify and/or distinguish bacteria clones from the distantly related or the unrelated ones *(78a)*. This method, Raman spectroscopy, works on the principle that Raman Spectra of each bacterial species are a unique clone and therefore could be used to identify the species or cluster them based on their phenotypic properties. Using a small number of *S. aureus* isolates, it has been shown that this method could be highly discriminatory and may reach the resolving power of PFGE *(78a,79)*.

Summary of Molecular Typing Methods. The three most common methods for genotyping *S. aureus* are PFGE, MLST, and *spa* typing. Each of these methods has its own advantages and disadvantages, but there is also a high level of concordance between these three methods. The epidemiologist should ask which genotypic approach will be most useful for a particular investigation. In general, disease outbreak investigations are preferably done by the PFGE because of the ease in interpretation. One of the main advantages of the PFGE approach is the characterization of major US MRSA clones described as USA100, USA200, USA300 (CA-MRSA), USA400 (CA-MRSA), etc. These USA reference strains are available from the NARSA database. *Spa* typing will likely gain acceptance as sequencing will be more easily accessible in clinical laboratories. MLST is the preferred method to study the population structure and global evolutionary genetics of *S. aureus*. Shukla et al. (58) showed that the strain-distinguishing ability of *spa* typing and PFGE were comparable but more discriminatory than MLST for clinical MSSA strains.

PATHOGENESIS OF HEALTHCARE-ASSOCIATED INFECTIONS

S. aureus is armed with many virulence factors housed on as many as 18 "genome islands." *(80)* Most of these virulence factors are highly regulated and are turned on and off depending on the ecological challenge the bacterium faces. Expression of *S. aureus* attachment and virulence factors results from the interaction of a global accessory gene regulator (*agr*), a staphylococcal accessory regulator (*sar*), and RNAIII, a central regulatory function unique to *S. aureus* (Fig. 28-2). Its regulatory flexibility gives *S. aureus* opportunity to attach, colonize, and invade many tissues and organs. Because of its invasive properties, *S. aureus* bacteremia (SAB) has been one of the most studied clinical syndromes *(81)*. In a Brazilian tertiary care hospital, *S. aureus* caused 21% of all bloodstream infections (BSIs) compared to 26% caused by coagulase-negative staphylococci *(82)*. Clinical laboratories have observed an increased incidence of bacteremia caused by *S. aureus* since 1980 *(83,84)*. In a study of healthcare-associated bacteremia of unknown origin, both *S. aureus* and *Pseudomonas aeruginosa*

caused 15% of the cases *(85)*. *S. aureus* also caused 50% of catheter-related bacteremias, the majority of infections associated with insertion of prosthetic materials, and the majority of cases of septic arthritis and osteomyelitis. MSSA as well as MRSA strains are extremely prevalent in the intensive care unit (ICU). Among 49 ICUs in Italy, *S. aureus* caused almost 10% of all ICU infections *(86)*. Understanding the pathogenesis of such a diverse group of infections arising both in the community and in the hospital can be approached by examining the stages of host–pathogen interaction: colonization, attachment, adherence, tissue damage, invasion, dissemination, and metastatic infection (Fig. 28-3) *(4)*.

Colonization

Relationship of Colonization to Infection The major reservoir of *S. aureus* is the anterior nares. Carriage there influences carriage at other sites, including the axillae, perineum, denuded dermis, and mucous membranes *(4,87–89)*. People who are *S. aureus* carriers may harbor *various strains* persistently or intermittently, with intermittent carriage occurring in as much as 90% of a sampled population of carriers *(4,90)*. Some humans, based on genetic and nasal mucus constituents, are noncarriers. Factors that promote colonization include coincident respiratory infection, prolonged hospitalization, needle use (as in intravenous [IV] drug users), diabetics, patients requiring hemodialysis and patients receiving allergy shots, exposure to cold weather, and dermatologic conditions such as eczema *(4,91)*. The elderly, even when they are inpatients, have no higher rate of colonization *(92)*. Antibiotic administration also promotes an ecologic, nasal niche, perhaps through alteration of normal flora that is known to provide resistance to

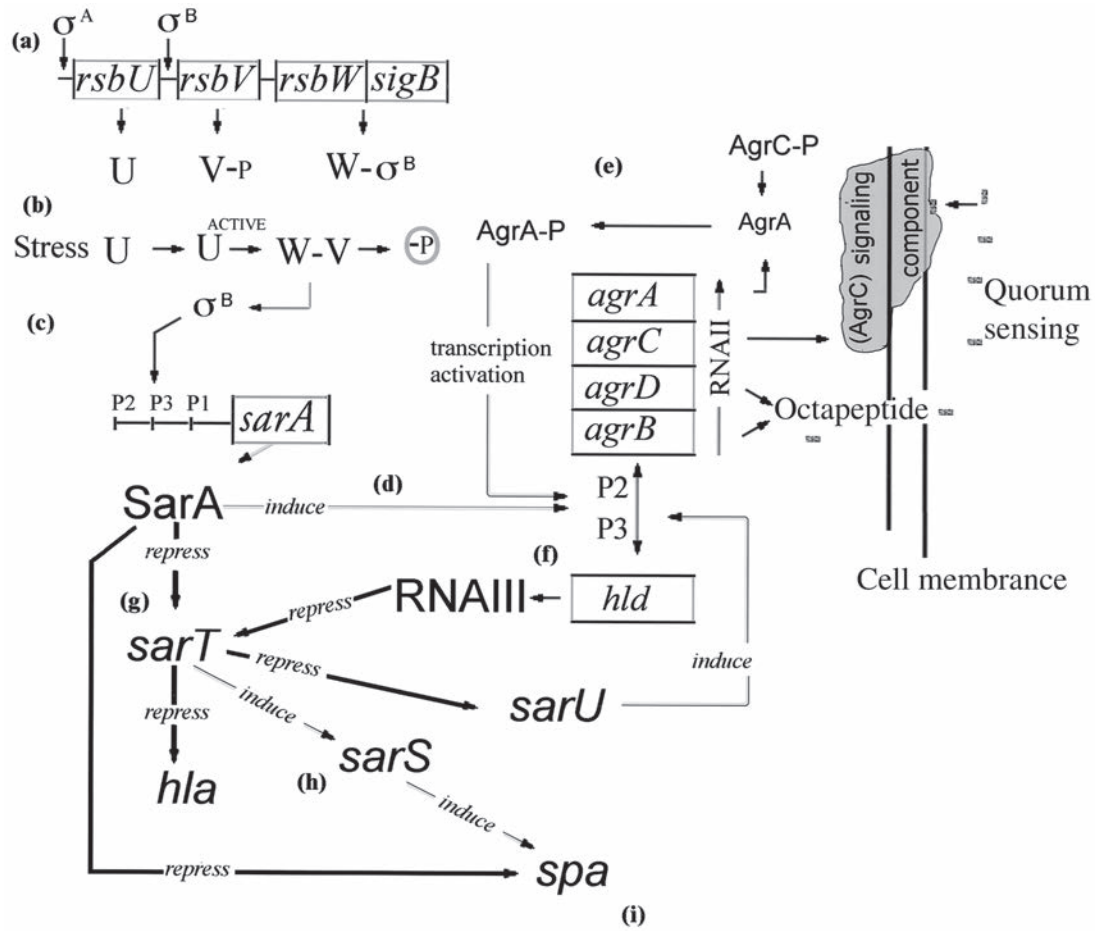


FIGURE 28-2 Overview of the predicted regulatory pathways involved in gene expression for *S. aureus:* (*a*) the *sig*B operon, transcribed under regulation of τ^A, encodes *rsb*U, *rsb*V, *rsb*W, and *sig*B. RsbW is an anti-τ^B factor that binds to τ^B, blocking its activity; (*b*) stress (e.g., high temperature, high osmolarity, or low pH) activates *rsb*U to U active that then can dephosphorylate *rsb*V-P to *rsb*V. *Rsb*V then binds to *rsb*W, releasing τ^B; (*c*) τ^B binds to a consensus sequence on the *sar*A P3 promoter, activating transcription of *sar*A (as well as other promoters); (*d*) *sar*A binds to the interpromoter region between P2 and P3 of the accessory gene (*agr*) locus, stimulating transcription of *agr* RNAII, which encodes *agr*B, *agr*D, *agr*C, and *agr*A, elements of a two-component quorum-sensing system. *Agr*B and *agr*D produce an octapeptide that diffuses through the membrane to bind to and activate *agr*C, a membrane-associated signaling component; (*e*) activated *agr*C phosphorylates *agr*A, which induces transcription of *agr* RNAIII; (*f*) RNAIII, a pleiotropic regulator for expression of virulence proteins, represses *sar*T; (*g*) increased expression of *sar*T during exponential growth causes repression of *sar*U, an inducer of RNAIII expression. *Sar*T represses expression of *hla* (encoding α-hemolysin), and induces expression of *sar*S; and (*h*) *sar*S induces expression of *spa* (protein A). *Sar*A represses expression of *spa (i)*. (Courtesy of Katherine A. Schmidt and Ambrose Cheung.)

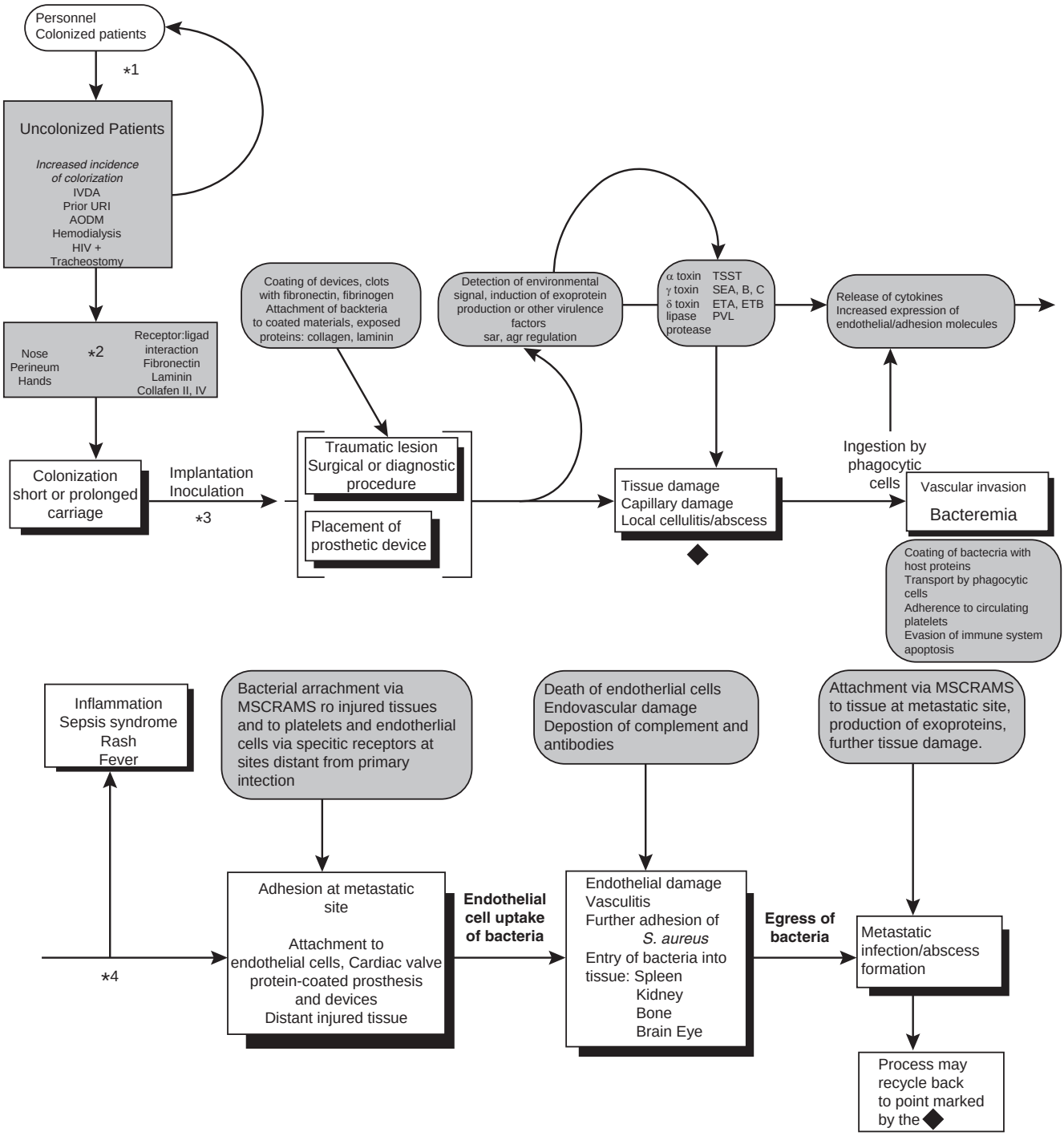


FIGURE 28-3 Pathogenesis of healthcare-associated infection caused by *S. aureus*. *Potential strategies to interrupt the development of a healthcare-associated *S. aureus* infection: (*1*) barrier precautions and decolonization procedures; (*2*) bacterial receptor (microbial surface components recognizing adhesive matrix molecules [MSCRAMMs]) antagonists and competitive colonization; (*3*) perioperative prophylaxis, antibiotic impregnated materials, materials to which *S. aureus* adheres poorly, and active vaccination; (*4*) prompt institution of effective antimicrobials, cytokine antagonists, MSCRAMM inhibitors, and passive vaccination with monoclonal antibodies; (*5*) prolonged treatment of bacteremia to cure foci of metastatic infection.

S. aureus colonization *(93)*. Once a patient is colonized with *S. aureus*, the particular strain may disseminate by person-to-person contact, particularly by spread on the hands of personnel *(94)*, or by the dispersion of *S. aureus* carried on rafts of desquamated skin *(95)*. In this manner, *S. aureus* strains spread among hospitalized patients. Adhesion factors and global regulators also interact to determine the establishment of colonization *(96)*. Since it usually precedes infection, colonization with *S. aureus* remains an important risk factor. The importance of the infection of

concomitant colonization is shown by the analysis of pathogens in surgical site infections (SSIs) and device-related infections. SSI rates were higher in colonized patients than in noncolonized patients *(97–99)*. This relationship is also quantitative: when the density of colonizing flora exceeds 10^6 colony-forming units (CFU), rates of postoperative infections are higher among carriers than among noncarriers. Patients in one surgical ICU study who were nasal carriers not only induced cross-colonization but also were significantly more likely to incur a staphylococcal infection than noncarriers *(100)*. Treatment upon admission to the ICU with nasal antistaphylococcal ointment was associated with a lower rate of *S. aureus* colonization while in the ICU. RFLP patterns were identical for those strains colonizing the nares and causing SSI. Molecular analysis also has been used in clusters of SSIs after heart operations to distinguish between the nasal strain and the strains isolated from SSIs or blood *(101)*.

The relationship between nasal carriage and subsequent SSIs is not straightforward. For example, in a study of 414 patients undergoing elective surgery in Khartoum, Sudan, only 6 of the 98 nasal carriers incurred SSIs caused by the strain inhabiting the nose *(101a)*. Besides demonstrating that nasal carriage was not a significant risk factor for development of SSI, the elegant molecular analysis further demonstrated that noncarriers were at significant risk of acquiring an independent SSI caused by strains with a high degree of genetic heterogeneity.

Further implicating *S. aureus* carriage, the same strains colonizing nonsurgical patients on admission are often the infecting strains *(89)*. Specifically, the same strain colonizing the noses of drug addicts with endocarditis is recovered from blood cultures. Hemodialysis patients are more frequently infected if anterior nares are colonized; 93% of hemodialysis-related infections are caused by the phage type colonizing the anterior nares *(102)*. The same relationship between colonizing and infecting strains was observed for patients on peritoneal dialysis. Nasal carriers had a fourfold higher incidence of dialysis catheter exit site infections *(103)*. It has been estimated that there is a 4% to 16% probability of catheter loss in patients with *S. aureus* peritonitis who are nasal carriers, compared with a negligible risk for noncarriers *(104)*. Finally, in hospitalized patients, there may be preferential colonization of non-nasal sites, for example, the oropharynx in patients undergoing long-term endotracheal intubation *(105)*. Patients admitted to a large hospital in Meunster, Germany, who developed SAB, were found to be infected 80% of the time with their own nasal-colonizing strain *(2)*. MRSA strains were not a problem in that section of Germany at the time of the study. A larger analysis done in Oxford, England, of the relationship of nasal-colonizing strains to subsequent invasive disease, was conducted by Day et al. *(77)* using MLST followed by additional analysis using an elegant whole genome microarray analysis for characterizing isolates *(76)*. The major implication of these landmark studies was to show that *(106)* hypercolonizing community strains mirror the invasive strains and *(8)* no genes including virulence genes are particularly associated with invasive isolates. Thus, these studies have far-reaching implications for infection control in the community as well as in the hospital.

Most recently, we have further evidence that elimination of nasal strains carried by patients admitted to the hospital will reduce subsequent surgical infections *(99,107)*. In the first study, a randomized, double-blind multicenter trial in The Netherlands, the rate of infection in patients decolonized with nasal mupirocin and chlorhexidine baths was 3.4% compared to 7.7% in patients who remained colonized (relative risk (RR): 0.42; 95% confidence interval [CI]: 0.23–0.75) *(99)*. The second study showed mupirocin decolonization of nasal carriers resulted in a reduction of 6.28 to 3.32 cases per 1,000 patient days *(107)*. These data form the rationale for rapid screening of *S. aureus* nasal carriers with subsequent decolonization before surgery.

Adherence and Attachment Strains of *S. aureus* have many potential surface adhesions (Smeltzer book). These adhesions are upregulated by *agr* once a *S. aureus* strain contacts a tissue or a surface, a crucial step in the initiation of infection. Adherence is mediated by a group of surface protein adhesins called microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) and regulated by the *sar/agr* system (*108*). There are three major groups of MSCRAMMs depending on whether they bind fibronectin, collagen, or fibrinogen, and these are present in strains from asymptomatic carriers *(109)*. Early adhesion is facilitated by upregulation of *sar*-mediated MSCRAMMs. Furthermore, *sar*S, a *sar* homologue, is an activator of *S. aureus* protein A *(110)* (Fig. 28-3). Access and adherence to host tissues or implanted materials is mediated by surface receptors that involve host protein interactions. More specifically, the interaction occurs between MSCRAMMS and target structures of the eukaryotic cell. For procedures in which foreign materials are implanted or that result in a thrombus at the surgical site, plasma proteins such as fibronectin are immediately deposited on the materials. Host proteins then act as bridging molecules in the adherence of *S. aureus* to protein-coated surfaces *(111)*.

S. aureus binding can be blocked by antibodies specific for a particular receptor *(6)*. An additional effect of staphylococcal-protein interaction may allow evasion of the immune system *(112)*. Binding of host proteins to the staphylococcal cell wall effectively coats the bacteria and may prevent host recognition of the microbe. *S. aureus* may also adhere to uncoated foreign material through electrostatic forces. This interaction is mediated by surface charge and hydrophobicity of the material and bacteria. *S. aureus* has a net negative charge due to ribitol teichoic acid and protein A *(113)*. Preventionn of infection, however, may require blockade of more than one receptor, a factor that has thwarted development of efficacious staphylococcal adhesion vaccines.

Studies that examine the binding of *S. aureus* to an extracellular matrix typically use a foreign material such as methylmethacrylate coated with a specific protein. Except for albumin, which markedly diminishes *S. aureus* binding to polymethylmethacrylate (PMMA), most host proteins augment attachment. For example, *S. aureus* binding to PMMA is markedly enhanced when fibronectin is present, and this binding is not strain dependent. Fibronectin coats implanted prosthetic material and plastic surfaces and is a major component of the fibrin matrix of clots. Staphylococcal adherence to fibrin clots is increased in the presence of fibronectin *(114)*. Binding to fibronectin

is mediated by two related fibronectin-binding proteins, FnBPA and FnBPB, which have specific ligand-binding domains that recognize the N terminal and the C terminal region of fibronectin. When fibronectin coats surfaces, the N terminal end enhances the binding of *S. aureus*. Fibronectin also binds well to albumin-coated substances and mediates the adherence of *S. aureus* to collagen, endothelial cells, fibroblasts, platelets, and platelet-fibrin thrombi *(115)*. Strains of *S. aureus* that bind avidly to fibronectin are more likely to produce endocarditis in a rabbit model of catheter-induced endocarditis, probably because fibronectin is first deposited on valvular endothelial cells traumatized by the catheter *(116)*. In another experiment, fibronectin binding was shown to be crucial in the pathogenesis of endocarditis. Fibronectin-binding deficient mutants were less likely to adhere to damaged heart valves than was the intact parent strain *(117)*.

Similar interactions between *S. aureus* and other surfaces may also initiate infection. Fibrinogen enhances *S. aureus* binding to and may be preferentially deposited on IV devices *(118,119)*. Staphylococcal clumping factor has been shown to be the SSP1 that binds to fibrinogen *(120,121)*. Phase 2 clinical trials are underway to assess the therapeutic value of products that block clumping factor *(122)*. Laminin, a major component of the basement membrane, also binds *S. aureus* by a specific receptor like fibronectin. However, only a small enhancement of *S. aureus* binding to PMMA was shown *(111)*. Laminin binding may not be a significant factor in the production of intravascular infections, since laminin serum levels are so low. On the other hand, there may be a role for laminin in the production of primary tissue infections, since basement membrane may be exposed after traumatic injury to epithelial surfaces, one of several putative routes that *S. aureus* can escape the bloodstream *(123,124)*.

S. aureus binds to heparin and other glycosaminoglycans by two bacterial cell wall–associated proteins. Glycosaminoglycans are linked with proteins to form proteoglycans and are found in connective tissue, basement membranes, and eukaryotic cell surfaces. These substances bind to heparinized catheters *(125)*; however, the binding is not specific. Other components of connective tissue bind *S. aureus* as well. Type IV collagen binds less avidly than fibronectin and laminin to *S. aureus (126)* but is exposed at the site of tissue injury. Adherence of *S. aureus* to type IV collagen is enhanced in the presence of fibronectin. In addition, *S. aureus* binds to type II collagen by a unique receptor, which has been cloned and sequenced. Strains with type II collagen receptors, isolated from patients with osteomyelitis and septic arthritis, were shown to bind well to cartilage *(112)*. Cutaneous injury may promote exteriorization of cytocollagen 10, providing substrate binding not possible in normal skin *(126a,127)*.

Biofilm formation is discussed in Chapter 31 of this book by Fey et al. In brief, the so-called slime substance central to biofilm formation is a polysaccharide composed of beta-1,6-linked *N*-acetyl glucosamines with partly deacetylated residues. Mutations in the corresponding biosynthesis genes (*ica* operon) lead to a pleiotropic phenotype wherein staphylococcal cells are less adherent and invasive. Several biofilm-negative mutants have been isolated in which polysaccharide intercellular adhesin production appears to be unaffected *(128)*. Other proteins involved in biofilm formation include accumulation-associated protein (AAP), the clumping factor A (ClfA), the staphylococcal surface protein (SSP1), and the biofilm-associated protein (Bap). New antimicrobials are needed that penetrate and disrupt biofilm formation or that are combined with new polymers to resist adherence and attachment *(129)*. Several biofilm-penetrating antimicrobials as well as biofilm vaccines are under development *(130)*.

Virulence and Invasion

Several regulatory systems that control virulence have been described in *S. aureus* (Fig. 28-3). The most important of these are *sar* and *agr*, both affecting RNAIII, which is a global effector molecule capable of upregulating transcription of many staphylococcal virulence genes. Ironically, staphylococcal binding to platelets also causes release of platelet-bound peptide antibiotics that may ameliorate local infection *(4)*. The production of specific virulence factors by staphylococci results in a complicated cascade of effects depending on the interaction of the regulatory components present. Many of these factors contribute to the antiphagocytic and increased intracellular survival of *S. aureus (10)*. The effects that cause the most severe infections may be produced by strains that harbor a particular complement of regulatory and toxin-encoding genes.

Early events in abscess formation are *sar* mediated. Subsequent exoprotein and toxin production is regulated by *agr*. There are at least 34 known exoproteins elaborated by *S. aureus* and their genetic determinants are grouped in pathogenicity islands throughout the chromosome. Certain proteins are highly toxic and are considered virulence factors. These enterotoxins (A, B, $X_{1,2,3}$, Δ, and E) and toxic shock syndrome toxin-1 (TSST-1) compose a related family of toxins causing staphylococcal food poisoning and toxic shock syndrome and act as superantigens once they enter the systemic circulation *(131)*. Superantigens cause intense activation of certain T-cell populations, and subsequent cytokine production overwhelms the immune system, preventing a coordinated response to antigen processing. The net result of this activation, paradoxically, is similar to endotoxin-induced shock wherein excessive quantities of cytokines induce tissue damage *(132,133)*.

More limited in activity, the epidermolytic toxins (ETAs), exfoliatins A and B specifically, attack the epidermis, causing exfoliation seen in toxic epidermal necrolysis (TEN) and staphylococcal scalded skin syndrome (SSSS). The gene for *ETA* is located on the chromosome, whereas the exfoliatin B gene (*etb*) is located on a plasmid. The major pathologic effect of these toxins occurs at a site remote from the site of infection.

Unlike enterotoxins and exfoliative toxins, membrane-damaging toxins produce damage at the site of infection. α-Toxin (heat labile), one of four known hemolysins (α, β, γ, δ), is a major pathogenic factor in that it produces tissue damage after the establishment of infection *(134,135)*. Using allelic replacement to create isogeneic toxin-positive and toxin-negative strains, no lesions were generated by the toxin-negative strain in a murine model of mastitis *(135)*. A-Toxin is the only staphylococcal toxin known to damage actively growing nucleated animal cells and is both dermonecrotic and lethal (30 μg/kg) in a murine model *(135,136)*.

When α-toxin is injected subcutaneously, vasoconstriction and subsequent tissue ischemia result *(30)*. B-Toxin (a heat-labile sphingomyelinase) and δ-toxin (a heat-stable peptide) are dermonecrotic at high doses but are less potent than α-toxin *(134,137)*. B-Toxin is not produced in many strains because of a converting phage inserted in the *hlb* gene *(136)*. A staphylokinase (SAK) is carried by the phage and upregulated by *agr*. Nasal strains usually have SAK intact, whereas SAK-deficient isolates were more than four times as likely to cause a fatal outcome *(138)*.

The δ-toxin peptide is a 26-residue translation product of the *hla* gene located near the 5′ end of RNAIII encoded by the *agr* locus. Leukocidin (heat labile), which is toxic to neutrophils and macrophages, also is a potent dermonecrotic toxin *(137)*. It is composed of two proteins, F (32 kd) and S (38 kd), and induces formation of a transmembrane potassium channel *(138a)*. Both components are necessary for toxicity. Leukocidin and γ-toxin belong to the same family of bicomponent toxins *(139)*. The genes for all the dermotoxins (*hla*, *hlb*, *hld*, *hlg*) are located in the chromosome. One leukocidin, Panton-Valentine leukocidin (PVL), has gained special repute since it is carried by many USA 300 MRSA strains causing community-acquired infection including necrotizing and fatal pneumonia *(139a)*. The extent of the PVL determinant in MSSA strains has not been well studied, but PVL is present in a small number of MSSA isolates (MLST 188) from Malaysia *(140)*.

Other exoproteins, such as proteases, collagenase, hyaluronidase, and lipase, probably act as virulence enhancers and are not as destructive to tissues *(136)*. Although staphylococcal exoproteins are otherwise dissimilar, the expression of at least 12 genes (including α- and β-toxins, exfolitins, enterotoxins B, D, TSST-1, proteases, protein A, and coagulase) is upregulated by *agr (141)*. The *agr* locus is involved in a two-component regulatory system controlling the expression of virulence genes in other bacteria *(142)*. Other regulatory elements, several of which are *sar* homologs, have been recently identified (see Fig.28-3). Thus, the complexity of the regulatory elements suggests that virulence factor expression is most likely responding to a variety of environmental and physiologic conditions specific to the host. The *agr* type and function has recently been related to the mortality associated with staphylococcal bacteremia *(143)*.

Dissemination and Metastatic Infection

After the establishment of local infection, *S. aureus* may disseminate to other sites. Dissemination from cutaneous sites is infrequent in community-acquired infection but may be more common in healthcare-associated acquisition. Spread of staphylococci from a localized cutaneous infection to the bloodstream and then to deep tissue to form abscesses or to cause endocarditis requires access to the bloodstream and rebinding to potential target sites. In part, *S. aureus* may gain access to the capillary vascular tree as a result of local inflammation and tissue damage invoked by specific, highly regulated exoproteins. Phagocytic cells may also contribute to vascular entry by carrying viable microorganisms back into the capillaries. Once entry into the bloodstream occurs, binding to serum proteins would follow, and eventually bacteria might stick to a target cell bearing a receptor to either a staphylococcal MSCRAMM or a serum component bound to the staphylococcal cell wall.

S. aureus can also bind to platelets *(144)*, and the binding may increase the capacity of platelets to bind to injured endothelium. Thus, staphylococci may be transported to a distant site and establish a metastatic focus. The ability of bacteria to bind to platelets correlates with the capacity to induce infective endocarditis. *S. aureus*, with its high capacity to bind platelets, more often caused endocarditis in an animal model than did *Escherichia coli*, with its minimal platelet-binding capacity. Binding of staphylococci to platelets is direct, rapid, and saturable, suggesting that this property is receptor-mediated and dependent on the number of receptors present. Platelet binding is not dependent on protein A. The staphylococcal ligand is most likely a surface carbohydrate and, perhaps, capsular-based. This ligand is resistant to proteases and susceptible to agents that modify carbohydrates and specific anticapsular antigens *(145)*.

After dissemination, *S. aureus* must attach to distant tissues to cause a metastatic suppurative infection. Metastatic infections may develop through interactions of blood-borne staphylococci and endothelial cells. These infections may involve endovascular structures or deep tissues. This may be due, in part, to the higher degree of attachment and invasion of endovascular tissue exhibited by staphylococci *(146)*. The interaction of endothelial cells and *S. aureus* is so efficient that these bacteria adhere to uninjured endothelial cells. Affinity for a specific site usually leads to infection at that site; *E. coli* microorganisms have been shown to attach to specific uroepithelial cell receptors, and this interaction is a prerequisite for urinary tract infection (UTI) *(147)*. *S. aureus* appears to have a specific receptor for endothelial cell surface proteins, which promotes adherence and, perhaps, the initiation of endocarditis and graft infections. As with platelet binding, bacteria that bind avidly to endothelial cells are more likely to cause endocarditis than bacteria that bind poorly and consequently rarely cause endocarditis *(148)*.

S. aureus is also a common cause of prosthetic valve endocarditis. Binding of *S. aureus* to a porcine cardiac valve is a specific receptor-mediated event. In this instance, a binding protein of 120 kd was identified as a potential receptor. This protein was not related to fibronectin. Unlike injured tissues, fibronectin may not augment *S. aureus* binding to endothelial cells. No fibronectin is expressed on the luminal surface of endothelial cells, and no fibronectin is produced by valvular endothelial cells *(149)*. However, fibronectin may augment the binding of *S. aureus* to injured endothelial surfaces and if fibronectin binding is blocked, there is a decrease in adherence to subendothelial surfaces exposed after endothelial injury *(150,151)*.

Investigators have also shown that endothelial cells ingest attached staphylococci. A 50-kd protein from umbilical vein endothelial cell membrane binds to *S. aureus* and facilitates uptake into endothelial cells *(152)*. This protein was shown to be different from fibronectin using a fibronectin antibody assay. Binding is also specific, since albumin or fibrinogen does not inhibit this interaction. Bovine aortic endothelial cells actively phagocytosed *S. aureus*; 65% of bacteria applied to the endothelial cells were ingested. This action can be blocked by cytochalasin B and was independent of fibronectin and complement *(153,154)*. Complement-activated endothelial cells, conversely, have

increased fibronectin binding. Although *S. aureus* cells that were ingested did not multiply within endothelial cells, the endothelial cells eventually died, leading to exposed subendothelial surfaces. Adherence alone does not induce apoptosis since studies show that viable intracellular *S. aureus* is needed to induce apoptosis *(155)*. Ingestion and endothelial cell death, however, do depend on strain and inoculum *(156)*. The clinical impact, ultimately, is that intracellular *S. aureus* may not be affected by most antibiotics, particularly β-lactams, which fail to penetrate eukaryotic cells. Endothelial cell infection would consequently initiate invasion and infection of deeper tissues.

Subsequent interactions between the ingested *S. aureus* and the endothelial cell may lead to local vascular damage. Uptake of *S. aureus* by endothelial cells also increases expression of Fc receptors on the cell surface, hypothetically initiating vasculitis by the adherence of neutrophils and platelets to the endothelial cells. Immune complex deposition would next activate complement or initiate the coagulation cascade. These events could augment further metastatic seeding and invasion *(157)*. Finally, host factors elicited by extravascular infection may alter endothelial cells and increase bacterial adherence. For example, staphylococcal adherence to vascular endothelium is upregulated by *sar* and enhanced in the presence of tissue necrosis factor-α (TNF-α). TNF may further increase the endothelial leukocyte adhesion molecule-1 (ELAM-1) and intracellular adhesion molecule-1 (ICAM-1) *(158)*. Also, the exposure of endothelial cells to lipopolysaccharide increases adherence of bacteria. This effect is duplicated by incubation of cells with the cytokine interleukin-1 *(159)*. Classic agents like aspirin downregulate many pathways associated with complications of endothelial infection and by downregulating global staphylococcal regulons, create novel therapeutic strategies *(145)*.

Specific capsular types of *S. aureus* play a critical role in abscess induction, as well as in avoiding host phagocytic uptake. Capsules are produced by most clinical strains, and serotypes 5 and 8 together account for up to 50% of clinical isolates *(145a)*.

More than 80% of healthcare-associated isolates from bacteremic patients produce capsule type 5 or type 8 *(160)*. Clinical strains with a type 5 or 8 capsule are more resistant to opsonophagocytosis. In a mouse bacteremia model of infection, a capsule type 5 strain sustained a higher level of bacteremia than two capsule-defective mutants, likely due to the antiphagocytic nature of CP5 since *in vitro* assays indicated that the parental strain was only susceptible to phagocytic killing by human polymorphonuclear leukocytes (PMNs) in the presence of capsular antibodies and complement. Although capsule types 1 and 2 confer resistance to complement-mediated opsonophagocytosis by PMNs, strains producing these capsule types do not cause clinical disease. CP5 production has also been shown to block adherence of *S. aureus* to endothelial cells in culture *(161)*. Similarly, in a rat model of catheter-induced *S. aureus* endocarditis, both the type 5 and 8 parental strains are less pathogenic when compared with capsule-deficient mutant strains *(162)*. These findings suggest that CP5 and CP8 may interfere with staphylococcal attachment to the damaged aortic valve *in vivo*. Data from mouse models show that a capsule-defective mutant fails to persist in the murine nares *(163)*. Ways to exploit these observations through active or passive vaccination to reduce the risk of healthcare-associated infection await further study.

SCOPE OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY *S. AUREUS*

Bacteremia and Endocarditis

Bacteremia is a dreaded sequel of localized *S. aureus* infection that often results in production of metastatic foci in almost any organ. SAB is healthcare-associated 20% to 60% of the time, depending on the preponderance of certain variables such as IV drug users in the population at large (*164*, *164a*). SAB has become a field of study in itself (3,224 hits on PubMed on 22 January 2011). Up to 30% of patients with bacteremia fail to be cured when treated with parenteral antimicrobials *(165)*. In the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) program, *S. aureus* was the second most common cause of healthcare-associated bacteremia, with its coagulase-negative counterpart ranking first. Of 2,340 strains of staphylococci reported, 787 were *S. aureus*, 602 *S. epidermidis*, 61 *S. haemolyticus*, 45 *S. hominis*, and the rest different staphylococcal species *(166)*. One third of the cases of community-acquired SAB are associated with endocarditis and that number is rising. In the preantibiotic era, as many as 15% of patients with healthcare-associated staphylococcal bacteremia developed endocarditis, whereas one modern study uncovered no cases of endocarditis related with healthcare-associated staphylococcemia, perhaps because of the preponderance of hospital infections associated with IV catheters *(167)*. Conversely, in hospitalized patients with prosthetic valves, SAB often results in the development of new endocarditis *(165)*.

Healthcare-associated SAB has been closely studied over the last 50 years *(168,169)*. The variable rate of all SABs that are acquired in the hospital—40% to 60%—depends on the type of patients treated at the individual institution *(169)*. In 1989, the rate of *S. aureus* bloodstream infections per 1,000 discharges was lowest in small nonteaching and large nonteaching hospitals (0.46 and 0.44, respectively) and higher in small teaching and large teaching hospitals (0.89 and 1.13, respectively) *(170)*. The rate is also increasing in long-term care facilities, where *S. aureus* is the most common species causing bacteremia and accounts for about 15% of all cases *(171)*. In some countries, new MRSA strains may be particularly virulent and produce epidemics alongside endemic MSSA bacteremia *(172)*. The concern about the rising risk of bacteremic strains being MRSA led workers at Detroit Receiving Hospital to develop a prediction model. The model earmarks patients with a history of hospitalization, a longer hospitalization, comorbid conditions, and exposure to antimicrobials as at risk for MRSA bacteremia, whether healthcare- or community-associated *(173)*.

Patients most susceptible to SAB have underlying conditions such as cirrhosis, diabetes, chronic obstructive pulmonary disease, congestive heart failure, and renal failure requiring dialysis. In one quarter of bacteremic patients, however, the source cannot be found. Patients who have the greatest change in their Acute Physiology and Chronic

Health Evaluation (APACHE II) score after admission to an ICU tend to have the worst outcome *(174)*. Interestingly, nasal MRSA carriage had a RR for bacteremia of 3.9 compared to MSSA carriage in 488 patients admitted to an ICU. The severity of illness induced by SAB relates to the risk of dying, although poor outcome was not associated with poor opsonic activity *(174)*. In the Scottish BURDEN study, morbidity and mortality of in-hospital SAB within 90 days of admission was greater for MRSA than MSSA. The death hazard was high for both, 5.6 for MRSA and 2.7 for MSSA *(175)*.

Over the last 25 years, the proportion of healthcare-associated bacteremias associated with vascular access devices has increased to 30% to 59% *(176)*. At Crawford Long Hospital in Atlanta, the number of device-related bacteremias increased eightfold during the years between 1980 and 1983 and those between 1990 to 1993 *(177)*. Some studies suggest that part of the increase may be due to the emergence of certain clonal strains sharing a common phage type. For example, in a Danish study of 15,000 strains of *S. aureus* isolated from patients with bacteremia from 1977 to 1989, phage type 95 increased from 3.8% to 18.8% during a time when no methicillin resistance was detected *(178)*. Follow-up Danish studies indicate that MSSA is the primary cause of staphylococcal bacteremia and that death is most often associated with septic shock, age over 60, and a daily dose of penicillinase-stable penicillin <4 g *(179)*. MRSA is much more prevalent in the same setting outside of The Netherlands and Scandinavia.

Adults and children with leukemia or cancer, particularly those with granulocytopenia, have been historically at high risk for SAB associated either with the persistent nature of their *S. aureus* nasal carriage or with preventive antimicrobial chemotherapy *(180,181)*. The rate of SAB in patients with cancer increased from 5% in 1973 to 30% by 1979 *(182)*. Japanese hospitals had a reported rate of 6% *(183)*, which has recently increased to at least 10% *(184)*. Interestingly, in a group of patients with leukemia who developed SAB, endocarditis was an unusual outcome *(185)*.

Patients with human immunodeficiency virus (HIV) infection are also at increased risk of acquiring SAB. In one study, half of these cases were healthcare-associated, and IV catheters were considered the likely source of healthcare-associated bacteremia *(186)*. Both healthcare-associated and community-acquired cases had a higher rate of late complications (35%) than was reported in earlier studies not involving HIV-infected patients. Hospitalized hemophiliacs with acquired immunodeficiency syndrome (AIDS) compared to non-AIDS patients again had a higher rate of SAB related to increased exposure to antibiotics and central IV catheters *(187)*. In HIV-infected patients, colonization and infection due to MRSA are related to prior hospitalization, exposure to broad-spectrum antibiotics, presence of dermatologic disease, and presence of a central venous catheter *(188,189)*. In Barcelona from 1991 to 2006, among 1,777 BSI in HIV-infected patients, in the community *S. pneumoniae* and *S. aureus* caused 44% and in the hospital coagulase-negative staphylococci and *S. aureus* caused 38% *(190)*. At Johns Hopkins, SAB occurred in nearly 20 cases per 1,000 patient years, 43.5% of which were MRSA (191).

Bacteremia isolates of *S. aureus* contain a habitual feature of classical members of the pyrogenic toxin superantigen (PTSAg) gene family comprising the staphylococcal enterotoxin (SE) genes *sea-see* and the TSST-1 gene *(192)*. PTSAg/ET genes *seg* and *sei* were found in combination by a multiplex PCR in 55% of strains. The *tst* gene was found in 20.3%. Overall, about half of *S. aureus* isolates tested harbored genes of the classical members of the PTSAg family and ETs (50.8%), and an even higher percentage if the newer toxin genes were included. Newer biologic therapies may be necessary to ameliorate the effect of groups of toxins.

Many challenges remain for optimal therapy of SAB. More patients with risks for SAB emerge constantly making SAB a true continual challenge for infection control. We look to the large numbers of investigators in the staphylococcal field to develop new strategies for treatment and especially prevention *(81)*.

Burns

Infection remains the major cause of death among burn patients *(193)*. *S. aureus* is a threat to patients with burns throughout the course of their treatment. Burn units worldwide continue to report *S. aureus* along with *P. aeruginosa* as the major pathogens affecting these patients *(194)*. In a Brazilian burn unit from 1993 to 1999, 55% of 320 patients developed healthcare-associated infections, with primary bloodstream infection in 189 patients being the most common *(195)*. Overall, *S. aureus* was responsible for 24% of all infections, followed by *P. aeruginosa* (18%) and *Acinetobacter* species (14%). Modern topical therapy reduces the concentration of microorganisms on the burn wound surface, and thus the potential for cross-infection *(196)*. Nevertheless, studies from one unit that discharges burn patients only when their wounds have healed completely have shown that burn wound colonization with *S. aureus* results in prolongation of hospital stay *(197)*. Additionally, burn units allow facile dispersion of *S. aureus* strains, since burn patients disperse *S. aureus* more readily than other hospital patients *(198)*. Moreover, burn patients represent a threat of introducing multiresistant staphylococci to new treatment care areas *(199)*. Bacterial isolation environments have been developed that reduce cross-infection, but they have not enjoyed widespread use. Isolation rooms in burn units have served a similar purpose, but studies are lacking to prove that such rooms actually reduce cross-infection due to *S. aureus (193)*. Quantitative culture of burn wound biopsies has been reported, in some studies, to relate to the development of burn wound sepsis *(200)*. Topical antimicrobial therapy remains the mainstay of reducing the microbial burden in burn eschar, and current susceptibility studies are encouraging for lack of emerging resistance *(201)*. Further epidemiology of bacterial infections in burn units is discussed in Chapter 25.

Dialysis

Hemodialysis As early as 1967, *S. aureus* had become the most frequent pathogen causing hemodialysis shunt infections *(202)*. It has been known for many years that the skin flora in patients undergoing hemodialysis becomes dominated by *S. aureus (203)*. Increased nasal carriage leads to colonization of arm shunts. Replacement of perineal normal flora by *S. aureus* also leads to colonization of shunts in the lower extremity. Colonization of any shunt site results in a shunt infection in two thirds of the sites and in bacteremia in one third *(204)*. When studied carefully, carriage of

S. aureus at nasal, perineal, or shunt sites was either persistent or, more often, intermittent *(203)*. Even the throat may be a secondary site of colonization *(204)*. Since the rates of colonization for dialysis outpatients were just as high as rates for dialysis inpatients, dialysis support staff members with known high rates of *S. aureus* colonization may contribute to the colonization of both groups of patients *(204)*; other factors undoubtedly contribute to *S. aureus* colonization *(205)*. SAB is a major problem in hemodialysis patients especially those with double lumen catheters *(206)*. MSSA as well as MRSA are regularly isolated *(206)*. Metastatic infection is common in hemodialysis patients with SAB and endocarditis is not an uncommon end result. An early study showed that 70% of access site infections and 50% of the cases of endocarditis in hemodialysis patients were due to *S. aureus (207)*.

Because of the association of carriage with subsequent serious *S. aureus* infection, studies have been directed at the development of prophylaxis *(208)*. IV vancomycin reduced the risk of shunt infections but has been impractical for widespread use. Oral rifampin, which can eradicate nasal *S. aureus* carriage, was also effective in preventing *S. aureus* infections in patients on hemodialysis *(102)*. Nasal mupirocin clearly is effective in eliminating nasal as well as hand carriage in hemodialysis patients *(209)*. In another study, Dutch workers evaluated 172 patients to determine the efficacy of decolonization with mupirocin; 67 (39%) were determined to be *S. aureus* carriers *(210)*. Mupirocin given twice a day for 5 days eliminated carriage in 98.5%, of whom 94% and 91% remained negative at 3 and 6 months, respectively. Bacteremia occurred at a significantly lower rate in treated patients (0.03 per patient year) than in an untreated historical control group (0.25 per patient year, $p < .001$). Despite these early optimistic data, there has been an emergence of mupirocin resistance in nasal strains of *S. aureus*, particularly common in long-term mupirocin therapy in dialysis patients *(211)*. The current threat of mupirocin resistance suggests the need for the development of new decolonizing agents and strategies other than antimicrobial chemotherapy to alter the carrier state *(212–214)* (see also Chapter 63).

Peritoneal Dialysis As with hemodialysis, *S. aureus* infections in patients on continuous ambulatory peritoneal dialysis (CAPD) have a clear association with nasal carriage *(208)*. Using molecular tools, Pignatari et al. *(215)* showed that peritonitis was caused by the same subtype as that carried in the nose. In a 10-month study of 63 carriers and 77 noncarriers, the 11 episodes of peritonitis due to *S. aureus* occurred only in carriers, as did 22 of 24 exit-site infections. Exit-site and tunnel infections in these patients are particularly troublesome and are caused by *S. aureus* 44% of the time. Nasal carriage again seems to be the major risk factor *(216)*. Carriage and resultant infection can be more effectively reduced by intranasal application of mupirocin than by neomycin *(217)*. It is not known if hospitals are the origin of *S. aureus* strains colonizing these patients, although the proximity of many hemodialysis units to inpatient units implies a close connection. The morbidity of *S. aureus* infections can probably be reduced by effective decolonization of the *S. aureus* carriers who enter CAPD programs, but the evidence for efficacy in CAPD patients is less convincing than for hemodialysis patients *(218)* (see also Chapter 64).

Gastrointestinal *S. aureus* Infections

Staphylococcal enterocolitis is a controversial disease, since the finding of *S. aureus* in the stool is not unusual and assays for cellular cytotoxicity of stool isolates are tedious to perform. Enterocolitis has been associated with indwelling feeding catheters, antimicrobial exposure, and high-risk neonates *(219)*. In the last group, a small outbreak of necrotizing enterocolitis was due to a strain of *S. aureus* that produced δ-toxin *(220)*. Wound strains more frequently produce staphylococcal enterotoxin C compared to diarrheal strains that more often produce staphylococcal enterotoxin B (SEB) *(221)*. The potential for enterotoxin production by healthcare-associated strains may assume greater importance since SEB-producing strains have been associated with toxic shock–like illness and TSST-1 production. SEB behaves like a superantigen capable of nonspecific cytokine stimulation *(222)*. As many as one quarter of asymptomatic *S. aureus* carriers have strains that produce at least one type of enterotoxin *(223)*, though it is not known if the hospital environment selects out toxin-producing strains. MRSA as well as MSSA clearly have the capacity to cause enterocolitis. An interesting observation from Japan found that enterocolitis caused by the same MRSA PFGE type was preexistent in the respiratory tract *(224)*.

Institutional outbreaks of *S. aureus* gastroenteritis are often overlooked, because the major manifestation is vomiting. In a food-borne outbreak in a Florida prison, 65% of inmates had diarrhea, vomiting, or both. *Salmonella infantis* and *S. aureus* phage type 29/52 and 52A (weak) were isolated from leftover turkey *(225)*. *S. aureus* phage type 29/52 was isolated from two of ten food handlers. Thus, such food-borne outbreaks in institutions can involve multiple enteric pathogens including *S. aureus*.

There have been new observations that microorganisms other than *Clostridium difficile* cause antibiotic-associated colitis. It is true that colonization of the bowel with *S. aureus*, particularly MRSA, increases during hospitalization *(226)*. With other microorganisms like *C. perfringens* and *Klebsiella orazae*, *S. aureus* can be associated with diarrhea after antibiotics, but these microorganisms are not yet accepted as causes for classic antibiotic-associated colitis.

Meningitis—Central Nervous System Infections

Historically, most adult cases of *S. aureus* meningitis have been community-acquired and are secondary to focal staphylococcal disease and endocarditis. Modern neurosurgery with its plethora of cerebrospinal fluid access devices, however, has created a new setting for healthcare-associated *S. aureus* meningitis, discitis, and subsequent vertebral osteomyelitis *(227)*. Prior neurosurgery, placement of ventricular shunts *(228)*, IV catheter–induced bacteremia *(229)*, postpartum endometritis *(230)*, and spinal analgesia (231) are risk factors for the majority of healthcare-associated cases. Very-low-birth-weight newborns with sepsis constitute another major group who acquire healthcare-associated meningitis *(232)*. In this group, predictors of cure included central nervous system (CNS) shunt infections, age less than 1 year, and normal

results with neurologic examinations. Shunts should be placed in newborns with hydrocephalus using a double glove technique with the outer pair removed before handling the shunt catheter *(233)*. Predictors of mortality in adults with shunts include diabetes mellitus, age over 60 years, obtundation or coma on presentation, and bacteremia *(227)*. With the increasing frequency of MRSA carriage in hospitalized patients, it is increasingly more likely that neurosurgery-induced meningitis will be caused by MRSA *(227,234)* (see also Chapter 27).

Pneumonia

Pneumonia caused by *S. aureus* has traditionally been a community-acquired illness associated with influenza virus infection, IV drug use, septic thrombophlebitis, and right-sided endocarditis (235). Patients are at higher risk in contracting *S. aureus* healthcare-associated pneumonia if they are under 25 years of age, suffer trauma, or are infected with HIV *(236)* (see also Chapter 22). The advent of the pandemic of MRSA healthcare-associated infections allows a more precise determination of the prevalence of healthcare-associated *S. aureus* infection, since most of these strains reside within the hospital. Epidemiologic studies of MRSA suggest that healthcare-associated *S. aureus* pneumonia is more frequent than generally is appreciated. In fact, NNIS system data reveal that 20% of all healthcare-associated pneumonia is due to *S. aureus (17,237)*. More recent studies have shown almost 40% of *S. aureus* healthcare-associated pneumonias are still caused by MSSA *(238)*. In one study, rates of mortality, need for mechanical ventilation, or admission to an ICU were no different in the MSSA compared to MRSA group *(238)*.

Other countries do not necessarily reflect this high incidence of healthcare-associated pneumonia caused by *S. aureus*. In a Spanish study of 15,803 isolates of *S. aureus* from healthcare-associated infections, the highest rates were 21% from the skin and 14.7% from the blood *(239)*. Perhaps this discrepancy is due to the high percentage of patients hospitalized in the U.S. who require mechanical ventilation, a major risk factor for *S. aureus* pneumonia. In a study of 1,000 consecutive hospitalized patients, 21.9% developed bacterial pneumonia, and in 23.2% of these the pneumonia was caused by *S. aureus*; six additional patients had polymicrobial pneumonia from which *S. aureus* was isolated *(240)*. Ventilator-associated pneumonia due to MSSA and MRSA has increased over the last decade *(241)*. For example, ventilator-associated pneumonia in 11 of 49 episodes was caused by MRSA, and these MRSA-infected patients were much more likely to have received antimicrobials and to have a fatal outcome *(242)*. In German ICUs, *S. aureus* has become the most common (24%) pathogen followed by *P. aeruginosa* (17%) *(241)*. *S. aureus* can be recovered by the protected specimen brush in 20% of ventilator patients who develop pneumonia and, although some experts advocate bronchoscopic sampling to best guide therapy, some studies suggest quantitative endotracheal aspirate cultures are equally useful *(243–245)*. In less developed countries, about 11% of all healthcare-associated *S. aureus* isolates are from the respiratory tract *(246)*. Most recently, in a large multicenter study of 480 patients with healthcare-associated pneumonia, 89% had *S. aureus* with 30% MSSA *(247)*.

Newborns

S. aureus infection has always been a problem in the nursery, where many factors serve to perpetuate colonization and infection. About 20% of newborns are colonized with *S. aureus* upon leaving the nursery; this figure doubles by 6 weeks after birth. These rates appear to be independent of whether neonatal care is given in a well-baby nursery or in an neonatal intensive care unit (NICU). Other factors, such as the type of device used for circumcision, influence *S. aureus* colonization *(248)*. In neonates, *S. aureus* infections are probably related more to colonization of the umbilicus than of the nares *(249)*. Umbilical infection can be reduced by decolonization of the area *(250)*. In any case, from 2000 to 2007, MRSA caused over one third of *S. aureus* infections in neonatal ICUs. Overall *S. aureus* causes 15 to 20 infections per 1,000 patient admissions, very-low-birthweight infants being the most susceptible *(251)*, as a cause of central-line infection, coagulase-negative staphylococci well outnumber *S. aureus (322)*.

Epidemics due to MRSA in modern NICUs suggest that such strains are healthcare-associated *(252–254)*. Some clones are clearly transferred from adult wards, as can be shown by using a combination of PFGE and *spa* typing *(255)*. Some outbreaks are so difficult to control that at times neonatal units have to be closed to break the cycle of cross-infection *(256)*. Methicillin resistance is not the only resistance marker that can be linked to outbreak strains, as was demonstrated by an erythromycin-resistant strain that caused conjunctivitis in several neonates in one nursery *(257)*. TSST-1 production in nursery strains has been another marker used to follow the spread of a strain causing the toxic shock syndrome in a nursery *(258)*.

Another molecular study has shown that multiple strains of *S. aureus* may circulate in some nurseries. Whereas phage typing could distinguish only nine strains, molecular analysis suggested that at least 20 strains from 23 neonates were involved *(259)*.

Crystal violet reactions of neonatal isolates of *S. aureus* were hoped to become a promising marker for detecting strains that persist after discharge from the nursery. In a study that showed a rise in the rate of colonization from 18% at discharge to 40% by 6 weeks after discharge, the purple-reacting strains, usually of phage groups I and III, were more likely to persist than strains from other phage groups *(260)*. It is becoming increasingly important to conduct surveillance of *S. aureus* clones in neonatal units. One recent study suggested that microbiologic surveillance using nasal cultures is sufficient for the detection of MRSA isolates, and it would seem prudent to use this strategy also for MSSA isolates *(251,261)* (see also Chapter 52).

Prosthetic Devices

There is a broadening spectrum of infections associated with insertion of prosthetic devices including intraocular lenses, cerebrospinal fluid shunts, prosthetic joints, vascular biomaterials, genital prostheses, and breast prostheses. The staphylococci predominate in these infections *(262)*. It is well known that coagulase-negative staphylococci tend to form biofilms on biomaterials more efficiently than *S. aureus*, but almost any staphylococcal species, including *S. aureus*, can produce a complex infection on prosthetic

material, which may include selection of small colony variants (SCVs), making treatment of prosthetic infection difficult *(263,264)*. Ica, one biofilm operon, has been detected in all *S. aureus* isolated from orthopedic prostheses compared to only 46% of coagulase-negative staphylococci *(264)*. A prospective study of Spanish patients with joint prostheses showed that an etiologic diagnosis could be made in 60% of the patients and most of the 58% of gram-positive infections were staphylococcal *(262)*. Seeding of prostheses after SAB is surprisingly common, as was shown by a collaborative study between Duke University and an institution in Auckland, New Zealand, which reported that 15 of 44 (34%) patients with SAB had subsequent infection of the indwelling prosthesis (see also Chapter 65).

Skin and Soft Tissue

In the preantibiotic era, pustules, carbuncles, furunculosis, cellulitis, and surgical site sepsis were common healthcare-associated infections in the United States, and they continue to be major problems in large areas of the world *(4)*. In modern hospitals, healthcare-associated staphylococcal cellulitis often occurs as a manifestation of infected indwelling intravascular devices and prosthetic implants. Pyoderma in healthy neonates and decubitus ulcers in residents of long-term-care facilities remain problems and are addressed elsewhere in this text (see also Chapter 52) *(297)*. Specific problems may arise in NICUs. For example, a group III phage type 42E/54/75 strain of *S. aureus* caused the scalded skin syndrome, which spread through a six-room special care nursery *(265)*. A recent broad-based study from Wenzhou, China, of skin and soft tissue infection caused by *S. aureus* showed that of 111 isolates, 57% were healthcare-associated and over half of all strains were MRSA *(266)*. Many strains harbored PVL genes, but the molecular profiles (per PFGE types) were quite heterogeneous (32 PFGE types). SCCIII was the most common type among both healthcare and, surprisingly, community strains.

Surgical Site Infection

Patients undergoing surgical procedures are at increased risk of developing a healthcare-associated infection; SSIs remain the most common and serious type of infection *(267,268)*. Through 1960, *S. aureus* was by far the most common cause of SSIs *(269)*. Studies done in the early 1960s found that SSI was associated with *S. aureus* nasal carriage and hospitalization during the month of January; this trend was consistently observed over 3 years *(90)*. In the data from the older NNIS system, *S. aureus* accounted for 19% of 11,724 SSIs *(270)*, but NNIS always suffered from proper adjustment of patient case mix *(271)*. New data come from the National Healthcare Safety Network (NSHN) that concentrates on device-related infections (central line–associated BSI), ventilator-associated pneumonia, and UTIs *(271a)*. In developed countries, *S. aureus* is the major pathogen in 30% of SSIs *(272)*. In developing countries, rates are even higher (i.e., *S. aureus* causes almost half of the SSIs) *(273,274)*. In-hospital SSI data are always affected by delayed infections—often due to *S. aureus*—that are manifested months or even years after surgery *(275)*. Diagnosis of other surgical infections, like psoas abscess and mediastinitis, can also be difficult, though Dutch hospitals have collected 4,066 CT procedures producing 183 infections, 2.4% sternal wounds, and 3.2% harvest sites (*276*,277). There was a large variation among hospitals (0.0%–9.7%) suggesting surprising room for improvement. Tammelin et al. in Uppsala did an exhaustive microbiologic study over 2 years of sternotomy patients who were reexplored. Using strict criteria for tissue infection and multiple tissue samples, they found *S. aureus* in 10/32 and *S. epidermidis* in 10/32 infected patients *(278)*. By PFGE, they found eight different patterns among 40 *S. aureus* isolates. Interestingly, the surgeon was readily identified as the source for all cases of *S. aureus* infection but could only be suspected as the source for 30% of the infections due to coagulase-negative staphylococci.

Guidelines for prevention of SSIs have been published many times and, if followed, probably reduce the rate of SSIs to 1% to 2% *(279)*. Adherence to these guidelines is important, because most SSIs result from exogenous strains of bacteria *(280,281)*, some of which are carried in the nares and on the hands of hospital personnel who contact surgical patients. For example, as many as 50% of ungloved examiners may carry *S. aureus* on their hands *(282)*. Because hair carriers have been associated with epidemics of SSI, proper head covering is mandatory during surgery *(283)*. Body coverings and face masks, however, do not guarantee containment of *S. aureus* during surgery. Mask wiggling contributes to an increase in recovery of *S. epidermidis* and *S. aureus* from cultures taken around the operating table *(284)*. In staff working in a cardiothoracic unit, the risk for hand carriage in nasal carriers was 7.4 (95% CI: 2.7–20.2; $p < .001$) (*284a*). Why the high risk? At least half of these hand carriers carried strains self-inoculated from their own nares!

The preponderance of *S. aureus* as a primary cause of SSI has spawned extensive research into the mechanism of SSIs using animal models. Progress has been slow, but several concepts are worth noting. SSIs are influenced by many complex variables in the operating room. The size of the inoculum of *S. aureus* delivered to the surgical site is related to the development of infection *(285)*. In an animal model, by increasing the inoculum from 3×10^6 to 8×10^6 CFU, the infection rate rose from almost 0% to 45%. Surgeons have recognized this fact for years and have tried using quantitative bacterial cultures to predict the likelihood of subsequent infection *(286)*. Size of the inoculum is only one element, however, in a complex process that produces SSIs. For example, the presence of remote infection, including those due to *S. aureus*, may increase the SSI rate two to five times *(287)*. Another study has shown that personnel working overtime (because of understaffing) resulted in an increase in the number of SSIs *(288)*.

For surgery involving exposure of tissues at the surgical site to adjacent contaminated or colonized sites, perioperative antimicrobial prophylaxis using antistaphylococcal agents is now universally advised. Even though antimicrobial prophylaxis is aimed primarily at *S. aureus*, it has been reported as the most common cause of SSI in cardiothoracic surgery *(289)*. B-lactamase production in *S. aureus* may be one factor that has reduced the efficacy of prophylactic cephalosporins to prevent *S. aureus* mediastinal infections *(290)*. New studies have emerged to address

which prophylactic antimicrobial regimens are effective in this era of multiresistant staphylococci *(291)*. A new challenge is judging the significance of contamination of cryopreserved tissue. As many as 64% of arterial homografts may be contaminated at the time of implantation, mostly with staphylococci *(292)*.

Infections after surgical procedures categorized as clean-contaminated, contaminated, and dirty are more likely to be due to nonstaphylococcal species. Yet, *S. aureus* infections after gastroduodenal procedures occur in up to 15% of cases *(293)*, suggesting a need to broaden traditional antibacterial coverage before certain operations. Specific procedures like placement of percutaneous enteral gastrostomy (PEG) feeding tubes, perhaps because of the cutaneous interface, are increasingly complicated by *S. aureus* infection *(294)* (see Chapter 21).

Toxic Shock Syndrome

After being initially described in 1978, staphylococcal toxic shock syndrome (TSS) gained increased notoriety during the early 1980s, notoriety spurred by the paradox that innocent commensals like *S. aureus* could elicit through their toxins a massive, catastrophic, superantigen cytokine response. The study of the interaction of TSST-1 positive strains and the immune system suggests a true duality of the interaction *(295)*. The cell wall of *S. aureus* contains toll-like receptor 2 (TLR2) ligands that trigger proinflammatory and also anti-inflamatory cytokines.

The first healthcare-associated cases were associated with SSIs *(296)*, often after minor surgery. In 12 of 13 patients described, *S. aureus* was isolated from the surgical site. Four were menstruating women but four patients were males. Classic signs of TSS including fever, profound multisystem dysfunction, and desquamative erythroderma usually began within 48 hours of the operation. A gentamicin-resistant strain of *S. aureus* that produced TSST-1 caused recurrent TSS in a nurse working in a burn unit. The strain was shown to spread to patients and other workers *(297)*. Relatively benign procedures *(298)*, including simple mastectomy in a male *(299)*, correction of a bat ear *(300)*, nasal packing after septoplasty, abdominoplasty *(301)*, enhanced external counterpulsation *(302)*, and arthroscopy *(270,303)*, have also been associated with TSS. Another report of an erythromycin-resistant TSST-1 producing strain carried by a neurosurgeon resulted in TSS in two of his patients; the strain from the neurosurgeon and those from the patients were shown to be related by endonuclease restriction-length polymorphism seen with *Tn*554 hybridization studies *(304)*. A moderate number of healthcare-associated strains of *S. aureus* produce TSST-1. In a study of 997 strains of *S. aureus*, 128 occurred with confirmed or probable cases of TSS. Following in frequency those strains associated with menses were those isolated from patients with septicemia, burns, and surgical sites *(305)*. Kikuchi et al. *(306)* at Tokyo's Women's Medical University described TSST-1 in MRSA strains that caused a disease termed neonatal toxic shock syndrome-like exanthematous disease (NTED). Clonal TSST-1 strains of MRSA were widespread in an NICU and a general neonatal and maternal ward where 12.9% of 62 newborns carrying such strains developed NTED *(306)*. SSSS, similar to TSS but caused by another staphylococcal toxin, can also present as healthcare-associated clusters, as has been the case after interarticular injection *(307)*. Strains causing TSS may contain other toxin genes capable of producing similar clinical signs and symptoms *(308)*.

These studies collectively suggest that healthcare-associated strains capable of causing TSS circulate among patients and hospital personnel. The diagnosis of healthcare-associated TSS should be suspected in hospitalized patients who have undergone surgical procedures, who have sites of suspected staphylococcal infection, and who manifest multisystem organ failure, fever, and shock with or without rash. Clustering of such cases that may involve a limited number of clones should alert the healthcare epidemiologist to search diligently for a carrier or common origin of a TSST-1–producing strain of *S. aureus*.

Urinary Tract Infection

Unlike the dogma for the significance of gram-negative bacillary UTIs, there are no quantitative standards for evaluating the clinical significance of staphylococci in urine. Several early studies have shown that *S. aureus* is infrequently cultured from urine *(309,310)*, but the last two decades have seen a change in that dictum. The clinical significance of small numbers of *S. aureus* in the urine of hospitalized patients remains unclear but may often be suggestive of some site of infection in the urinary tract (235,*309*). *S. aureus* bacteriuria in concentrations of at least 10^5 CFU/mL also occurs in the absence of renal infection. In one study using a criterion of $\geq 10^5$ CFU/mL as indicating infection, *S. aureus* was isolated from only 3.3% of the isolates from 17,437 urine cultures. Of 373 patients with *S. aureus* isolated from urine, 132 had $\geq 10^5$ CFU/mL of *S. aureus* in pure culture, and 96 had *S. aureus* in mixed culture *(235)*. Renal carbuncles, which complicate SAB, are localized to the cortex of the kidney and may release small numbers of microorganisms into the urine *(235)*.

Bacteriuria occurs in 15% to 25% of patients with SAB, not a result of colonization but a result of SAB and metastatic infection in the urinary tract or the vertebral column *(311,312)*. One recent study suggested that *S. aureus* bacteriuria may be a predictor of complications, even mortality associated with SAB *(313)*. Otherwise, *S. aureus* with or without a bloodstream origin can infect multiple sites in the urinary tract of hospitalized patients.

Up to 50% to 81% of cases of *S. aureus* UTIs are healthcare-associated in origin and, as such, carry a moderate risk of producing bacteremia. Of 69 patients who did not receive appropriate therapy for their *S. aureus* UTI, 11% had secondary bacteremia, compared with none of 63 who received appropriate therapy *(75)*. Predisposing factors included an indwelling catheter, urinary obstruction, surgical manipulation, or malignancy—factors similar to those predisposing to healthcare-associated gram-negative bacillary UTI (see also Chapter 20). Urologic patients may carry separate risks for *S. aureus* UTI. In a large 10-year study from Japan of 139 patients with *S. aureus* UTI, (45 MSSA, 94 MRSA), a febrile response was associated with certain toxin genes, and those genes were more common in MRSA than MSSA isolates *(314)*. In children with catheter-associated UTI, following *E. coli* (39%), *S. aureus* was the second most frequent pathogen (16%) *(315)*.

Vascular Access Device Infections

S. aureus causes about half of the cases of IV catheter–related phlebitis and bacteremia *(316)*. Over a 10-year period at a hospital in Atlanta, healthcare-associated device-related bacteremias increased eightfold, and 56% of these were due to *S. aureus* in the period 1990 to 1993 *(177)*. It is important to remember that phlebitis is evident in fewer than half of the patients with IV catheter-related sepsis and that sepsis is infrequent when a catheter has been in place <4 days. Many studies have used semiquantitative or quantitative culture techniques to identify the catheter as a source of bacteremia, but the positive predictive value of a single catheter culture remains low.

The suggestion that an IV catheter is the source of SAB has heretofore prompted many clinicians to use short-course antimicrobial therapy. This approach to therapy is surprising, since the frequency of late unpredictable complications of IV catheter–related bacteremia ranges from 0% to almost 70%. These complications include endocarditis, osteomyelitis, and pyelitis *(317)*. With current technology, it is not possible to predict prospectively which patients develop late complications. Nevertheless, short-course therapy has become popular for patients with SAB thought to be related to an IV catheter. In those studies of short-course therapy, the combined late complication rate was 6.1%, which is probably an unacceptably high figure for most clinicians *(317)*. Specifically, endocarditis develops in 2% of patients with catheter-related bacteremia, compared with 6% in other bacteremia patients *(318)*. Thus, short-term therapy (10–14 days) should be reserved for only those patients carefully selected to be at minimal risk for metastatic disease *(319)*. The quantitation of *S. aureus* adherent to a catheter or its related parts may become more meaningful when it helps identify those patients who will benefit from short-course therapy *(320)*.

Colonization of device materials or the surrounding skin precedes infection. With time, the extraluminal or the luminal colonization of the IV device predisposes to phlebitis and subsequent bacteremia. The mechanism of colonization involves development of a biofilm resistant to the bactericidal effects of serum or antimicrobial agents. The role of colonization by *S. aureus* at sites distant to the IV device remains unclear. In fact, one study suggests that nasal colonization with *S. aureus* may reduce the likelihood of phlebitis, but supportive data are lacking *(321)*. The authors suggest that immune mechanisms that reduce nasal colonization may also protect the catheter site from inflammation. In that study, the presence or the absence of *S. aureus* at the phlebitis site was not investigated, so more studies of this nature need to be performed. It has been shown that dwell time for catheters in neonates constitutes a major risk *(322)*.

Patients with catheter-related SAB are at increased risk for developing septic thrombosis or deep-seated infections exclusive of endocarditis. The development of these sequelae is heralded by persistence of fever for more than 3 days *(323)*. One of the most severe complications due to extension of the infected thrombosis is suppurative thrombophlebitis (see also Chapters 17 and 18).

S. aureus accounts for 81% of bacteremias associated with permanent endocardial pacemakers *(324)*. Although this infection may present like an intravascular sepsis, the portal of entry most often is the subcutaneous site where the pacing system is implanted. Similarly, permanently implantable cardioverter defibrillators (ICDs) and other cardiovascular implantable electronic devices (CIED) are an emerging risk for development of local and systemic *S. aureus* infection *(324a)*. One study found that 36% of patients with CIED infection had SAB *(324b)* with about one third presenting a year or more after the device was implanted. Cure usually requires removal of part (the generator) or all of the ICD *(325)* (see also Chapter 61).

Because of their severity, there has been public outcry to reduce vascular-access infections. Meticulous attention to the detail of inserting and maintaining these catheters (with accompanying checklist) can certainly reduce infection *(326)*. Other approaches to prevention have been reviewed recently *(327)*. In particular, a number of antimicrobial-impregnated catheters have been studied to determine if they can reduce the incidence of phlebitis and BSI, and many of these studies are very encouraging *(328,329)*.

EPIDEMIOLOGY

Along with the classic work of Spink et al. already described, the careful study of the epidemiology of *S. aureus* infections in hospital patients performed by Finland and Jones *(30)* shortly thereafter established the basis for modern hospital infection control. The spread of infections caused by *S. aureus* phage type 80/81 is analogous to the problem with infections caused by MRSA in hospitals today. That phage type was responsible for many serious hospital outbreaks of furuncles, carbuncles, pneumonia, and SSI *(330)*. So pervasive was *S. aureus* infection, that, at the University of Iowa Hospital in 1957, *S. aureus* caused infections in 17% of all surgical and 12% of all medical patients; 38% of these infections in both groups were healthcare-associated.

Since the outbreaks of the 1950s, *S. aureus* persisted as the preeminent healthcare-associated pathogen. The NNIS system found that *S. aureus* was the cause of 12% of 70,411 healthcare-associated infections, the number one cause of SSIs (19%), pneumonia (20%), and infections at all other sites (17%) *(17)*. Since the NNIS data, the number of cases of healthcare-associated pneumonia caused by *S. aureus* has increased (from 17% to 20%), and only recently has started to decline *(331)*.

The rise in the number of infections caused by MRSA has also brought attention to staphylococcal infection in long-term-care facilities (see also Chapter 98). Rates of *S. aureus* infections in a nursing home care unit ranged from 0.29 to 0.47 per 1,000 resident-care days *(332)*. Demographics for patients with MSSA and MRSA infections were similar. One study in a skilled-nursing facility found that 35% of residents were colonized with *S. aureus* at least once during a 1-year prospective surveillance study. Surprisingly, rectal carriage alone was present in 13% of residents who became colonized during their stay *(333)*. Outbreaks of MRSA infections have occurred in pediatric residential care facilities as well. One such outbreak was reported in an Arkansas state facility for mentally challenged children *(334)*. From 1978 to 1981, in one cottage, an average of 10 *S. aureus* infections occurred per month, affecting 29 of 35 cottage residents. In July 1981, residents and workers in this cottage were

decolonized with antibiotics, and all residents and personnel were inoculated intranasally with *S. aureus* strain 502A. At a Spanish geriatric hospital, using MLST typing CC5 was found to be the predominate MLST type, but there was a variety of other types among blood and wound isolates *(335)*. Residents of a Spanish LTCF experienced up to a 20% change from MSSA to MRSA carriage annually *(336)*. Yet, one hopeful study from Germany suggested that long-term endemicity with MRSA can be avoided after an MRSA epidemic in the same LTCF *(337)*.

Reservoirs

The many studies of the inanimate hospital environment suggest that *S. aureus* persists on surfaces and fomites in hospitals *(338)*. Since there is usually a human component of contagion during hospital epidemics, it is always difficult to incriminate environmental sources alone *(94)*. Indeed, the contamination of the environment by skin scales from humans is a general index for human colonization *(95)*. In the surgical suite, both settle plate techniques and air sampling have been used to evaluate the potential for contamination. Such studies have not proven a cause-and-effect relationship but suggest that the environment may serve as a way station for strains that preferentially colonize hospital personnel. Nevertheless, because we know that there is heavy contamination of the environmental surfaces, there has been a recent movement to determine how to best modify the hospital environment and its touch surfaces in order to minimize persistence of hospital pathogens in the patient environment *(339)*.

Modes of Transmission

Staphylococci are efficiently transmitted by contact and less efficiently by the airborne route *(340)*. Strains from patients with *S. aureus* pneumonia or burn infections may spread by the airborne route in the hospital. Epidemics are most efficiently maintained by human carriers, both patients and workers, who carry the microorganism in their nares and contaminate other parts of their body, particularly their hands. Modern studies have shown that contemporary MRSA strains can spread quickly and displace susceptible nasal flora in hospital patients and personnel *(254)*.

There are some classic concepts of transmission that are often lost in modern hospital epidemiology. One group of nasal carriers who efficiently spread the microorganism are so-called shedders; 13% of male and 5% of female carriers are shedders with a heavy nasal inoculum who disperse, with normal movement, large numbers of microorganisms from their lower extremities and perineum into the air around them *(341)*. One physician shedder who contracted an upper respiratory infection (URI) was incriminated in an MRSA outbreak *(342)*. The physician carried large numbers of MSSA ($2.8–4.5 \times 10^5$) in both nares but fewer MRSA in either nare. After an experimentally induced rhinovirus infection, the physician could disperse *S. aureus* up to 20 ft, leading to the term cloud adult, in the descriptive tradition of cloud babies who similarly spread *S. aureus* in the nursery *(343)*. In the operating room, similar dispersal is likely related to wearing permeable clothing, including scrub suits *(344)*, and is blocked by polyethylene covering the lower extremities. Fifty years ago, Walter et al. *(344a)* performed many studies to show that orderlies and anesthetists in the operating suite may have twice the *S. aureus* carriage rate as surgeons and nurses, and that carriage may be persistent or intermittent. The modern healthcare epidemiologist would do well to apply these classic concepts.

There has been a historical debate between proponents of the airborne versus the contact routes of spread of *S. aureus* in hospitals. Goldmann *(338)* has aptly summarized the debate, emphasizing that whereas older outbreaks caused by one *S. aureus* phage type may have incriminated a point-source shedder of airborne *S. aureus*, modern outbreaks that feature multiple strains of *S. aureus* are probably initiated and perpetuated by contact transmission. That overview should not totally discount earlier work that showed that personnel who were shedders of *S. aureus* and worked in the operating room were associated with outbreaks of SSIs *(256)* and that removal of shedders from the clinical area resulted in cessation of the epidemics *(346–348)*. A causal relationship between colonization among personnel and subsequent *S. aureus* sepsis in patients remains unclear after years of study. Nevertheless, the "search and destroy" methodology of certain Dutch medical centers respects the potential for personnel to be involved in perpetuating the cycle of colonization and infection of patients, thus allowing for personnel to be removed from work until they are clearly decolonized of the offending strain *(349)*.

Hospitalization itself is a risk for colonization with *S. aureus*. Patients become progressively colonized throughout their hospitalization, though the maximum carriage rate is about 25% in studies from hospitals in the Western Hemisphere *(348,350)*. A deterministic model tested against data derived for the acquisition of tetracycline-resistant *S. aureus* demonstrated that, by about 35 days of hospital stay, the nasal carriage rate stabilizes at 25% *(351)*. Moreover, the nares are not the only site of *S. aureus* colonization. In women followed in a maternity unit, 33% were nasal carriers, but 25% carried *S. aureus* in their perineal region *(352)*. Earlier, in his classic studies, Solberg found that 12% of carriers harbored *S. aureus* at multiple sites *(95)*.

Tracing Spread of Healthcare-Associated Strains

The question of how many different strains of *S. aureus* circulate through a hospital at one time is not easy to answer. Historically, phage typing of strains—a system much inferior to modern molecular methods—formed the basis of epidemiologic analyses. One study of MSSA strains at Walter Reed Army Medical Center found four predominant phage types of 31 *S. aureus* bacteremic strains during a 6-month period in 1979 *(207)*. Control measures reduced bacteremia but not carriage. In the former East Germany, the prevalence of the 94/96 phage complex increased from 9% in 1978 to 16% by 1985 *(353)*. These strains were very similar with regard to biochemical reactions, antigenic structure, and the presence of 16-Md plasmids determining resistance to cadmium and penicillin. Yet, additional experimental phage reactions and the sites of resistance determinants on the plasmids could further differentiate the strains. Such studies raised the question of how far an investigation should proceed in an attempt to establish a relationship between strains.

Newer molecular methods already discussed may simplify this process somewhat (see earlier discussion in section "Molecular Typing Techniques"). Whatever technique is chosen, it is necessary to determine discriminative indices among strains to establish a strong epidemiologic relationship in order to draw valid conclusions. More advanced typing methods using staphylococcal genomics are just now being applied to MSSA strains, suggesting that relationships among healthcare-associated *S. aureus* strains are complex and certainly beyond the implications of phages *(76,77,354)*. Studies from newer multicenter molecular analyses of *S. aureus* strains from healthcare-associated outbreaks suggest that multiple methods are needed to establish clonal relationships among healthcare-associated strains *(58,69,355)*.

PREVENTION AND CONTROL OF *S. AUREUS* HEALTHCARE-ASSOCIATED INFECTIONS

S. aureus has persisted as the predominant cause of healthcare-associated infections. This microorganism is the second most common isolate from blood (16.5%), the most common isolate from SSIs (17.1%), and the second most common respiratory isolate (16.1%) *(356)*. Outbreaks within hospitals continue to occur and have been controlled, historically, by the institution of meticulous infection control measures. Less commonly, epidemics were controlled by the identification and treatment of carriers who were implicated in the transmission of *S. aureus* during such outbreaks *(41)*. The close relationship between colonization and subsequent infection has most recently been reemphasized by the work of von Eiff et al. *(2)*. In Münster, Germany, they found that over 80% of patients with bacteremia at the time of or after admission have a bloodstream clone that matched their nasal clone present on admission. Perl et al. *(357)* further demonstrated that the largest impact in decolonizing nasal carriers was a reduction in SSIs. Thus, the most effective measures for the prevention of staphylococcal infections are those that diminish or eliminate colonization.

Perioperative Prophylaxis

The appropriate use of perioperative antimicrobials has been shown to reduce the rate of clean SSIs at practically any site studied. Such prophylaxis has had a major impact on lowering the incidence of *S. aureus* SSIs, although the emergence of more resistant strains threatens that success *(291)*. In reviewing prophylaxis policies, one should follow several principles. First, determine whether published studies have shown that prophylaxis leads to a significant decrease in infections for the specific procedure. If so, choose an antibiotic with a spectrum that includes the microorganisms most likely to cause infection resulting from the specific procedure, realizing that no antimicrobial agent is capable of preventing infection by all pathogens. Next, determine if the chosen antibiotic achieves effective tissue levels at the site of the procedure. Also, consider the incidence of adverse reactions to the antimicrobial agent. Antimicrobials with high rates of allergic reactions would be undesirable as prophylactic agents. Finally, consider the cost of the antimicrobial agent. Less expensive, but efficacious, agents would control costs because of the large number of patients requiring prophylaxis. For all sites studied at which *S. aureus* is a predominant pathogen, cefazolin or a nearly equivalent cephalosporin (cefamandole, cefuroxime) has been the agent of choice *(358–361)*. With the marketing of several new antistaphylococcal compounds and a rise in strains of *S. aureus* (both MRSA and MSSA) that are only intermediately susceptible to vancomycin, there are now pressures to extend that spectrum of choices *(291)*.

The addition of vancomycin to prophylaxis regimens could be considered if there is a significant incidence of SSIs caused by methicillin-resistant staphylococci. In a study whose findings suggested the value in the use of vancomycin prophylaxis in this setting, the vancomycin prophylaxis group had fewer SSIs than the cefazolin and cefamandole prophylaxis groups, respectively *(285)*. However, there were several SSIs in the vancomycin treatment group due to cephalosporin-resistant coagulase-negative staphylococci. It is important to remember that antimicrobial prophylaxis may cause alterations in the normal flora. When compared to control patients not receiving antibiotics, two studies have shown the emergence of bacteria, including staphylococci, resistant to the prophylactic agents in patients administered prophylactic antimicrobials *(220,362)* (see also Chapter 21). With the marketing of several new antistaphylococcal compounds and a rise in strains of *S. aureus* (both MRSA and MSSA) that are only intermediately susceptible to vancomycin, there are now pressures to extend that spectrum of choices *(291)*.

Antimicrobial prophylaxis cannot prevent all *S. aureus* infections even those caused by susceptible strains. Many patients do not receive prophylactic antimicrobials for certain procedures such as intravascular catheter insertions or dialysis. Other patients may develop SSIs with susceptible strains of *S. aureus* despite adequate perioperative antimicrobial prophylaxis *(290)*. As previously stressed, the initiating event in healthcare-associated *S. aureus* infection is colonization, and we are making inroads in understanding that complex process *(96)*. We do know that patients colonized with *S. aureus* prior to a procedure are more likely to develop a staphylococcal infection after the procedure than are those patients who are not colonized *(363)*. Up to 80% of adults may be colonized if repeated cultures are obtained *(364)*, and those strains colonizing the anterior nares become infecting strains *(2,365)*. For these reasons, numerous strategies for reducing surface colonization have been tried, and there is a search for newer, more effective topical antimicrobial sterilizers, particularly since there is a significant percentage of mupirocin resistance globally *(366)*.

DECOLONIZATION

Use of preoperative showers with a topical antiseptic scrub is a simple decolonization strategy. One study compared povidone–iodine, chlorhexidine, and soap. Only chlorhexidine significantly reduced the numbers of staphylococci inhabiting skin sites. This study did not examine the effect

on infection rates *(367)*. A variety of topical and oral agents have also been studied. Topical gentamicin eliminated carriage rapidly. However, recolonization occurred within 10 days and was usually with the same phage type noted on initial sampling. With oral trimethoprim/sulfamethoxazole, eradication was not observed in a high proportion of patients, and resistance to this agent emerged frequently among patients in the study group *(345)*. Oral clindamycin has also been tried, but resistant strains frequently emerged *(368)*. In a study with limited enrollment, Klempner and Styrt *(369)* found that clindamycin was useful; 3 of 11 untreated patients versus 9 of 11 treated patients were free of infection after 3 months, but relapse of colonization was common.

Rifampin has been used in three studies either as a single agent or in combination with other antimicrobials. Chow and Yu *(370)* reported that rapid resistance to rifampin was observed if this agent was used alone. In a second study, the application of a topical antibiotic, bacitracin, to the external nares plus orally administered rifampin decreased the recovery of *S. aureus* on the forearm and from air samples and eliminated nasal carriage of *S. aureus* in hemodialysis patients. Infection rates were significantly lower in decolonized patients *(102)*. An earlier study, however, showed that application of bacitracin alone was ineffective but that the combination of bacitracin and rifampin was better; the latter combination was not as effective as rifampin alone *(371)*. Widespread use of rifampin and the subsequent increase in rifampin resistance would limit the long-term use of this agent for decolonization. Oral ciprofloxacin appeared promising, as most staphylococci were susceptible to ciprofloxacin. Ciprofloxacin was successful as a single agent in eradicating colonization, but resistance emerged in 7 of 22 patients. If patients were recolonized, the new strain was more resistant to ciprofloxacin than the initial isolate. Eradication did not occur rapidly and required treatment for 2 to 3 weeks *(345)*. Another study corroborated the frequent emergence of strains resistant to ciprofloxacin *(372)*. Other than the bacitracin and rifampin combination, none of the decolonization strategies above could be recommended. Rifampin plus an older antimicrobial, novobiocin, seems to be a promising alternative for decolonization *(57)*.

Topical mupirocin (pseudomonic acid) has been shown to eradicate carriage of *S. aureus* in many studies. Reagan et al. *(373)*, in a double-blinded study, reported that mupirocin decreased nasal carriage. Three months after therapy, 71% of treated subjects versus 18% of controls remained free of colonization ($p < .0001$). Casewell and Hill reported similar success with attempts at eradication *(374)*. In an analysis of six different double-blinded, independently randomized clinical trials of healthy carriers of *S. aureus*, nasal carriage was eliminated based on cultures taken 48 to 96 hours after completion of treatment in 91% of volunteers receiving mupirocin but in only 6% of placebo-treated control subjects *(375)*. The effect lasted at least 4 weeks after therapy. In a smaller study, topical mupirocin eliminated *S. aureus* carriage in 100% of volunteers. In 60% of these subjects, carriage relapsed within 1 year *(376)*. Decolonization of surgical ICU patients with mupirocin has been shown to be effective in preventing subsequent infections with *S. aureus* (RR: 2.78; 95% CI: 1.00–7.78) *(100)*. In this study, an added potential benefit of decolonization was evidence that bronchopulmonary strains were identical to nasal strains and bronchopulmonary colonization was decreased by nasal decolonization. Ultimately, a very well-designed study of MSSA carriage at Erasmus Medical Center in Rotterdam showed that a double-blinded study of decolonization resulted in a nearly 60% reduction in SSIs *(99)*.

On a cautionary note, as mentioned, high-level resistance to mupirocin has been reported *(377)*. A study performed at a long-term-care facility illustrates this point. A prospective study evaluated the effect of mupirocin on MRSA colonization and endemic infections. Carriage was eliminated from 94.7% when both nares and wounds were treated. Nares treatment alone did not significantly decrease overall colonization. The overall rate of recurrence was 34%. Unfortunately, the infection rate did not change with reduction in colonization. Resistance to mupirocin was detected and was mostly low level (MIC = 3.1–62.5 μg/mL); however, for one strain, an MIC greater than 5,000 μg/mL was reported. High-level mupirocin resistance was transferable and plasmid-mediated. Low-level resistant strains were cleared. Because of these findings, the authors did not recommend the use of mupirocin in long-term care patients (378). At a Canadian hospital, mupirocin resistance increased in MRSA strains from 2.5% in 1990 to 65% in 1993 *(379)*. In Brazil, emergence of resistance was related to the extent of mupirocin use: 63% of MRSA strains were resistant in a district hospital where mupirocin was used daily compared to a rate of 6.1% in a region where the topical agent was used infrequently *(380)*. (For a more specific discussion of MRSA, see the following Chapter 29.)

Thus, resistance to topical and systemic antimicrobials remains the major limitation of antibiotic-based decolonization treatments. One must not overlook the fact that *S. aureus* colonizes other sites in addition to the nares. A prospective study has shown that hospitalized patients without nasal colonization may be colonized with *S. aureus* at other sites. The axillae were colonized in 7% of patients, the perineum in 12%, and the toe webs in 5% *(381)*. Up to 13% of nursing home residents may harbor *S. aureus* only in the rectum *(333)*. Therefore, it may be worthwhile to choose strategies for decolonization that are effective at multiple sites. Although nasal carriers may disseminate and spread microorganisms to other body areas, heavy shedders also disseminate from the perineum *(382)*. Few studies have shown that widespread decolonization of hospitalized patients actually reduces the rate of infection. Moreover, in regard to carriers, less than 1% of hospital outbreaks have been caused by colonized personnel *(383)*. Except for selected groups of high-risk patients during MRSA outbreaks or those on hemodialysis, widespread and prolonged use of antimicrobial agents for decolonization is not indicated *(383a)*. Several new agents may soon be available for topical use. Lysostaphin has been shown to be rapidly bactericidal against *S. aureus* and able to decolonize quickly in one or two intranasal applications *(213)*. Alkyl esters are also gaining some attention as topical antistaphylococcal agents since they select minimally for resistance in serial passage *(384)*. Compounds involved in the so-called quorum-sensing mechanism in *S. aureus* may also emerge as candidates to turn off signals necessary for staphylococcal pathogens to persist *(384a)*.

Bacterial Interference

Several other new strategies for prevention of infection besides decolonization have been tried. Competitive interference using a strain of *S. aureus* of low pathogenicity (the 502a strain) was used in nurseries by application of a bacterial suspension to the umbilical stump. The incidence of infections was reduced, but outbreaks caused by the 502a strain occurred *(385)*. Use of this method requires previous treatment with antibiotics to establish 502a colonization. This method has also been used successfully to treat adult patients with recurrent skin infections *(364)*. A major disadvantage of bacterial interference is the ease with which the interfering strain may be eradicated with the additional use of antibiotics. Nevertheless, several worldwide centers are proceeding with studies of recolonization using interfering *S. aureus* strains after decolonization of pathogenic strains.

Vancomycin Resistance

Over 40 resistance genes have already been identified in strains of *S. aureus (386)*. Vancomycin has been utilized for staphylococcal infections for over 30 years. For a decade after the emergence of widespread vancomycin resistance in enterococci, resistance in *S. aureus* to vancomycin remained theoretical. The long-awaited appearance of strains of *S. aureus* with decreased (intermediate) susceptibility to vancomycin (vancomycin-intermediate *S. aureus* [VISA]) finally occurred in Japan in May 1996 *(387)*. The first patient was a 4-month-old child who had undergone open-heart surgery and developed a chronically draining sternal SSI. The patient was treated with several courses of vancomycin and subsequently, after decreased susceptibility to vancomycin was determined, with other antimicrobial regimens. Therapy with all of the antimicrobial regimens failed, and only deep debridement ultimately eradicated the VISA.

The *S. aureus* strain responsible for this first vancomycin-resistant infection termed Mu-50 grows well in 4 μg/mL of vancomycin and displays a heteroresistance to vancomycin in concentrations up to 10 μg/mL. The whole genome sequence of Mu50 and of a related strain Mu3 has been published *(5)*. These strains heralded an emergence of VISA worldwide, which have a variable response to vancomycin presumably because vancomycin is sequestrated in cell walls that have altered cross-linkages of peptidoglycan *(388,389)*. Early surveys conducted in Japan reveal that 1.3% of MRSA strains from nonuniversity hospitals and over 9% of strains from university hospitals display heteroresistance to vancomycin *(390)*. When examined for expression of heteroresistance, Dutch workers also found a surprisingly high (7.6%) rate of isolates with reduced susceptibility to vancomycin *(391)*. VISA isolates are not as concerning as they were a decade ago since there are alternative antimicrobials marketed that are active against VISA strains.

The specter of highly vancomycin-resistant *S. aureus*—VRSA (MICs to vancomycin of over 20 μg/mL) — continues to loom since its first identification in 2001 *(392)*. Most of the 11 well-characterized VRSA strains have been confined to the United States, but several cases of VRSA have now been isolated outside the United States *(392)*. Most of these patients have had extensive exposure to vancomycin *(390,393)*. For infection control personnel, these first VRSA strains of *S. aureus* with high-level vancomycin resistance were very alarming, particularly since the *vanA* gene commonplace in strains of vancomycin-resistant enterococci (VRE) was found to be located on a plasmid *(394,395)*. For reasons that are not clear, spread has been minimal *(392)*. For now, those patients with MRSA infections who fail vancomycin therapy, particularly after long-term therapy, should signal a need for determination of the presence of high-level vancomycin resistance or of heteroresistance in the emerging strain.

Initial recommendations for control of VRSA emphasized extremely stringent isolation of the patient particularly by limiting the number of healthcare workers caring for the patient. Healthcare-associated transmission, when documented, was cautioned to trigger the closure of the ward to new admissions *(396)*. If VRSA strains appear nationwide and worldwide, hospitals will have to wrestle with the issue of how many resources they can expend on the infection control and epidemiologic analysis of these multiply resistant strains of *S. aureus*. Fortunately, there are more antimicrobial options for treatment of patients with VRSA infections *(392)*.

Future Possibilities for Control

The saga of *S. aureus* continues from its early stature as a community- and healthcare-associated pathogen to its acquisition of multiple antibiotic resistance coining a unique eponym, MRSA. The evolution of *S. aureus* as a human pathogen reflects its genetic flexibility including the spectrum of infections it causes as a healthcare-associated plague. Future strategies for the control of healthcare-associated *S. aureus* infections may include more persistent topical decolonizing agents, use of genetically engineered interfering strains of *S. aureus*, more efficacious passive vaccines and biologics *(397)*, use of probiotics, and peptide therapy to modulate pro- and anti-inflammatory cytokines. Catheters impregnated with antimicrobial compounds have been shown to reduce catheter-related infections and bacteremia, but their long-term clinical efficacy is not known *(398)*. New materials used for wound care such as hydrophobic wound dressings would absorb bacteria and tissue proteins. One study showed that fibronectin analogues blocked the binding of *S. aureus* to plastic surfaces coated with human proteins *(399)*. Aspirin has been shown to mitigate the effects of *S. aureus* endocarditis *(145)*. Our growing understanding of biofilm formation offers a host of new targets to discourage adherence and biofilm accumulation.

Such measures may diminish or eliminate colonization and lower healthcare-associated infection rates while reducing antimicrobial selective pressure on susceptible strains. Manipulation of the healthcare environment will likely include ways to use ambient air treatments to cleanse floors and walls, incorporation of antimicrobial elements like copper into touch surfaces, and novel, space-age barrier protection. Clearly, new vaccine strategies are needed to reduce the morbidity of staphylococcal bacteremia *(33,400)*. We await, in fact, a huge clinical trial with a vaccine containing a staphylococcal iron siderophore. A cellulitis model in mice was used to show that vaccination with RAP reduced cellulitis and decreased death suggesting that other vaccine targets in the complex regulatory pathways of *S. aureus* await exploitation (Fig. 28-3) *(401)*. These new advances should be pursued with utmost haste as our foe grows stronger and our patients grow impatient *(402)*.

ACKNOWLEDGMENTS

The authors thank Jeanette Augenstein and Alex Harvin for help with references; Jean Lee and Jodi Lindsay for help with specific sections; and Katherine Schmidt and Ambrose Cheung for work on the *sar/agr* graphic. The authors thank Neil Barg, MD for his contributions as coauthor in previous editions.

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CHAPTER 29

Methicillin-Resistant *Staphylococcus aureus*

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INTRODUCTION

Purpose of Chapter

For many decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has been regarded as an important microorganism within acute healthcare, and much has been described pertaining to MRSA as a cause of healthcare-associated infections (HAIs), factors that place patients at risk for MRSA infections, and the impact of such infections on patients, hospitals, and the healthcare system at large in countries all over the world. Researchers have provided scientific evidence describing how MRSA emerged, how the microorganism has been transmitted, and measures that have been effective for prevention and control. Of note, within the last 15 years, the epidemiology of MRSA has changed considerably with emergence of the microorganism as a cause of infections among community members who lack traditional risks for MRSA acquisition. This has not only captured the interest of scientists and clinicians, but also that of public health officials, consumer groups, print and television media, as well as government officials. There is renewed focus on MRSA and despite all we have learned about this pathogen, many facilities and communities continue to struggle from its effects and with how to implement evidence-based practices for control.

Scope of Chapter

This chapter describes several aspects of the epidemiology of MRSA including its laboratory characteristics, molecular typing characteristics, clinical and surveillance definitions, as well as its emergence and importance within healthcare and the community. Information regarding how to characterize the reservoir for MRSA are also discussed including methods for detecting colonized individuals. Finally, discussion is provided of basic as well as advanced strategies to prevent transmission both within and outside of healthcare.

EPIDEMIOLOGY

S. aureus is a common component of the normal flora of humans and many animals. Population-based studies suggest that approximately one third of the human population is asymptomatically colonized with *S. aureus (1)*. Persistent or transient carriage of *S. aureus* is most commonly detected in the anterior nares, but carriage on other mucous membranes (such as the oropharynx) and the skin is also frequently detected. Common sites of cutaneous carriage include the axilla, groin, perianal and perineal areas, wounds and sites of chronic skin disease, as well as foreign body (e.g., gastrostomy tubes and vascular access devices) exit sites. *S. aureus* is also a highly effective pathogen and is one of the most common causes of bacterial infection in humans. Common sites of *S. aureus* infection are the skin and soft tissues, lower respiratory tract, and bloodstream (including endocarditis) *(2)*, but infection can occur at essentially any body site.

Based on studies performed in Canada and Sweden between 1999 and 2005, estimates of the incidence of invasive *S. aureus* infection have ranged from 28.4 to 33.9 infections per 100,000 persons per year *(3,4)*. Invasive infections are associated with substantial morbidity and mortality, with outcomes dependent to some degree on the site of infection, host- and treatment-related factors. One study reported an overall in-hospital mortality of 19% among patients with invasive *S. aureus* infection *(3)*, and a number of studies that have assessed the outcomes of patients with *S. aureus* bacteremia report crude mortality rates from 18.9% to 34.4% *(5–7)*.

S. aureus is a common cause of HAI. In fact, *S. aureus* was the second most common cause of device- and procedure-related infections and accounted for 15% of all HAI reported by US hospitals participating in the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN) between 2006 and 2007 (8). The proportion of HAI caused by *S. aureus* varied among types of infection reported to NHSN. For instance, *S. aureus* was the most common cause of surgical site infections (SSIs) and ventilator-associated pneumonias (VAPs), accounting for 30% and 24%, respectively. *S. aureus* was the fourth most common cause of central line-associated bloodstream infections (CLABSI) (10% of cases) and the eighth most common cause of catheter-associated urinary tract infections (CAUTIs) (2%). A number of factors, including capsular polysaccharides, surface proteins, enzymes, toxins, and superantigens, contribute to the success of *S. aureus* as a pathogen and result in its ability to cause a variety of clinical syndromes. Discussion of these factors is provided in other chapters of this textbook.

General Laboratory Characteristics

S. aureus is a gram-positive, nonmotile, facultatively anaerobic coccus. In the laboratory, staphylococci tend to grow in grape like clusters of cells, hence the genus name *Staphylococcus*, which is derived from the Greek word *staphylé* or "bunch of grapes." The species name, *aureus*, Latin for golden, describes the color of *S. aureus* colonies growing in culture. Unlike many other bacteria, staphylococci can grow in environments in which there is a high concentration of salt. This feature is commonly used to assist in the laboratory identification of *Staphylococcus* species. The presence of catalase activity can be used to distinguish staphylococcal species from several other genera of gram-positive cocci, including *Streptococcus* and *Enterococcus*. The production of the enzyme coagulase differentiates *S. aureus* from the other staphylococcal species (i.e., the coagulase-negative staphylococci). Similarly, mannitol fermentation can also differentiate *S. aureus* from most other staphylococcal species.

Historical Perspective

Penicillin-resistant strains of *S. aureus* were identified relatively soon after penicillin became widely available in the 1940s. The mechanism of resistance was production of penicillinase, a beta-lactamase enzyme encoded by the *bla* gene. Subsequently, rates of penicillin resistance increased rapidly among hospital and community isolates of *S. aureus*. By the early 1950s, penicillin was no longer effective for the treatment of most *S. aureus* infections in many parts of the world. In response to the emergence of penicillin-resistant *S. aureus*, semisynthetic penicillinase-resistant penicillins were developed and introduced into clinical practice in the late 1950s and early 1960s. Methicillin was the first of these agents to be developed. In 1961, shortly after methicillin became available for clinical use, the first isolates of MRSA were reported *(9)*. The prevalence of resistance to methicillin among *S. aureus* isolates did not increase as rapidly as had occurred with penicillin resistance in the 1940s, and, in fact, the prevalence remained low until the 1970s and 1980s. Since that time, however, MRSA has become endemic in most hospitals in the United States, Europe (with a few notable exceptions such as Denmark and the Netherlands), Australia, and many other parts of the world.

Until relatively recently, MRSA was considered to be almost exclusively a healthcare-associated pathogen. During the past decade, however, MRSA has emerged as a significant pathogen among persons without typical healthcare-related risks associated with MRSA (*10*,11,*12*). In fact, MRSA has become the most commonly identified cause of purulent skin and soft tissue infections in persons presenting to emergency departments and other outpatient settings in many parts of the United States (13,*14,15*), and its prevalence in this type of infection is increasing in many other countries as well *(16–18)*. Based on data from the CDC's Active Bacterial Core surveillance program, it has been estimated that almost 14% of invasive MRSA disease in the United States in 2004 to 2005 occurred in persons without typical healthcare-associated risks (19). The emergence of community-associated MRSA (CA-MRSA) is the result of clonal dissemination of MRSA that is genetically distinct from typical healthcare-associated MRSA (HA-MRSA). The epidemiologic and genetic differences between CA-MRSA and HA-MRSA will be discussed in greater detail later in this chapter.

Laboratory Definition of MRSA

General Laboratory Characteristics Although typically referred to as MRSA, these strains are resistant not only to the antistaphylococcal penicillins, such as methicillin, nafcillin, and oxacillin, but also to all other currently available beta-lactam antibiotics (with the exception of the recently FDA-approved ceftaroline), including the first- through fourth-generation cephalosporins and the carbapenems.

The antibacterial effect of beta-lactam antibiotics is the result of inhibition of penicillin-binding proteins (PBPs), which are bacterial proteins acting as catalysts of cell wall assembly. *S. aureus* resistance to the antistaphylococcal penicillins, currently available cephalosporins, with the exception of ceftaroline, and carbapenems is the result of production of an altered PBP known as "PBP2a" or "PBP2′." PBP2a has very low affinity for binding beta-lactam antibiotics, which results in the inability of these drugs to exert their antibacterial effect. PBP2a is encoded by the *mecA* gene located on a resistance island, known as the "staphylococcal cassette chromosome *mec*" (SCC*mec*), which can integrate into chromosomal DNA. Several different types of SCC*mec*, known as "SCC*mec* types I-VIII," have been identified to date.

Heteroresistance refers to the situation in which only a subpopulation of the *S. aureus* cells with the resistance determinant (i.e., the *mecA* gene) actually express resistance *in vitro*. This has important implications for detection of resistance because, in the laboratory, the subpopulation that is susceptible to the penicillinase-resistant penicillins may grow more rapidly than the resistant subpopulation at temperatures above 35°C. In order to improve the ability to detect these heteroresistant strains, the Clinical Laboratory Standards Institute (CLSI) recommends incubation of *S. aureus* isolates at 33°C to 35°C for a minimum of 24 hours before assessing susceptibility to oxacillin, methicillin, or nafcillin (20).

In addition to resistance to the beta-lactam antibiotics, most strains of MRSA are also resistant to one or more other classes of antimicrobial agents. This can be the result of mutations in chromosomal DNA or acquisition of exogenous antibiotic resistance genes. In HA-MRSA strains, resistance to several classes of antibiotics is common. In many instances, these additional resistance determinants reside within the SCC*mec*. Two of the more common chromosomal mutations associated with antibiotic resistance are mutation of the DNA gyrase gene (*gyrA*) leading to fluoroquinolone resistance and mutation of rpoB leading to rifampin resistance. In *S. aureus*, intermediate resistance to the glycopeptides (vancomycin and teicoplanin), defined by CLSI as a vancomycin MIC of 4 to 8 μg/mL and teicoplanin MIC of 16 μg/mL, is also due to mutations in the bacterial chromosome. These mutations cause changes in the structure of the peptidoglycan component of the cell wall, leading to a thicker wall with more uncrosslinked D-alanyl-D-alanine terminals. These excess D-ala-D-ala terminals bind to glycopeptide molecules preventing them from reaching their true target *(21)*. Although the terms "vancomycin-intermediate *S. aureus*" (VISA) and "glycopeptide- intermediate *S. aureus*" (GISA) are often used interchangeably, some VISA isolates retain *in vitro* susceptibility to the glycopeptide teicoplanin.

Acquisition of exogenous resistance genes is responsible for resistance to several other classes of antimicrobials among MRSA isolates. Some of the more common and well-described acquired resistance determinants include *erm* (conferring macrolide and lincosamide resistance), *mupA* (conferring high-level mupirocin resistance), *tet* (conferring resistance to the tetracyclines), *msrA* (conferring macrolide resistance), and *dfrA* (conferring high-level trimethoprim resistance). One of the most feared scenarios has been the potential for the development of high-level vancomycin resistance in *S. aureus* (VRSA) due to acquisition by MRSA of the plasmid-mediated vancomycin resistance gene, *vanA*, from vancomycin-resistant *Enterococcus* (VRE). Conjugative transfer of *vanA* from *E. faecalis* to *S. aureus* was achieved in the laboratory in 1992 *(22)*, raising concerns that this transfer of genetic material could occur spontaneously *in vivo* as well. The first clinical isolate of VRSA was identified a decade later *(23)*. Since this first description in Michigan, nine additional cases have been identified between 2002 and 2007 *(24,25)*. In each case, vancomycin resistance was the result of the presence of the v*anA* gene, localized to a plasmid, within a methicillin-resistant strain of *S. aureus*. Commonalities identified among most of the reported cases include significant underlying medical conditions (such as diabetes, end-stage renal disease, and chronic lower-extremity wounds), prior history of VRE colonization or infection, prior history of MRSA colonization or infection, and prior receipt of vancomycin therapy. It is thus presumed that each of these cases developed in the setting of cocolonization with MRSA and VRE with transfer of the *vanA* gene from VRE to MRSA. Fortunately, these all appear to have been isolated, rare events and contact investigations have found no evidence of transmission of VRSA from case patients to their household or healthcare contacts.

Laboratory Methods for Identifying MRSA

A variety of options exist for detection of MRSA in clinical and surveillance specimens. These include conventional culture methods, novel culture-based techniques, and molecular methods. Each method has its own advantages and disadvantages relative to the issues of cost, turnaround time, complexity, performance characteristics (e.g., sensitivity and specificity), and approved uses. Detection of the *mecA* gene or PBP2a, the protein expressed by *mecA*, is the most accurate method for prediction of methicillin resistance (20). In this section, laboratory methods used specifically for the detection of methicillin-resistant strains of *S. aureus* will be discussed. A detailed discussion of the various laboratory methods available for isolation and identification of *S. aureus* in general is beyond the scope of this chapter.

Culture Methods

Oxacillin Screen Agar The CLSI-recommended agar dilution screening test for oxacillin-resistance in *S. aureus* isolates is known as the oxacillin screen agar test. Oxacillin screen agar consists of Mueller-Hinton agar containing 4% sodium chloride and 6 μg/mL oxacillin. In this test, a standardized suspension of *S. aureus* is inoculated onto oxacillin screen agar and incubated at 33°C to 35°C. Identification of growth of one or more colonies after 24 hours of incubation indicates that the tested isolate is oxacillin resistant. The sensitivity of the oxacillin screen agar test is 82.5% to 98%. Specificity has been reported to range from 46% to 100%, with most studies reporting specificities at the higher end of this range (*26–29*).

Cefoxitin Disk Test The cefoxitin disk diffusion screening test can be used to determine the presence of *mecA*-mediated oxacillin resistance. Because cefoxitin is a more potent inducer of the *mecA* gene, the use of cefoxitin disks, rather than oxacillin disks, is preferred for disk diffusion testing. In this test, standard disk diffusion procedures are used to inoculate Mueller-Hinton agar with a suspension of *S. aureus* that has been isolated from a primary specimen. A 30-μg cefoxitin disk is applied, and the plate is incubated at 33°C to 35°C for 16 to 18 hours. If the zone diameter is <21 mm, the isolate is deemed to be *mecA*-positive and reported as oxacillin resistant (*30*). The reported sensitivity and specificity of the cefoxitin disk diffusion test have ranged from 89.7% to 100% and 87.5% to 100%, respectively (*28,31,32*).

Chromogenic Agar Chromogenic agars that allow for simple and relatively rapid identification of methicillin-resistant strains of *S. aureus* are available for use in screening patients for MRSA colonization using swab specimens obtained from the nares, throat, groin, axilla, and perineum. These are selective agars that inhibit the growth of methicillin-susceptible strains of *S. aureus* and many other microorganisms and produce specific color changes in colonies of *S. aureus*. This distinctive color change allows MRSA to be distinguished from other methicillin-resistant microorganisms that grow on the agar plate. Unlike the previously described culture-based methods for detection of methicillin-resistance, specimens can be plated directly onto chromogenic agar, reducing the time interval between specimen collection and detection of MRSA. Positive results can be obtained in as little as 24 hours and final results, positive or negative, are available in 48 hours. The sensitivity and the specificity of chromogenic agars for the detection of MRSA, as compared with conventional culture-based methods and PCR, have ranged from 73% to 100% and 89.7% to 100%, respectively (*32–37*). Use of an overnight broth enrichment step prior to plating samples on chromogenic agar has been shown to increase the sensitivity of this method (38), although it also increases the turnaround time of the test by approximately 1 day. Because similar color changes may occur in colonies of some other microorganisms (e.g., coagulase-negative staphylococci, *Corynebacterium* species, some gram-negative bacilli), false-positive results can occur. The use of additional tests (e.g., Gram stain, coagulase test, and *S. aureus* latex agglutination test) to confirm that isolates suspected to be MRSA based on colony color are truly *S. aureus* has been shown to improve the specificity of these media (*33,34*).

Detection of PBP2a In addition to conventional phenotypic tests, tests that detect the presence of the mechanism of resistance, the altered drug target PBP2a, are available for use in the laboratory to identify MRSA in clinical specimens. As compared with traditional methods of testing for antimicrobial resistance, tests that detect PBP2a allow for more rapid detection of resistance (24–48 vs. <1 hour, respectively). Methodologies for detection of PBP2a include latex agglutination and immunochromatographic

assays. Latex agglutination assays use latex particles that have been sensitized with monoclonal antibodies against PBP2a. These latex particles react with PBP2a that has been extracted from a clinical isolate to result in macroscopically visible agglutination. Isolates that do not produce PBP2a do not cause agglutination of the latex particles. Sensitivity of latex agglutination tests has ranged from 83% to100%, and specificity has been reported to be as high as 100% (*28,29,39–41*). More recently, immunochromatographic membrane assays for the detection of PBP2a have been developed. In a study that used a tube coagulase test and an immunochromatographic assay for the identification of MRSA in blood cultures positive for gram-positive cocci in clusters, the sensitivity and the specificity of the immunochromatographic assay were 94.4% and 100%, respectively, as compared with PCR-based testing (*42*).

Molecular Methods

Polymerase Chain Reaction (PCR) In recent years, PCR-based assays for the detection of MRSA in nasal swab samples have been developed for use in MRSA screening programs. Commercially available PCR assays detect a unique gene sequence at the junction created by the integration of the SCC*mec* (the *mecA*-containing transposon) into the *S. aureus* chromosome. As compared with culture-based methods, these assays have been shown to be highly sensitive (80–100%) and specific (91–98.6%) for the detection of MRSA (*38,43–46*). Positive and negative predictive values for these assays have ranged from 66% to 95.8% and 96.6% to 100%, respectively. The low positive predictive values reported in some studies may be due in part to the identification of a larger number of MRSA carriers by the more sensitive PCR-based technology than detected by the culture-based reference standard due to the ability of PCR to detect a lower density of microorganisms than is possible with culture-based methods. The turnaround time for PCR-based detection of MRSA directly from nasal swabs is shorter than that associated with culture-based testing. As compared to a minimum turnaround time of 24 to 48 hours for culture-based testing, PCR has the potential to provide results within a few hours.

Although the first commercially available PCR assays were approved for use only for nasal specimens, PCR-based assays are also now available for use in detecting MRSA in some clinical specimens. Currently approved assays allow for the detection of MRSA directly from swabs taken from sites of skin or soft tissue infection and from blood cultures in which growth of gram-positive cocci in clusters has been identified. These assays detect sequences within the *S. aureus* chromosome, the SCC insertion site, and the *mecA* gene. As compared with broth-enriched culture methods, this assay demonstrated sensitivity, specificity, positive predictive value, and negative predictive value for the detection of MRSA in skin wounds of 97.1%, 96.2%, 91.9%, and 98.7%, respectively, in a population in which the prevalence of MRSA in wounds was 30% *(47)*. For the detection of MRSA in positive blood cultures, the sensitivity, specificity, positive predictive value, and negative predictive values were 98.3%, 99.4%, 96.6%, and 99.7%, respectively. A second study found the test to be 100% sensitive and 98.4% specific for the detection of MRSA directly from positive blood cultures *(48)*. The ability to more rapidly determine the presence or the absence of MRSA with the use of such PCR-based assays has the potential to improve clinical outcomes of gram-positive bacteremia and skin or soft tissue infection and to reduce unnecessary antimicrobial use. In addition, more rapid detection of MRSA infection may allow more rapid implementation of infection control measures designed to reduce the risk of MRSA transmission. These potential benefits, however, have not yet been fully evaluated.

Laboratory Methods for Strain Typing MRSA

Strain characterization and typing of MRSA isolates has helped describe the epidemiology of the microorganism in many different circumstances such as the evolution of MRSA, epidemic and endemic spread within healthcare and the community, as well as for patient care when it has been necessary to determine the strain causing infection or colonization. Bacteriophage typing was relied upon for decades; however, newer methods such as multilocus sequence typing (MLST), pulsed-field gel electrophoresis (PFGE), staphylococcal protein A (spa) typing, and SCC*mec* typing are the most common techniques utilized today *(49–52)*. Each method of strain typing uses different nomenclature leading to multiple characterizations of the same strain. Furthermore, there is no universally accepted nomenclature for strain typing MRSA and thus, comparison analysis between different labs in different geographic locations has been difficult. Each typing method has its own advantages and disadvantages that include the level of training and equipment necessary to conduct the procedure and interpret the results, discriminatory power, and cost.

Multilocus Sequence Typing MLST is based on sequencing DNA fragments of seven highly conserved housekeeping genes within *S. aureus*. Housekeeping genes are used because they are always present in the species (as they encode for the enzymes necessary for cell survival) but have sufficient variation to produce numerous alleles at a given locus. The resulting sequences of these genes are compared to known alleles at each locus via an electronic database located on the MLST Web site (http://www.mlst.net). Here, each isolate has been described by a seven-integer allelic profile defining a sequence type (ST), and clusters of related STs are defined as clonal complexes (CCs) *(53)*. The sequences that serve as the target for MLST are not subject to rapid change as they are not influenced greatly by selective pressures such as antibiotic-resistance encoding genes. Because of this, MLST has been useful for studying the evolutionary genetic relationships between known MRSA lineages and their precursor MSSA strains *(54)*. In 2000, Enright and colleagues *(52)* validated the use of MLST for *S. aureus* and subsequent studies performed on numerous MRSA isolates have supported the notion that the species population is strongly clonal, but gives rise to well-defined divergent lineages capable of rapid dissemination *(52–55)*. After initial dissemination, the strains may evolve regionally *(56)*.

MLST is particularly useful for these types of large population studies, and its Web-based data analysis system allows it to be extremely portable. However, this method does lack some discriminatory power (when compared to methods such as PFGE) for detecting more subtle differences between strains. Thus, it is often not

the method of choice for smaller outbreak investigations, determination of the relatedness of strains in the same patient, or in any situation where it is imperative to study close genetic relationships between isolates *(49)*. Additionally, MLST is costly and requires special equipment, as well as laboratory expertise.

Pulsed-Field Gel Electrophoresis PFGE is the method most often used for strain typing of MRSA. The procedure involves incorporating the entire bacterial isolate into an agarose plug, which is then subjected to detergents and enzymes that lyse the bacteria and deproteinate the plug. The DNA is then digested with a restriction enzyme (usually *Sma*I for MRSA), and slices of the plug (containing the digested chromosomal DNA) are placed into wells of an agarose gel. The gel is exposed to an electrophoretic current that switches direction according to a predetermined pattern. During this process, the restricted DNA is resolved into a pattern of discrete fragments, which are visualized by staining the gel with a fluorescent dye. The PFGE restriction profiles from different isolates are then commonly compared visually by pairwise fragment for fragment analysis *(49)*. It is relatively easy for the examiner to evaluate the relatedness of strains from a single or a limited number of gels, as is typically the case when evaluating an outbreak, or a limited number of isolates from a single center. However, computerized gel scanning and analysis software is available and allows users to create databases of PFGE patterns that can be used to compare gels from different laboratories or a large number of isolates over an extended period of time *(57)*. The advantages of PFGE over other typing methods include its reproducibility and high discriminatory ability. Thus, it has been an effective tool for outbreak investigations and for determining the relatedness of individual patient isolates. Additionally, the procedure is relatively straightforward. Specialized equipment and training is required, but the cost is not prohibitive *(49,58)*. PFGE can be time consuming, and it is often difficult to compare banding profiles from gels created at different times or at different facilities if the procedure conditions have not been standardized.

Spa Typing spa typing is a DNA sequencing analysis method that targets a polymorphic region of the *spa* gene. This region consists of 24 to 27 base pair repeats that may vary in number and nucleotide sequence. Each resulting unique combination detected through the analysis is assigned a distinct spa type, and this allows objective comparison between bacterial strains *(50,51)*. The method is highly reproducible and with the creation of Web-based tools, which have been developed for classification of the sequences, the data are also portable. There are two major nomenclature models, one described by Ridom (*http://www.ridom.net*) and the other described by Kreiswirth (*http://tools.egenomics.com*) *(50)*. Because spa typing relies on a single genetic locus and requires only a single PCR reaction, it is much less complex and less costly than MLST but it has discriminatory power approaching that of PFGE *(59)*. The portability of the data simplifies information sharing between laboratories and facilities creating large-scale databases for studying global and local epidemiology *(60)*.

SCCmec Typing Several molecular methods for identifying SCC*mec* types have been reported *(61,62)*. Eight major SCC*mec* types have been described (SCC*mec* type I to SCC*mec* type VIII), and their presence in MRSA has been useful for designating whether or not the MRSA strain is of healthcare origin or community origin. Often, SCC*mec* typing is combined with MLST typing as SCC*mec* has been associated with a limited subset of MLST CCs. With this, each MRSA isolate would be classified by a specific chromosomal background defined by MLST as well as the SCC*mec* type (Table 29-1) (20). Understanding the evolution of MRSA isolates and particularly the emergence of the new community-acquired strains requires characterization of the isolate's SCC*mec* element (20). To date, HA-MRSA strains possess only a limited number of SCC*mec* types, including SCC*mec* I first described in the United Kingdom in 1961, SCC*mec* II first described in Japan in 1982, and SCC*mec* III first described in New Zealand in 1985; whereas CA-MRSA strains possess smaller SCC*mec* types IV described in the United States in 1996, type V described in Australia in 1993, type VI described in Portugal in 1996, VII described in Sweden in 2007, and VIII described in Canada in 1996 (20).

Emergence of MRSA

As stated previously, the first MRSA was described from London in 1961, only a year after methicillin was introduced into the clinical arena *(9)* and within that decade came the first reports of healthcare-associated outbreaks due to MRSA in the United States *(63)*. By the early 1990s, MRSA strains were on the rise as a prevalent cause of HAI *(64)*. In a report released by the National Nosocomial Infections Surveillance system, the percentage of *S. aureus* HAIs caused by strains that were resistant to methicillin, oxacillin, or nafcillin was found to have increased among all hospitals more than 10-fold from just 2.4% in 1975 to 29% in 1991. Furthermore, the rate differed depending on bed size of the hospital. For example, in 1991, in hospitals with <200 beds, 14.9% of *S. aureus* were MRSA; for hospitals with 200 to 499 beds, 20.3% were MRSA; and for hospitals with 500 or more beds, 38.3% were MRSA. The authors concluded that hospitals of all sizes were facing the growing problem of MRSA and that control measures, which were being advocated at the time, should be re-evaluated *(64)*. Throughout the 1990s, MRSA infections were largely reported to occur among those who frequented healthcare facilities (e.g., hemodialysis units) or among those admitted into acute or long-term care. It was only on rare occasions that infections originating in the community were due to MRSA and this was typically reported among special populations such as injection drug users *(65)*.

Epidemiologic Definitions of MRSA

Historically, the major determinant in characterizing an MRSA infection as either "healthcare-acquired" or "community-acquired" has been the time of onset, or the time to identification of the infection after admission to the hospital. For example, if the patient had an infection incubating at the time of admission or if the infection was identified within 48 hours of admission, the infection would be classified as community-acquired; and if the patient had an infection develop after 48 hours of admission, it would be classified as healthcare-associated. Over the past 10 to

TABLE 29-1

Typing Designations of Common MRSA Strains

Historical Geographic Distribution	*MLST*	*SCCmec*	*PFGE (CDC, USA)*	*PFGE (Canada)*	*spa (Ridom)*	*spa (Kreiswirth)*
—	1	IVa	USA400	CMRSA-7	t128	UJJFKBPE
New York, Japan (pediatric)	5	II IV	USA100 USA800	CMRSA-2	t002	TJMBMDMGMK
	8	IVa	USA300	CMRSA-10	t008	YHGFMBQBLO
	8	II, IV	USA500	CMRSA-5	t064	YHGCMBQBLO
—	8	VIII	—	CMRSA-9	t008	YHGFMBQBLO
EMRSA-15	22	IV		CMRSA-8	t022	TJEJNF2MF2 MOMOKR
—	30	IV	USA1100	—	t019	XKAKAOMQ
EMRSA-16	36	II	USA200	CMRSA-4	t018	WGKAKAOMQQQ
Berlin	45	II	USA600	CMRSA-1	t004	A2AKEEMBKB
—	59	IV	USA1000	—	t216	ZDMDMNKB
—	72	IVa	USA700	—	t126	UJGFMGGM
Brazil, Hungary	239	III	—	CMRSA-3/6	t037	WGKAOMQ
The Netherlands (Pig Strain)	398	V	nontypeable	nontypeable	t034	XKAOAOBQO

Strain typing designations for some of the widely used typing systems as applied to prevalent strains of MRSA clones.
(Reproduced from CLSI, Surveillance for Methicillin-Resistant *Staphylococcus aureus*: principles, practices, and challenges; a report. CLSI document X07-R, 2010. Wayne, PA: Clinical and Laboratory Standards Institute.)

15 years, the healthcare delivery system has undergone substantial changes, the most striking of which has been the shift of treatment of more acute illnesses into the outpatient arena, home, and the long-term care facility (LTCF). With these newer models for delivering healthcare and with the continued emerging epidemiology of MRSA and its associated risk factors, it became more difficult to accurately classify MRSA as strictly healthcare-associated or community-acquired. Recently, in two landmark studies by Klevens and colleagues, which described the incidence of invasive MRSA infections in the United States, the epidemiologic classifications of MRSA infections were redefined using two broad categories, "healthcare-associated" and "community-associated"(19,*66*). HA-MRSA infections were characterized as MRSA infections occurring among persons with at least one of the following healthcare-related risk factors: presence of an invasive device at the time of admission, previous history of MRSA colonization or infection, history of surgery, hospitalization, dialysis, or residence in an LCTF in the previous 12 months prior to culture date. Community-associated infections were characterized as occurring in persons who have none of these healthcare-related risk factors. HA-MRSA infections were further characterized as either community or hospital onset. Community onset refers to cases with a positive culture within 48 hours of admission and with at least one healthcare-associated risk. Hospital onset refers to cases with a positive culture result obtained >48 hours after hospital admission (19).

Prevalence of MRSA in Healthcare

Unfortunately, today, most would consider MRSA infections endemic in the majority of healthcare centers not only in the United States, but also in many countries throughout the world. In the United States, the proportion of *S. aureus* HAI resistant to methicillin has continued to increase, with rates of 63% reported from intensive care units (ICUs) in 2004. However, even though this proportion has continued to increase, recent data suggest that the incidence of MRSA CLABSIs has actually decreased in several ICU types since 2001 (Fig. 29-1) *(67)*. Although these findings are encouraging and highlight success in prevention of HAI, it is still important to realize that MRSA remains high in most facilities and many patient groups continue to be at risk for acquisition and infection from the pathogen.

In 2008, the NHSN released a report of antimicrobial-resistant pathogens associated with HAI in the United States between 2006 and 2007. The pooled mean proportion of all device-related HAI due to MRSA was 8%; however, this varied by type of infection and by patient care area within the healthcare facility (8). For example, higher rates of MRSA CLABSI were reported from burn ICUs (0.93 per 1,000 device days), moderate rates from trauma ICUs (0.30 per 1,000 device days), inpatient medical wards (0.28 per 1,000 device days), and medical cardiac ICUs (0.27 per 1,000 device days), and lower rates ranging from 0.11 to 0.20 per 1,000 device days from other areas of the hospitals. Similarly, higher rates of MRSA VAP were reported from trauma ICUs (1.36 per 1,000 device days) and neurosurgical ICUs (1.08 per 1,000 device days), lower rates from pediatric ICUs (0.17 per 1,000 device days), and more moderate rates ranging from 0.43 to 0.75 per 1,000 device days from other areas of the hospitals (8).

In 2009, a report similar to the NHSN document was released by the International Nosocomial Infection Control Consortium (INICC), which presented data regarding antimicrobial-resistant pathogens associated with HAI among 173 ICUs from 25 countries in Latin America, Asia, Africa, and Europe (68). Rates of methicillin resistance among

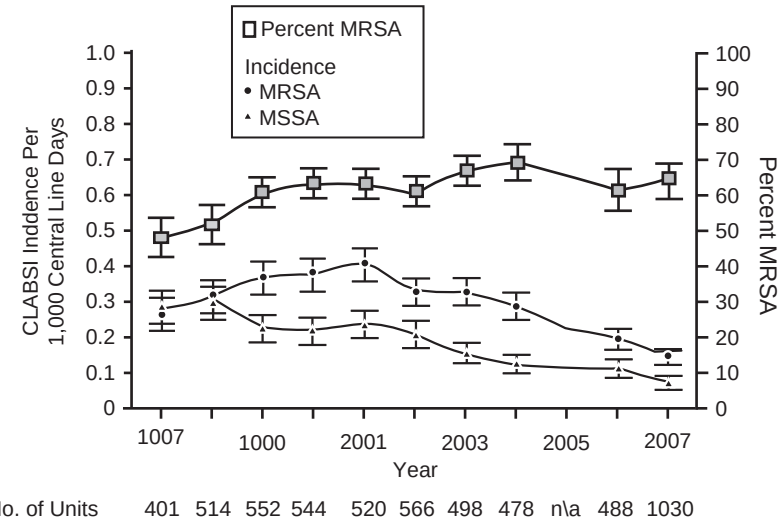

FIGURE 29-1 Trends in percent MRSA and incidents of *S. aureus* central line–associated bloodstream infections in intensive care units—National Nosocomial Infections Surveillance System, 1997–2004; National Healthcare Safety Network, 2006–2007. (Redrawn from Burton DC, Edwards JR, Horan TC, et al. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997–2007. *JAMA* 2009;301(7):727–736, with permission. Copyright © 2009 American Medical Association. All rights reserved.)

S. aureus HAI in INICC ICUs were significantly higher than the rates reported from NHSN ICUs. For example, the proportion of *S. aureus* CLABSI resistant to methicillin among INICC ICUs was 84.1% versus the 56.8% reported among NHSN ICUs. The authors speculated that these higher rates were likely a reflection of the limited resources available for hospitals in these countries to devote toward effective infection control programs, invariably low nurse to patient staffing ratios, and furthermore that the majority of hospitals lacked official regulations for infection control training or compliance (68). Similarly, methicillin-resistance rates reported among *S. aureus* VAP from INICC were 77.5% and among catheter- CAUTIs were 74.4%.

Since 1999, the European Antimicrobial Resistance Surveillance System (EARSS) has been collecting and reporting data from now 33 different European countries (*http://www.rivm.nl/earss/Images/EARSS%202008_final_tcm61-65020.pdf*). The median incidence rate for MRSA bloodstream infections (BSIs) among all countries reporting data was 4.8 per 100,000 patient days in 2008, increased from 3.5 per 100,000 patient days in 2007; however, this incidence rate varied considerably among the different countries from <1.0 per 100,000 patient days in Germany, Estonia, Finland, Iceland, the Netherlands, Norway, and Sweden to more than 8.0 per 100,000 patient days in Cypress, France, Ireland, Israel, Malta, Portugal, Turkey, and the United Kingdom. In 2008, these 33 countries reported susceptibility data for more than 30,000 invasive *S. aureus* isolates and found that 21% were MRSA. These proportions also varied from <1% in Northern Europe to >50% in Southern Europe; however, for the first time since EARSS began reporting summary resistance data, more countries showed decreasing MRSA proportions instead of increasing trends. Nevertheless, MRSA proportions are still above 25% in one third of European countries and >50% in the Mediterranean.

Importance in Healthcare

Healthcare-Associated Infections Caused by MRSA

MRSA is a well-described and common cause of many HAI including CLABSI, hospital-acquired pneumonia (including VAP), CAUTIs, wound infections, and SSIs. The impact of MRSA infections in the acute-care facility may be substantial. For example, a recent study by Filice and colleagues retrospectively analyzed excess costs and utilization associated with methicillin resistance for patients with *S. aureus* infections in their large VA hospital *(69)*. The median 6-month unadjusted cost for patients with MRSA infections was $34,657 compared with $15,923 for patients with MSSA. For patients with Charlson scores ≤3, the adjusted 6-month mean cost for an MRSA infection was $51,252 compared to $30,158 for MSSA, and for patients with Charlson scores 4 and above the adjusted 6-month mean cost for MRSA was $84,436 versus $59,245 for those with MSSA. Additionally, the mortality rate for those with MRSA infection was significantly higher compared to those with MSSA infection (23.6% vs. 11.5%; $p < .001$).

Bloodstream Infections The outcomes and impact associated with MRSA BSI have been the focus of numerous reports and depending on the type of study, patient population, and the methodologies used, results have varied *(7,70–77)*. Mortality rates for MRSA BSI patients have ranged from 20% to more than 35% *(7,71,73–75,77)* and among studies controlling for confounding variables, including severity of illness, when compared to mortality from MSSA, that from MRSA has been reported as significantly higher *(71,73,74)* as well as no different *(7,75,77)*. Regarding outcomes other than mortality, the impact of methicillin resistance has been described in terms of increased length of stay (LOS) and increased costs. An early study by Abramson et al. reported that the median LOS attributable to methicillin resistance among patients with healthcare-associated *S. aureus* BSI was 8 days (4 days for MSSA vs. 12 days for MRSA; $p = .023$), and the excess hospital cost was $17,422 ($9,661 for MSSA vs. $27,083 for MRSA; $p = .043$) *(76)*. A retrospective cohort study at a large academic hospital reported LOS attributable to methicillin resistance among patients with *S. aureus* BSI as increased by 1.29-fold ($p = .016$) and hospital charges as increased by 1.36-fold ($p = .017$) *(7)*, and another found that the average total charge during hospitalization for MRSA BSI was $45,920 as compared to $9,699 for MSSA BSI ($p = .0003$) After stratifying by case mix index (CMI), for those with a CMI >2 the average cost per day for a patient with MRSA was $9,744 versus $4,442 for patients with MSSA *(75)*. A recent

study of 182 patients with healthcare-associated *S. aureus* BSI found that compared to ICU patients with MSSA BSI, those with MRSA BSI had increased median total hospital costs ($42,137 vs. $113,852), increased costs after diagnosis of infection ($17,603 vs. $51,492), and increased LOS after infection (10.5 vs. 20.5 days); however, after analyzing the data utilizing a propensity score to estimate the predicted probability of acquiring a methicillin-resistant pathogen (and thus analyzing the effect among comparable patient populations) no significant differences were found *(70)*.

The impact of MRSA has also been studied outside the tertiary-care academic hospital. Kaye and colleagues conducted a cohort study to compare the outcomes of patients with MRSA infection (BSI or SSI) in community hospitals to that in tertiary care. One third of patients with MRSA infections died during hospitalization and of those that survived, 36.4% required readmission within 90 days and 57% of all MRSA-infected patients died within the subsequent year after diagnosis. Patients treated in community hospitals were less likely to receive effective antimicrobial therapy within 7 days of diagnosis compared to tertiary care (58.9% vs. 74.8%; $p < .001$), and they had a significantly higher 1-year mortality rate (62.5% vs. 52.5%; $p = .02$) *(72)*.

Healthcare-Associated Pneumonia The prevalence of MRSA as the cause of hospital-associated pneumonia has been recently reported by several investigators. For example, a retrospective cohort study of 59 hospitals from 2002 to 2003 to characterize the microbiology and outcomes among patients with pneumonia *(78)* reported MRSA as the cause of 56.8% of *S. aureus* healthcare-associated pneumonia, 48.6% of *S. aureus* hospital-acquired pneumonia, and 34.4% of *S. aureus* VAP. In another retrospective analysis of patients with healthcare-associated pneumonia, 16% to 18% were due to MRSA *(79)*. Similarly, a four country prevalence survey of HAI in England, Wales, Northern Ireland, and the Republic of Ireland found that MRSA was the cause of 7.6% of pneumonias and 18.1% of other lower respiratory tract infections *(80)*.

The attributable mortality that methicillin resistance contributes to those who suffer from *S. aureus* VAP has been debated. Older studies, which compared patients with MRSA VAP to those with MSSA VAP, reported that crude mortality was significantly increased for those with MRSA. For example, Rello and colleagues prospectively analyzed the outcome of 49 patients with *S. aureus* VAP who were similar with regards to sex, severity of illness, prior surgery, and presence of renal failure, diabetes, and coma. They reported that mortality related to pneumonia was significantly higher for those with MRSA compared to those with MSSA (RR, 20.72; 95% CI, 2.78–154.35) *(81)*. Other more recent, larger studies that have controlled for confounding variables such as receipt of appropriate empiric antibiotic therapy and LOS have reported that mortality is not increased for patients with MRSA VAP compared to those with MSSA VAP *(82–84)*. One large retrospective study of 154 patients with *S. aureus* VAP in 59 US hospitals (16 teaching hospitals and 43 nonteaching hospitals) reported that there was no increased mortality due to MRSA compared to MSSA (29% vs. 36%) *(82)*. Similarly, a prospective study of 134 patients with *S. aureus* VAP who had received appropriate initial empiric antibiotic therapy in 12 French ICUs found that after adjusting for differences in populations and controlling for length of ICU stay at time of VAP diagnosis, there was no difference in ICU or hospital death among those with MRSA compared to MSSA (OR, 2.06 and 1.75; $p = .07$ and .10, respectively) *(84)*. However; the impact of methicillin resistance goes beyond mortality with several studies describing increased morbidity and cost of care. Shorr et al. *(82)* found that the average cost of an MRSA VAP was $40,734 and after multivariate analysis, compared to those with MSSA VAP, those with MRSA consumed excess resources of 4.4 days on mechanical ventilation ($p = .03$), 3.8 inpatient days ($p = .05$), 5.3 days in the ICU ($p = .02$), and $7,731. Furthermore, among those with *S. aureus* VAP who received appropriate antibiotic therapy, when controlling for demographics, reason for ICU admission and mechanical ventilation, severity of illness, and duration of mechanical ventilation prior to VAP, infection with MRSA (vs. MSSA) doubled the probability of needing continued ICU care (HR, 2.08; 95% CI, 1.09–3.95; $p = .025$) and increased median ICU stay by 11 days (33 vs. 22 days; $p = .047$) *(82)*. Similarly, a large prospective study in three teaching hospital ICUs found that there was a significant delay in resolution of hypoxemia for those with MRSA (10 vs. 2 days) and after multivariate analysis, regardless of receiving appropriate antibiotic therapy, MRSA required significantly longer mechanical ventilation compared to other pathogens *(85)*. Excess resources included 6.8 days of antibiotic receipt, 13.8 days of mechanical ventilation, and 11 days of ICU care. Another study reported that among 160 patients with MRSA pneumonia, the expected estimated median daily billed hospital charges were $2,888 to $2,993 and the median total hospital charges were $32,024 to $32,636 *(79)*.

Surgical Site Infections As with other HAI, MRSA has increased as a cause of SSI. Among 2,045 *S. aureus* SSI reported to NHSN from 2006 to 2007, 49% were due to MRSA (8). In a study conducted to describe the epidemiology of severe SSI among patients from 26 community hospitals in the southeastern United States, from 2000 to 2005, the prevalence of MRSA doubled from 0.12 infections per 100 procedures to 0.23 infections per 100 procedures *(86)*. Another study of patients with microbiologically confirmed SSI from 97 US hospitals conducted from 2003 to 2007 reported that the proportion of MRSA as the cause of SSI significantly increased from 10.6% to 20.6% ($p < .0001$) *(87)*, and another study reported that among the elderly, MRSA increased as the cause of SSI from 15% in 2000 to 20% by 2005 *(88)*. A recent large retrospective cohort study of adults undergoing orthopedic, neurosurgical, cardiothoracic, and plastic surgeries at 11 hospitals in North Carolina and Virginia (nine community hospitals and two tertiary-care hospitals) found that MRSA was responsible for 50% of SSI in community hospitals and 43% of SSI in tertiary-care hospitals. Among those with *S. aureus* SSI, MRSA was the cause in 62% of cardiothoracic SSI, 54% of orthopedic SSI, 43% of neurosurgical SSI, and in 35% of plastic surgeries *(89)*.

Patients with MRSA SSI also suffer increased morbidity, mortality, and hospital costs. This was initially described by Engemann and colleagues in 2003 *(90)*. This cohort study compared the outcomes of patients who suffered MRSA SSI to patients who suffered MSSA SSI and to patients who

did not develop an SSI. Compared to those with MSSA SSI, those with MRSA had a greater 90-day mortality (adjusted OR, 3.4; 95% CI, 1.5–7.2; $p = .003$) and after controlling for ASA score, hospital, surgery duration, diabetes, renal disease, and LOS prior to infection, methicillin resistance was responsible for a 1.20-fold increase in LOS (2.6 excess days) and 1.19-fold increase in mean hospital charges ($13,901). The median hospital cost for an MRSA SSI was $92,363 *(90)*. Two more recent studies have also described increased morbidity and costs *(87,91)*. One reported that compared to patients without an SSI, those with SSI due to MRSA had an independently increased risk for readmission within 90 days (OR, 35.0; 95% CI, 17.3–70.7), death within 90 days (OR, 7.27; 95% CI, 2.83–18.7), 23 days of additional hospitalization, and $61,681 in excess charges. Compared to patients with MSSA SSI, those with MRSA SSI had 5.5 days of additional hospitalization and $24,113 in excess charges *(91)*. Another study found that compared to SSI due to other microorganisms, those caused by MRSA had significantly higher mortality (1.4% vs. 0.8%; $p = .03$) and that the MRSA SSI risk-adjusted attributable LOS was 0.93 days and attributable increased cost was $1,157 *(87)*.

MRSA in Long-Term Care Facilities

MRSA has also emerged as an epidemiologically important microorganism in other types of healthcare facilities including those that provide long-term care. Epidemiologic descriptions of MRSA in LTCFs are heterogeneous likely because the patient populations cared for in LTCF are heterogeneous, ranging from patients who require long-term physical rehabilitation, long-term psychiatric care, long-term acute care, and those that require permanent or long-term residence. Additionally, LTCF may differ in bed size, geographic location, and through an association with a large tertiary-care hospital, an academic teaching hospital, or a Veterans Administration hospital. Thus, it is important to consider these variables when reviewing studies conducted in LTCF of the prevalence of MRSA colonization or infection (92). Recent studies from the United States have reported a wide range of MRSA prevalence rates *(93–97)*. For example, Mermel and colleagues conducted a multicenter prevalence study of 6 LTCF and found that among 125 residents who had nares cultures performed, overall, 25 (20%) were positive for MRSA; however, this ranged from 10% to 100% among the facilities *(93)*. Furuno et al. reported a prevalence rate of 30% among residents of a 180 bed long-term acute care (LTAC) facility associated with a large university affiliated hospital in Baltimore, and Mody et al. reported that among 73 residents of a VA LTCF, 58% were MRSA-colonized and that among 54 residents of community-based LTCF, 35% were MRSA-colonized *(94,96)*. Another study performed in a 100-bed VA-associated LTCF in Atlanta prospectively assessed colonization rates by performing weekly surveillance cultures and classified carriers as persistently colonized or intermittently colonized. 49 of 83 (59%) residents had at least one nasal swab positive for MRSA, 30 (36%) were persistent carriers, and 19 (23%) were intermittent carriers. Of the 83 subjects who had enough surveillance cultures to be included, 43 initially negative subjects were designated as being at risk for intrafacility MRSA acquisition and ultimately 9 (21%) had a subsequent positive culture for MRSA *(95)*. A large study among nursing homes in four Canadian provinces (Ontario, Manitoba, Saskatchewan, and Alberta) and four nursing homes in adjacent US states (Michigan, Montana, North Dakota, and Minnesota) specifically designed to include only those facilities not associated with an acute care, university, or VA hospital reported that 33% of clinical S. *aureus* isolates were MRSA *(97)*. Outside the United States, MRSA prevalence in LTCF has also varied *(98–102)*. Two recent point prevalence studies from Italy reported disparate results. The first conducted among 551 residents of two LTCF reported that 43 (7.8%) were positive for MRSA and the other conducted in a 120 bed LTCF reported that 38.7% of residents were colonized *(98,100)*. The prevalence of MRSA in LTCF in France has been reported at 37.6% *(102)*, and in Spain a study among nine community LTCF reported an overall MRSA prevalence rate of 16.8%; however, this rate ranged from 6.7% to 35.8% *(101)*.

Risk factors for MRSA carriage in LTCF have also been well described and include antibiotic exposure *(98,100–102)*, recent hospitalization *(95,100)*, certain comorbidities *(98,100)*, and presence of medical devices *(101,102)*. Recently, Mazur and colleagues performed a cross-sectional study of MRSA prevalence and risks for MRSA carriage. Multivariate analysis found that compared to residents who were non-MRSA carriers, those older than 85 years (OR, 1.60; 95% CI, 1.16–2.21), those with impaired functional status, those with a Charlson Index of two or more (OR, 1.50; 95% CI, 1.09–2.08), those with decubitus ulcers (OR, 2.56; 95% CI, 1.58–4.17), those who had received antibiotics (OR, 2.44; 95% CI, 1.75–3.39), those with medical devices (OR, 2.47; 95% CI, 1.35–4.53) and those transferred from acute care (OR, 2.15; 95% CI, 1.39–2.41) were significantly more likely to be MRSA carriers *(101)*. With regards to antibiotic exposure as a risk for MRSA carriage in LTCF, exposure within 3 months of sampling to a fluoroquinolone *(98)* has been associated with a more than fivefold increased risk for MRSA, exposure to three or more antibiotic courses within 1 year of sampling *(100)* has been associated with a more than fivefold increased risk for MRSA, and exposure to third-generation cephalosporins or fluoroquinolones has been associated with a more than 12-fold increased risk of MRSA *(102)*. Decreased risk for MRSA carriage has been associated with use of antimicrobial soaps within the facility and with an increased staff to patient ratio (number of registered nurses per 100 residents) *(97)*.

Risk of MRSA infection among colonized individuals has been well described in acute care (and is discussed below); however, this risk has not been well described in long-term care. Bradley retrospectively reviewed data from six US studies from 1990 to 1997 and found that overall, the incidence of MRSA infection was 6.5% among carriers and that the associated mortality was just 1% *(103)*. Muder compared MRSA carriers to MSSA carriers and noncarriers and found that staphylococcal infections developed 3.6 times more often among MRSA carriers compared to the other groups *(104)*. The most frequently reported MRSA infections among residents of long-term care are skin and soft tissue infections; however, more serious invasive infections such as BSI and pneumonias have been reported (92,*105,106*). In a recent prospective study among community LTCF located in Spain, the incidence of

MRSA infection among colonized residents was 0.12 per 1,000 patient days and only two of those patients required hospital admission; however, MRSA colonization in LTCF should not be viewed as benign as when colonized LTCF residents enter acute care they are at increased risk for MRSA infection *(101)*.

There is also evidence to suggest that the epidemiology of MRSA within the LTCF is changing. In 2009, Tattevin and colleagues conducted a study to describe the prevalence and the genotypes of MRSA clinical isolates over a 10-year period at a large 1,000-bed LTCF in San Francisco *(99)*. Among *S. aureus* isolates, the proportion due to MRSA increased from 38.1% in 1997 to 72.3% in 2006 ($p < .0001$) and the USA300 CA-MRSA clone increased from 11.3% of MRSA isolates in 2002 to 64% of MRSA isolates in 2006 ($p < .0001$). The USA300 clone was most often isolated from skin and skin structure sites and of note, up to 30.9% of USA300 isolates were multi-drug resistant suggesting that these isolates were likely acquired under increased antibiotic use pressure within the facility *(99)*.

Risk of MRSA HAI among Colonized Patients in Acute Care

A relatively large proportion of asymptomatic carriers of MRSA in acute care will progress to invasive MRSA infection. A recent systematic review of ten observational studies determined that colonization with MRSA was associated with a fourfold increase in the risk of infection as compared to persons with colonization with methicillin-susceptible *S. aureus (107)*. This risk, however, is likely to vary substantially among individuals and populations depending on the setting and individual risk factors for infection. In a study of patients who were found to be colonized or infected with HA-MRSA during hospitalization, 29% of colonized and infected persons developed at least one episode of MRSA infection within 18 months *(108)*. Another study of nasal carriers of HA-MRSA identified at the time of hospital admission found that 18.3% of carriers had invasive MRSA infection documented concurrently (29%) or within 18 months of detection of nasal carriage (71%) *(109)*. In a similar study in which patients were tested for nasal *S. aureus* carriage at the time of evaluation for admission to the ICU, 24.1% of MRSA carriers developed an MRSA infection within 60 days. In contrast, only 0.6% of patients with nasal carriage of methicillin-susceptible *S. aureus* developed an MSSA infection *(110)*. One potential explanation for the higher rate of invasive infection among carriers of HA-MRSA as compared with carriers of MSSA is that carriers of MRSA may be at greater risk of infection due to greater or more severe underlying medical conditions and/or a more frequent need for medical interventions that place them at increased risk of infection with their endogenous flora. However, one recent study of patients who were screened for nasal *S. aureus* carriage at the time of ICU admission found that MRSA-colonized patients were more likely to develop *S. aureus* infection while in the ICU than MSSA-colonized patients, even after adjustment for patient-specific factors that are associated with MRSA carriage (adjusted hazard ratios of 4.70 and 2.47, respectively, as compared with patients without nasal carriage of *S. aureus*) *(111)*.

Risk Factors for MRSA Colonization and HAI

A number of risk factors associated with HA-MRSA carriage have been established. Some of these risks are at the level of the individual patient *(112–115)*. These patient-level factors include a variety of chronic medical conditions such as diabetes mellitus, chronic obstructive pulmonary disease, leukemia, HIV infection, and end-stage renal disease. Other patient-specific risk factors include older age, admission to a hospital or a LTCF within the preceding 12 months, prolonged duration of hospitalization, receipt of antibiotic therapy within 3 months, invasive procedures, and the presence of foreign bodies (such as indwelling urinary and vascular catheters, tracheostomy tubes, and feeding tubes). These factors likely all represent exposure to the healthcare system resulting in an increased risk of exposure to or prolonged exposure to HA-MRSA and perhaps an increased risk of acquisition and persistent carriage if exposed to MRSA as compared to persons without these factors.

In addition to patient-specific risk factors, a variety of factors associated with the healthcare system and the healthcare delivery process have been associated with acquisition or transmission of MRSA. Studies have demonstrated that the risk of acquisition of MRSA during hospitalization increases as the prevalence of MRSA among hospital patients increases. In one study, it was observed that when the weekly colonization pressure (i.e., weekly prevalence) exceeded 30%, the risk of MRSA acquisition was five times higher than that when colonization pressure was <10% *(116)*. This finding may be the result of an increased environmental burden of MRSA with subsequent patient-to-patient spread by contaminated healthcare workers and equipment. The role of the environment in MRSA transmission is further highlighted by a study that demonstrated that the odds of acquiring MRSA were significantly higher among persons admitted to a hospital room in which the prior room occupant was colonized or infected with MRSA (OR, 1.4; $p = .04$) *(112)*. Several studies have reported an association between healthcare worker hand hygiene practices and the incidence of MRSA within healthcare facilities *(117–121)*. These studies have observed reductions in MRSA infection and acquisition in temporal association with improved rates of adherence to hand hygiene guidelines or increased consumption of alcohol-based hand rubs (ABHRs). Other investigators have associated increased rates of MRSA infection and colonization with staffing deficits and patient overcrowding *(122,123)*. These findings may reflect an increase in the environmental burden of MRSA or reduced compliance with infection prevention measures such as hand hygiene and Contact Precautions in the setting of understaffing and overcrowding.

Reservoir for MRSA Transmission

In Acute-Care Facilities

Patients There are several reservoirs of MRSA within an acute-care facility that may contribute to the risk of transmission of the microorganism. One such reservoir consists of patients who are colonized or infected with MRSA. As previously noted, the risk of acquisition of MRSA during hospitalization has been shown to be correlated with the prevalence of MRSA among facility patients (*116*). It should be noted, however, that the true prevalence of MRSA

among patients in most acute-care facilities is generally not known and likely varies substantially among acute-care facilities. In a survey of 1,237 US hospitals (representing approximately one quarter of all US hospitals) performed in 2006, the overall reported prevalence of MRSA was 4.6% (*124*). There was substantial variation among the states, with prevalence ranging from 0% to 9.1%. The findings from this survey likely represent a significant underestimation of the true burden of MRSA in US hospitals, because participating facilities provided data based on information that was readily available to the facilities' infection preventionists and most participating hospitals were not using active surveillance testing to identify all colonized patients. Thus, the information reported by most of the participating facilities was based on the results of clinical cultures. Previous studies have demonstrated that clinical cultures alone identify as few as 15% of colonized patients (*125*) and underestimate the monthly average prevalence in ICUs by 18% to 63% (*126*). Recent studies that have used active surveillance to assess the prevalence of MRSA among hospital patients suggest that the true prevalence of MRSA is higher than the estimate derived from the previously described national survey. Rates of MRSA colonization of 2.8% to 6.8% have been observed among patients being admitted to hospitals for cardiac and orthopedic surgery (*127–130*). Assessment of all patients being admitted to an urban hospital in Atlanta, Georgia, found that 7.9% of patients were carriers of MRSA at the time of hospital admission (*113*). In studies of adult patients being admitted to ICUs in hospitals in New York City and St. Louis, 13% to 14.5% of subjects have been identified as carriers of MRSA (*110,111*).

Environment Contamination of environmental surfaces and healthcare equipment in the rooms of MRSA colonized or infected patients is relatively common. Once in the environment, *S. aureus*, including methicillin-resistant strains, can persist for relatively long periods of time (*131*). *S. aureus* in the environment can theoretically be transmitted to other patients either directly, through contact with the contaminated surface or item, or indirectly, by the hands of healthcare workers who come into contact with the contaminated item and then interact with a patient without proper hand hygiene prior to patient contact. This concept is discussed in greater detail later in this chapter.

Healthcare Personnel As mentioned above, healthcare personnel (HCP) may transmit MRSA to patients by transient contamination of their hands or clothing following contact with colonized patients or contaminated environmental surfaces and equipment. MRSA-colonized HCP are an additional potential reservoir for MRSA transmission. Several studies have assessed the prevalence of MRSA carriage among HCP. In an analysis of data from 127 published studies, the average MRSA prevalence among HCP was found to be 4.6% (95% CI, 1.0%–8.2%) (132). The prevalence observed in individual studies varied from as low as 0% to as high as 59%. This dramatic variability is likely the result of differences in the settings in which HCP screening occurred (e.g., outbreak vs. endemic setting, end of a shift vs. beginning of a shift), the occupation of the personnel included in the study, the year(s) in which the study was performed, and the method by which screening was performed (e.g., single vs. multiple site sampling, culture vs. molecular testing). The timing of specimen collection may have a substantial impact on the prevalence of MRSA detected among HCP. This is because a substantial proportion of colonized workers carry MRSA only transiently. For example, 12 (46%) of 26 nurses working on a designated MRSA ward were demonstrated to have nasal or hand carriage of MRSA at the end of a work shift with subsequent loss of carriage before the beginning of their next shift (133,134). Thus, sampling personnel during or immediately after patient care duties may find a larger number of carriers than sampling personnel before beginning a work shift.

Other Healthcare Facilities

Long-term Care and Acute Rehabilitation Facilities As discussed above, MRSA is certainly not limited to the acute care hospital. In fact, the prevalence of MRSA among residents of LTCFs has been shown to be even higher than that observed among patients in acute care hospitals. This is likely due, at least in part, to the fact that many of the patients in these facilities are patients with multiple MRSA risk factors that have been transferred from acute care hospitals. The prevalence of MRSA colonization among LTCF residents has ranged from 9.9% to 40% (*96,135,136*). Of note, the study that reported the highest rate of MRSA colonization sampled multiple sites (nares, oropharynx, groin, perianal area, wounds, and enteral feeding tube exit site) and reported that only 65% of colonized residents were nasal carriers, suggesting that nasal sampling alone may grossly underestimate MRSA prevalence in this population (*96*). Studies that reported lower rates (9.9%–30.3%) assessed residents with the use of nasal swabs alone (*135*). Surveillance testing of persons admitted to an acute rehabilitation facility found that 12% of patients were carriers of MRSA (*137*).

Other Settings and Persons

Household environments Although MRSA contamination of the healthcare environment has been most well characterized, MRSA contamination of other environments has also been detected. These environments include the homes of persons known to be carriers of MRSA (*138*) as well as randomly selected homes (*139*). Surfaces and items within these households that have been found to be contaminated with MRSA include dish towels, sinks, and faucet handles in kitchens and bathrooms. In a study of randomly selected homes, 7% of the sampled kitchen faucets, 6% of sampled kitchen dish towels, and 3% of bathroom sink and tub fixtures were contaminated with MRSA (*139*).

Close personal contacts of persons with MRSA colonization or infection Transmission of HA-MRSA from colonized or infected patients to their household and personal contacts has been well described. In studies that have assessed the prevalence of MRSA among these contacts, MRSA carriage has been detected in 14.5% to 67% of study participants *(140–143)*. In some of these studies, molecular analysis demonstrated that the strain of MRSA carried by the household contact(s) was the same strain as that carried by the index case. Factors that have been associated with acquisition of MRSA by household contacts include providing healthcare to the index patient and having prolonged exposure to the index case.

Importance of MRSA in the Community

Historically, MRSA was considered to be almost exclusively acquired in healthcare; however, over the past 10 to 15 years, MRSA has emerged as a significant pathogen among persons without typical healthcare-associated risk factors (*10*,11,*12,144*). Data from the CDC's Active Bacterial Core surveillance and Emerging Infections Program Network indicate that 13.7% of the 95,000 cases of invasive MRSA disease in the United States between July 2004 and December 2005 occurred in persons without established healthcare-associated risks (19). This rapid change in the epidemiology of MRSA is the result of clonal dissemination of novel strains of MRSA that are genetically and epidemiologically distinct from typical HA-MRSA strains (Table 29-2). CA-MRSA appears to have arisen as the result of migration of SCC*mec* type IV into methicillin-susceptible strains of *S. aureus*. More recently, SCC*mec* types V-VIII have been identified but SCC*mec* type IV continues to be identified in the vast majority of CA-MRSA isolates. Unlike SCC*mec* types I-III that are common among strains of HA-MRSA, SCC*mec* type IV is smaller and more mobile and has thus been able to move into several lineages of MSSA. In the United States, pulsed-field type USA400 (multilocus sequence type ST1) was the first identified clone, but since that time USA300 (ST8) has become the predominant clone. Other than the *mecA* gene, SCC*mec* type IV typically contains few or no additional antibiotic resistance determinants. Thus, CA-MRSA strains are frequently resistant only to currently available beta-lactam antibiotics and perhaps one or two additional classes of antibiotics (such as the macrolides and, increasingly common, the fluoroquinolones) (145). However, resistance to additional classes of antibiotics is being reported with increasing frequency *(146–148)*. For example, isolates of CA-MRSA with resistance to oxacillin and erythromycin as well as clindamycin, mupirocin, and, in many cases, tetracycline have been reported from Boston and San Francisco *(147)*. In those isolates, resistance to the additional antimicrobial agents was due to the presence of the pUSA03 conjugative plasmid that contains multiple resistance determinants, including the genes *ermC* and *mupA* that result in constitutive resistance to macrolides and clindamycin, and mupirocin, respectively. Related plasmids, presumed to have been transferred from USA100 strains of HA-MRSA, have been detected in other USA300 MRSA isolates *(148)*. These findings suggest that the problem of multidrug resistance that has been associated with HA-MRSA for many years may begin to complicate the treatment of CA-MRSA infections as well. An additional genetic difference between most CA-MRSA isolates and typical HA-MRSA strains is the presence of genes encoding the Panton-Valentine leukocidin (PVL) in the former. Because most CA-MRSA strains are PVL-positive and CA-MRSA has been associated with severe purulent skin and soft tissue infections and necrotizing pneumonias, some have questioned whether PVL is responsible for the increased virulence associated with CA-MRSA strains. Studies performed to date have not provided conclusive evidence that PVL is a major virulence factor in CA-MRSA, but the clinical significance of PVL remains controversial and continues to be investigated *(149–156)*.

Skin and soft tissue infections, especially furuncles, abscesses, and other purulent infections, are the most common type of infection caused by CA-MRSA (*14*,145,*157*). In fact, CA-MRSA has become the most common cause of purulent skin and soft tissue infections among patients presenting to emergency departments in several regions of the United States (13). Clusters of CA-MRSA skin infections have also been described among several specific populations, including men who have sex with men *(147,158,159)*, sports participants *(160,161)*, military personnel *(162)*, prisoners *(163)*, rural communities *(164,165)*, and families *(166,167)*. These populations likely represent groups at increased risk for the spread of MRSA and/or for invasive infection if exposed to MRSA due to close skin-to-skin contact, the presence of cuts or abrasions that can serve as portals of entry for MRSA, shared use of contaminated items and surfaces (such as towels and razors), crowded living conditions, and/or poor hygiene. CA-MRSA infections

TABLE 29-2

Genetic and Epidemiologic Differences Between HA-MRSA and CA-MRSA

Characteristic	*HA-MRSA*	*CA-MRSA*
SCC*mec* types	I, II, III	IV (V, VI)
PFGE types	USA100, USA200	USA300, USA400
MLST	ST5, ST8, ST22, ST36, ST45	ST8, ST30, ST1, ST80
PVL gene	Rare	Common
Additional antimicrobial resistance	Resistance to multiple classes of antimicrobial agents is common	Often resistant to ≤2 additional classes of antimicrobial agents
Epidemiologic risk factors	Exposure to healthcare: hospitalization, residence in LCTF, surgery, dialysis	Crowded living conditions; skin-to-skin contact; cuts, abrasions, or other breaches in skin integrity; exposure to contaminated surfaces and items (i.e., fomites); poor hygiene
Common sites/types of infection	BSI, SSI, pneumonia, UTI	Skin and soft tissue infection, pneumonia

HA-MRSA, healthcare-associated methicillin-resistant *Staphylococcus aureus*; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*.

are not, however, limited to the skin and soft tissues. CA-MRSA is also a well-described cause of respiratory tract infections, particularly necrotizing pneumonia (including postinfluenza pneumonia), BSI, otitis media and externa, and joint infections *(109,168)*.

Risk of CA-MRSA Infection among Colonized Persons

The proportion of asymptomatic carriers of CA-MRSA that progress to invasive infection has been demonstrated to be quite high, often higher than the rate of invasive disease among carriers of HA-MRSA. In a longitudinal study of nasal carriers of the USA300 strain type identified through an active surveillance program at the time of hospital admission, 17.9% of nasal carriers had an episode of invasive MRSA infection documented at the study facility concurrently or within 18 months of detection of nasal colonization *(109)*. In a study of nasal carriage of *S. aureus* among community-dwelling children, 23% of the identified MRSA carriers developed MRSA skin or soft tissue infection within 6 months *(169)*. Among the MRSA carriers included in that study, 5 (33%) of the 15 children with carriage of CA-MRSA developed SSTI as compared with none of the 9 children with carriage of the HA-MRSA ($p = .12$). In a study of military personnel living in communal barracks while undergoing training as combat medics, 38% of nasal carriers of CA-MRSA developed soft tissue infection within 10 weeks of detection of carriage *(162)*. In both of these latter studies, the proportion of carriers of CA-MRSA who developed invasive infection was much greater than that observed for carriers of methicillin-susceptible *S. aureus* (8% and 3%, respectively). In a study performed in a clinic in Boston that served largely a population of men who have sex with men, participants were screened for MRSA colonization of the nares, perianal area, and wounds (if present) *(159)*. The overall prevalence of MRSA in that population was 3.8%, and most of the MRSA detected was CA-MRSA. During the 1-year follow-up period, 36.7% of the MRSA-colonized subjects developed skin and soft tissue infection as compared with only 8.1% of those without MRSA ($p < .001$).

Environmental Reservoirs for CA-MRSA Transmission

Several published studies have reported an association between CA-MRSA infection and participation in sporting events, particularly contact sports. This has led to investigation of the potential role of the environment as a reservoir for MRSA transmission in athletic facilities. When environmental sampling was performed in 10 high school athletic training facilities, MRSA was isolated from samples obtained from 90% of the facilities and 46.7% of all surfaces sampled, including water coolers, treatment tables, sink faucet handles, and locker room shower handles *(170)*. A second group of investigators obtained environmental samples in college athletic team training facilities and isolated MRSA from 37 (25%) of the 147 samples that had been obtained *(171)*. After education of the athletes regarding preventive measures and education of custodial staff regarding proper cleaning protocols, subsequent environmental sampling yielded no *S. aureus*. Environmental contamination is not, however, limited to athletic facilities. MRSA has also been recovered from commonly touched items and surfaces in households, such as dish towels, kitchen sink faucet handles, and bathroom sinks and tubs *(139)*.

Emergence of CA-MRSA in the Healthcare Facility

Recent epidemiological studies have also reported that the MRSA strains initially described in the community (such as USA300, SCC*mec* type IV) are now a cause of invasive HAI. From 2003 to 2010, several studies were published describing the emergence of CA-MRSA as a cause of HAI among several different types of patient populations and in areas all over the world including the United Kingdom *(172,173)*, Greece *(174)*, Denmark, as well as Korea *(175)*. Community strains of MRSA have been reported as the cause of healthcare-associated skin and soft tissue infections in postpartum women *(176)*, healthcare-associated prosthetic joint infections *(177)*, HAI among patients with end stage renal disease on hemodialysis *(178)*, healthcare-associated BSI *(175,179–182)*, and invasive HAI among neonates being cared for in the neonatal ICU *(173,183–185)*. Klevens et al. and the Active Bacterial Core surveillance system of the Emerging Infections section at the CDC described the proportion of invasive MRSA HAI due to community strains among three groups of patients from 2004 to 2006. Nine thousand one hundred forty-seven isolates were included and were classified as healthcare-associated hospital onset, healthcare-associated community onset, or community associated. Twenty-eight percent of the healthcare-associated isolates were USA300 strains, 14% of the healthcare-associated community onset isolates were USA300, 2% were USA400, and 2% were USA1000; in other words, 18% to 28% of isolates in patients who had healthcare-associated risks had PFGE banding patterns typical for community strains *(66)*.

The prevalence of community strains as a cause of HA-MRSA BSI has ranged from 19% to more than 60% depending on the patient population and geographic location *(175,179–182)*. One study of consecutive MRSA BSI isolates at a large urban tertiary-care hospital in Atlanta found that overall, 34% of isolates were USA300 by PFGE (28% of healthcare-associated isolates and 20% of hospital-associated isolates). Having a USA300 strain as a cause of your BSI was independently associated with IV drug use (OR, 3.67; 95% CI, 1.10–12.28) and the presence of a concurrent skin and soft tissue infection (OR, 4.26; 95% CI, 1.08–16.84). Admission from an LTCF (OR, 0.09) and receipt of antibiotics within the previous year (OR, 0.10) were associated with a significantly lower likelihood of having USA300 *(180)*. In another large epidemiologic study of HA-MRSA BSI caused by USA300 among three hospitals in Denver from 2003 to 2007, the rates of MRSA BSI due to CA-MRSA strains varied from 19% in one hospital, to 36% in another to 62% in the other. IV drug use and HIV infection were independently associated with having a USA300 strain as the cause of your HA-MRSA BSI (OR, 3.9; 95% CI, 1.0–14.4 and OR, 15.0; 95% CI, 2.5–89, respectively) *(182)*. Evidence also exists that not only describes CA-MRSA isolates as occurring within the healthcare arena, but that these isolates are increasing in their prevalence *(178,179,182,185–187)*. Maree and colleagues retrospectively examined all clinical HA-MRSA isolates (blood, sputum, wounds) from 1999 through 2004 and reported that the inferred SCC*mec* IV phenotype increased

from 17% to 56% over the study period ($p < .0001$). Multivariate analysis identified significant risks for an SCC*mec* IV phenotypic isolate from a wound as the source, MRSA isolated in the later years of the study, and MRSA isolated earlier in the hospital course *(187)*. Popovich et al. compared MRSA BSI isolates from 2003 to 2006 to those from 2000 to 2003 and found that the rate of hospital onset MRSA BSI remained constant; however, the community genotypes responsible for the HA-MRSA BSI increased from 24% in 2000 to 2003 to 49% in 2003 to 2006 (RR, 1.9; 95% CI, 1.2–3.1; $p = .01$). The authors suggested that traditional healthcare-associated strains were being replaced by community strains as the cause of HA-MRSA BSI *(179)*. Patel conducted a retrospective lookback from 2000 to 2004 to determine when USA300 first entered the healthcare system. Isolates were classified as community-associated or healthcare-associated by clinical characteristics (isolated 48 hours or more after admission). USA300 first appeared in the outpatient arena in 2001 and in the inpatient hospital in 2003. By 2004, USA300 was responsible for 40% of inpatient MRSA isolates independent of where patients were being cared for (35.7% of surgical ICU isolates, 16.7% of medical ICU isolates, and 53% of floor isolates) *(186)*. In neonates, Seybold and colleagues found community clones were first described as a cause of colonization or infection in their neonatal ICU in 1998 and that the proportion had significantly increased between this time and 2004, with USA300 accounting for MRSA colonization in 68% of patients in 2004. Vaginal delivery and maternal smoking were associated with community strains of MRSA colonization *(185)*.

Recently, a study by Freitas from a large university hospital in South Carolina, which has been conducting active surveillance for MRSA colonization since 2001, reported that the proportion of patients found to be MRSA colonized by USA300 strains significantly increased from 2005 to 2007 (17%–27%; $p = .003$) *(109)*. Among those colonized with USA300 strains, 18% went on to develop MRSA HAI, and this was no different than those colonized with nonUSA300 strains. Also, risk factors for MRSA HAI between the two groups were similar *(109)*. Mathematical models have been developed to attempt to predict when community strains of MRSA will replace healthcare strains of MRSA as the most common cause of HAI *(188,189)*. Skov *(188)* reported that depending on the number of isolation rooms available, and whether or not active surveillance was performed to identify MRSA colonized patients, after MRSA was introduced into the community and transmission was permitted for 30 years, a new equilibrium would be reached within 7 to 14 years, leading to a prevalence of MRSA carriers with community strains in hospitals as high as 20%. D'Agata *(189)* also reported that the increasing influx into the hospital of patients who are colonized or infected with CA-MRSA will lead to a rapid reversal of dominance with community strains replacing healthcare strains. Additionally, because community isolates of MRSA have been thought to behave more virulently, causing more serious infections compared to healthcare strains, the outcomes of patients who acquire invasive MRSA infections in the hospital due to community strains may be worse. Moore and colleagues conducted a retrospective analysis to compare the epidemiology and outcomes between community-associated and healthcare-associated USA300 infections in their 900-bed tertiary-care hospital in Detroit. Among 160 patients, 47.5% had community-associated infections due to USA300 and 52.5% had HAI due to USA300 (20% acquired in the hospital). Patients with HAI had significantly greater treatment failure rates (38.1% vs. 23.7%; $p = .05$). Independent risks for failure included osteomyelitis as the infection type (OR, 43.56; $p < .001$), pneumonia as the infection type (OR, 3.74; $p = .036$), and previous history of MRSA (OR, 6.18; $p < .001$) *(190)*. These findings have led leaders in the field of healthcare epidemiology to stress the importance of close monitoring of the epidemiological situation and to conduct high-quality research regarding measures for prevention and control of MRSA HAI, including those due to community strains *(191)*.

DETECTION OF MRSA RESERVOIR IN THE HEALTHCARE FACILITY

Surveillance Definitions

Depending on the type of data collected, surveillance can help to quantify or estimate the burden of MRSA within a facility (e.g., the incidence and prevalence of MRSA), the incidence of one or more specific types of MRSA infection (e.g., the incidence of MRSA bacteremia), and the incidence of MRSA transmission within the facility. When surveillance is performed over time, the data can be used to monitor changes in the epidemiology of MRSA. This can be particularly valuable in determining the effectiveness of an MRSA prevention program. In order for the data to be meaningful and for comparisons to be valid, surveillance must be performed using standardized methods and consistent definitions.

Laboratory-Based Surveillance Because of the recognized importance of monitoring multidrug-resistant microorganisms in healthcare facilities and the lack of a standardized approach to do so, the Society for Healthcare Epidemiology of America (SHEA) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) published surveillance definitions and recommended metrics for multidrug-resistant microorganisms, including MRSA, in healthcare settings (192). Although these metrics have not yet been validated for interfacility comparison, they may be useful for monitoring MRSA within an institution. Unlike classic infection surveillance methods, the metrics recommended in the SHEA-HICPAC document are based solely on readily available laboratory and administrative data and, in some cases, basic epidemiologic data. Because extensive review of clinical documentation is not required, this type of surveillance is substantially less resource intensive. In these recommendations, definitions have been provided to assist with epidemiologic classification of MDRO isolates (Table 29-3). Temporal classification definitions categorize MRSA isolates as either "hospital-onset" or "community-onset," based solely on the date of specimen collection and the date of admission to the healthcare facility. Clinical classifications are based on the timing of specimen collection and an evaluation of the patient's clinical and epidemiologic risk factors for acquisition of MRSA. Clinical classifications include "healthcare-associated," "nosocomial," and "community-associated" MRSA. This classification can be used to classify a patient's first MRSA isolate as well as any subsequent MRSA event.

TABLE 29-3

Epidemiologic Classification of MRSA Isolates and Infections

Classification Strategy	*Classification*	*Definition*
Temporal	Hospital-onset MRSA[a]	The specimen from which MRSA was isolated was obtained more than 3 calendar days after the patient was admitted to the hospital. (Note: The day of admission is the first calendar day.)
	Community-onset MRSA	The specimen from which MRSA was isolated was obtained 3 or fewer calendar days after admission to the hospital (or other healthcare facility).
Clinical	HA-MRSA	MRSA that is isolated from a patient with documented healthcare-associated risk factors for MRSA acquisition such as: current or recent admission to a hospital, long-term care, or rehabilitation facility; indwelling vascular catheter; recent surgery; or outpatient hemodialysis.
	Nosocomial MRSA	A subset of HA-MRSA, this classification refers to MRSA that is likely to have been acquired during the patient's admission to the hospital (or other healthcare facility).
	Community-associated MRSA	MRSA that is isolated from a patient without documented healthcare-associated risk factors for MRSA acquisition.

[a]Although the term is "hospital onset," it is meant to indicate that the onset of MRSA occurred within the healthcare facility in which surveillance is being performed. Thus, a better term may be "facility onset" in order to allow wider applicability, such as in long-term care and other types of healthcare facilities.

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Infection Surveillance Unlike surveillance that is based on laboratory data alone, infection surveillance includes a review of relevant clinical data to allow identification of specific types of infection and to determine which MRSA isolates represent true infection and which represent colonization. The CDC/NHSN surveillance definitions of HAI and criteria for specific types of infection are widely used for clinical surveillance purposes *(193)*. Surveillance for specific types of MRSA infection, such as CLABSI, SSI, and/or pneumonia, can provide important information to a healthcare facility's MRSA prevention and control personnel. The amount of infection surveillance that can be performed within a facility, however, is often limited because of the resource intensive nature of this type of surveillance. Thus, a combination of laboratory-based and focused infection surveillance may be an effective approach to MRSA surveillance.

Methods for Detection of Patients with MRSA

The cohort of patients who serve as the reservoir for transmission of MRSA is, often likened to an iceberg, composed of (a) a small group representing the tip of the iceberg with clinical MRSA infection and (b) a much larger group who are merely colonized (without infection) with the microorganism, representing the mass beneath the surface of the water. These patients may be identified through the use of clinical cultures or active surveillance cultures.

Clinical Specimens Patients with MRSA infection are most often identified by routine clinical microbiology cultures from specimens obtained when infection is suspected (e.g., blood, urine, sputum, wound cultures). Some patients with MRSA colonization may be identified with clinical microbiology cultures; however, this method lacks sensitivity and the majority are identified through the use of active surveillance cultures.

Surveillance Culture Specimens Active surveillance for MRSA is defined as performing diagnostic testing for the purpose of detecting asymptomatic MRSA colonization (194). With regards to identifying the reservoir of colonized patients in a hospital, studies have demonstrated the benefit of active surveillance over that of relying on clinical cultures *(125,195–197)*. One study from a large tertiary-care academic hospital with a long history of employing the use of active surveillance for identifying MRSA-colonized patients found that of 437 patients discovered to be colonized with MRSA upon admission to the hospital, only 66 (15%) of those patients would have ever been identified as MRSA-colonized if a positive clinical culture was used for this purpose *(125)*. Among those hospitalized in the general wards, this proportion was 12.9% and among those hospitalized in the ICU, this proportion was 21.4%. Another study from a French ICU reported that 12.9% of patients with MRSA colonization discovered on admission through surveillance ultimately had a positive clinical culture during the 3 days before or after transfer to the ICU *(196)*, and another reported similar findings demonstrating that compared with admission surveillance, clinical samples would have identified only 15.8% of known MRSA-positive elderly patients in the hospital *(197)*. Additionally, in a study to determine the value of performing active surveillance cultures on ICU discharge, Furuno and colleagues *(195)* reported that nine (14%) of 65 patients identified as MRSA-colonized by surveillance subsequently had a clinical culture positive for MRSA after discharge from the ICU; however, 54 (83%) would have remained unidentified by relying on clinical cultures.

Sites to Sample The nares are the most common sites of *S. aureus* colonization in humans, including that due to methicillin-resistant strains. Data from two National Health and Nutrition Examination Survey (NHANES) projects describe nares colonization for noninstitutionalized healthy individuals for the periods 2001 and 2002 as well as 2003 and 2004 *(1,198)*. In 2001 and 2002, 32.4% (95% CI, 30.7%–34.1%) of the population surveyed were nasally colonized with *S. aureus* (MSSA or MRSA); however, only 0.8% (95% CI, 0.4%–1.4%) of the study population carried MRSA in their nares. MRSA colonization was associated with age >65 years and female sex *(1)*. Compared to this, in 2003 and 2004, the prevalence of *S. aureus* colonization decreased significantly to 28.6% (95% CI, 27.2%–30%; $p < .01$), while the prevalence of MRSA colonization increased to 1.5% (95% CI, 1.2%–1.8%; $p < .05$) *(198)*. Tenover and colleagues characterized the isolates from the NHANES studies and compared more recent strains from 2003 and 2004 to those from 2001 and 2002 *(199)*. Among all those nasally colonized with MRSA, 45.9% carried the HA-MRSA strain type USA100, and this proportion did not change significantly between the two time periods, and 13.9% carried the CA-MRSA strain type USA300 which did increase significantly from the first time period to the second (8.0% to 17.2%; $p = .03$). The remaining strains consisted of a variety of less common healthcare and community strain types *(199)*.

In addition to the anterior nares, several investigators have evaluated the presence of MRSA at other anatomical sites including the throat, axilla, groin, wounds, sites of foreign bodies, perirectal area, umbilicus, vagina, and perineum *(200–203)*. For example, Currie and colleagues described the relative sensitivities of different body sites for detecting MRSA colonization through culture based methods among adults as part of their active surveillance program. The sensitivity of nares was 68% (95% CI, 64%–72%), the sensitivity of open skin areas was 73% (95% CI, 64%–80%), the sensitivity of the rectum was 62% (95% CI, 58%–66%), and the sensitivity of combining nares and rectal cultures was 96% (95% CI, 94%–97%), a 34% relative increase from the use of nares swabs alone *(204)*. Another study of cultures performed via active surveillance in a large Finland hospital from 1999 to 2004 reported that among MRSA carriers, the nares was positive 67% of the time, the throat 51%, the perineum 31%, the groin 32%, the axilla 19%, and an infected focus 70% of the time *(203)*. When throat cultures were combined with nares, 85% of the positive MRSA patients were identified and when nares, throat, and perineum were combined, 95% were identified. This combined rate is similar to that found by Coello and colleagues *(205)* where a sensitivity of all three sites was 98.3% when active surveillance was performed during an MRSA outbreak at a university hospital in Spain. An early study of the natural history of MRSA carriage reported that the sensitivity of nares cultures (often combined with chronic wound or sputum cultures) was 93% and was considerably more valuable for detecting MRSA than were cultures of the axilla, groin, or perineum (sensitivity <39%) *(206)*. In neonates, for routine surveillance in the endemic setting (absence of an outbreak), nares cultures alone may be sufficient to identify carriers and prevent spread *(207)*; however, Rosenthal et al. reported the sensitivity of surveillance cultures in neonates from two hospitals during a period where both facilities were experiencing an MRSA outbreak. Nares culture sensitivity was 68% to 72% when used alone and this improved to 92% to 100% at one hospital when combined with umbilical cultures, but only to 71% to 84% when combined with rectal cultures *(208)*.

Sites of colonization with community strains of MRSA have not been fully described; however, it has been documented that among patients being admitted to the hospital and undergoing active surveillance of the nares, USA300 CA-MRSA strains were recovered routinely (24% of the time) and that this proportion has increased over time *(109)*. Yang and colleagues examined the prevalence of MRSA at four body sites among patients with acute skin infections to assess the relationship between MRSA colonization and infection in patients with CA-MRSA and other types of *S. aureus*. Among patients with CA-MRSA skin infections, 37% were MRSA colonized, 25% were colonized in the nares, 6% were colonized in the axilla, 17% in the inguinal area, and 13% perirectally. Among those with CA-MRSA skin infections who were also colonized, 96% could be identified using a combination of nasal and inguinal screening *(209)*. Others have suggested that the pharynx (or throat) may be an important site of CA-MRSA colonization *(200)*.

Additional Contributors to MRSA Reservoir

Environmental Surfaces and Medical Equipment

Environmental and medical equipment contamination with MRSA and transmission of the microorganism to healthcare workers and patients has been the subject of numerous studies. Despite this, it has been difficult to fully describe this complex relationship. Staphylococci may survive for extended periods of time in the environment and are generally resistant to desiccation *(210,211)*. For example, staphylococci has been found on plastic charts for up to 11 days *(212)*, on laminated tabletops for 21 days *(212)*, and on stainless steel for 72 hours *(213)*. Similarly, there is ample evidence that MRSA contaminates the clinical patient care environment. This includes inanimate objects such as mattresses, bed linens, patient gowns, nurses' uniforms, doctors' ties, tourniquets, pens, televisions, blood pressure cuffs, infusion pumps, stethoscopes, and telephones as well as touch surfaces such as bed rails, overbed tables, furniture, door handles, sinks, and computer key boards *(214–216,*217,*218–221)*. During an MRSA outbreak, Rampling and colleagues sampled the clinical areas (patient bays) where patients were frequently acquiring MRSA. Approximately 24 items and surfaces were sampled in each bay on each occasion and the percentage of specimens positive for MRSA was calculated. In the beginning of the outbreak, MRSA was isolated from 9 of 28 (32%) samples. After almost 1 year into the outbreak, 72 of 673 (10.7%) samples from environmental sites were positive for MRSA. Radiators, medical equipment, and furniture were the most frequently contaminated items at 36.4%, 13.2%, and 11.3%, respectively *(215)*. In a nonoutbreak setting, Blythe et al. *(219)* conducted an environmental screening study of approximately 1,000 specimens from 41 rooms that had previously been occupied by patients with MRSA and had been terminally cleaned. Nineteen (46%) of these rooms were contaminated

with MRSA. This included furniture and medical equipment, electrical equipment, and surfaces. Boyce et al. conducted a prospective culturing survey of objects in 38 rooms of known MRSA patients. Overall, 96 (27%) of 350 surfaces sampled were contaminated with MRSA. Of note, when patients had MRSA in a wound or in their urine, 36% of surfaces were contaminated, and when MRSA was isolated from other body sites, only 6% of the surfaces were contaminated. Environmental contamination occurred in the rooms of 73% of patients suffering MRSA infections and 69% of patients colonized with the microorganism. Frequently contaminated objects included the floor (50–55%), bed linens (38–54%), patient gowns (40–53%), overbed tables (18–42%), and blood pressure cuffs (25–33%) *(216)*. Another study also demonstrated that the hospital environment can become extensively contaminated with MRSA. In a surgical ward of a London teaching hospital surface, cultures were taken from floors, overbed tables, bed frames, bed raising panels, bedside chairs, door handles, light switches, sink taps, televisions, and remote controls of bays, side rooms, and bathrooms of MRSA patients. Before cleaning, every side room, bay, and bathroom was contaminated with MRSA *(218)*. Additionally 50% of non-MRSA patient bathrooms and 43% of non-MRSA patient bed frames were contaminated with MRSA. After terminal cleaning, 66% of these surfaces remained contaminated. Another study similarly reported a high rate of MRSA contamination among rooms of MRSA patients and through strain typing was able to show that identical or closely related isolates were recovered from the patient and their environment in 70% of cases (217). A recent study by Chang and colleagues compared the degree of environmental contamination from patients who had MRSA identified through clinical cultures to those who had MRSA identified through active surveillance cultures. There were no significant differences in the frequencies of skin and environmental contamination between the groups. Of 24 sets of isolates (patient, skin, and environmental isolate) available for typing, 88% of skin and 79% of environmental isolates were identical to the corresponding patient nares isolate. After multivariate analysis, among patients colonized or infected with MRSA, being bedridden, having a density of 500 or greater CFUs of MRSA in the nares, age >65, and MRSA bacteremia were associated with a higher prevalence of skin and environmental contamination. Recent chlorhexidine bathing and use of antibiotics effective against MRSA were independently associated with lower prevalence of contamination *(222)*.

Even though patient hand carriage is thought to have the greatest impact on the amount of environmental MRSA contamination, other everyday activities such as bed making have been shown to disperse the microorganism within the environment as well if the linens come from an MRSA-colonized or MRSA-infected patient *(223)*.

Transfer of Environmental Contamination to Healthcare Workers and Patients Contamination in the clinical environment is readily transferred to the hands and clothing of healthcare workers who may then become a vector for transmission to patients or other staff. Boyce reported that 65% of nurses who performed patient care activities on patients with MRSA in a wound or in their urine contaminated their uniforms or gowns. Additionally, 42% of personnel who had no direct patient contact but who had touched contaminated surfaces in the patients room contaminated their gloves *(216)*. Another study reported that 17% of contacts between MRSA patients and their healthcare workers resulted in the contamination of the healthcare workers' gloved hands *(224)*. Chang et al. also reported the contamination rate of healthcare workers' gloved hands after touching the skin of an MRSA patient. Overall, 41% of the gloved hands became contaminated and furthermore, there were no significant differences between the proportion of gloved hands contaminated by MRSA patients identified by clinical culture (45%) and those contaminated by MRSA patients identified through active surveillance cultures (38%) *(222)*.

Investigators have also reported on patient acquisition of MRSA when it is present in their environment. Hardy obtained environmental samples for MRSA from the patient rooms in a nine-bed ICU over a 14-month period and correlated these samples with the MRSA isolates recovered from patients receiving care within the unit. Overall, MRSA was present in 188 (21.8%) of 864 environmental samples. Interestingly, there was no correlation between the number of MRSA colonized patients present in the ICU and the number of environmental sites positive for MRSA. When the PFGE profiles of the strains from the patients were compared to those in their immediate environment, they were indistinguishable 35.7% of the time and when they were compared to strains isolated anywhere in the environment, they were indistinguishable 57.1% of the time. Twenty-six patients acquired MRSA in the ICU during the study period and among these patients, 12 acquired a strain indistinguishable from that of another patient in the ICU at the time of acquisition *(225)*. In a multicenter cohort study among six ICUs from six different countries conducted to examine acquisition and crosstransmission of *S. aureus*, 14 patients (4% of the at-risk population) acquired MRSA over the 3-month study period. Preacquisition colonization pressure was significantly associated with MRSA acquisition; additionally, the mean number of beds per nurse was significantly higher for patients who acquired MRSA *(226)*. After spa typing, the authors calculated that crosstransmission possibly accounted for 40% of all *S. aureus* acquisition. Finally, in a 20 month retrospective cohort study, the relative odds of acquiring MRSA among patients admitted to a room in which the prior occupant was MRSA positive compared to patients admitted to other rooms was significantly higher (2.9% vs. 3.9%; $p = .03$). The crude odds ratio of MRSA acquisition was 1.4%, and this excess 1% risk accounted for 5.1% of all ICU MRSA acquisition over the study period and translated into a 1.1% population attributable risk and 1 in 94 exposed room patient stays *(112)*. The authors concluded that even though there was increased risk for acquisition of MRSA among patients admitted to a room previously occupied by an MRSA carrier, this was a minor contributor to the overall transmission of MRSA.

Environmental Culturing and Cleaning Cleaning of the patient care environment is a major component of many recommended strategies to reduce the burden of MRSA (*227*,228,*229,230*). However, cleanliness is difficult to assess and visual inspection does not always correlate with the microbiological risk. There are few modern studies, which have reported that environmental cleaning reduces

the risk of acquiring MRSA in healthcare facilities, and it is worth noting that in today's hospital, patients are generally older, have a greater number of comorbidities, have greater degrees of immunosuppression, and are exposed to far more invasive procedures and medical devices. Additionally, the patient care environments are far more complicated. Thus, patients today are likely at greater risk for acquisition and infection by MRSA from environmental reservoirs (20). Routine sampling of the patient care environment to ensure adequate cleaning has not been generally recommended as a control measure for epidemiologically important microorganisms such as MRSA; however, many experts recommend considering sampling the environment on occasion in high-risk areas of the healthcare facility or during an outbreak when other control measures have not adequately contained spread of the microorganism (20).

Culturing Healthcare Personnel As previously described, the prevalence of MRSA carriage among HCP varies widely (mean: 4.6%, range: 0%–59%) *(132)* and is often transient *(133)*. As seen in other populations of MRSA-colonized persons, colonized HCP are at risk of MRSA infection. Approximately 5% of the MRSA-colonized HCP described in published studies have had evidence or a history of MRSA infection, most commonly of the skin and soft tissues *(132)*. Risk factors that have been associated with MRSA carriage among HCP include many of the factors that have been associated with MRSA carriage in other populations, such as chronic skin diseases and recent antibiotic use. In addition, a number of work-related factors have also been identified, including poor attention to infection control (e.g., poor hand hygiene practices), high work load, close contact with patients, and employment in areas in which there is a high prevalence of MRSA among patients *(132)*. In a recent, single center convenience sample of emergency department, ICU, and prehospital services personnel in an urban hospital, the overall prevalence of MRSA as detected by nasal sampling was 6.6%. Among the various types of HCP included in the study, nurses had the highest rate of MRSA carriage (10% as compared with 3.8%, 3.6%, and 1.9% among physicians, clerical staff, and paramedic/EMT personnel, respectively). The highest rate of MRSA carriage was detected among emergency department personnel (9.6%) *(231)*. A similar study reported that 15% of emergency department personnel (physicians, nurses, and technicians) were carriers of MRSA *(232)*. The emergence of CA-MRSA has resulted in a change in the epidemiology of MRSA carriage among HCP. In recent studies, approximately 33% to 40% of MRSA-colonized HCP were colonized with CA-MRSA *(231,233)*. Whether acquisition of CA-MRSA by these employees occurred within the healthcare setting or the community is not known but the increasing prevalence of CA-MRSA among patients presenting to emergency departments with skin and soft tissue infections may be at least partly responsible for the relatively high rates of MRSA carriage among emergency department personnel reported in recent studies.

Several outbreaks in healthcare facilities have implicated HCP in the initiation or propagation of MRSA transmission. In some cases, transmission was associated with HCP who had active MRSA infections, such as skin infection, sinusitis, or otitis media *(234–236)*. In other cases, the implicated HCP were asymptomatic carriers of MRSA *(237–240)*. In most of these reported outbreaks, cessation of transmission was noted after decolonization therapy or reassignment of the implicated HCP. In addition to the risk of MRSA transmission from HCP to patients, transmission of MRSA from these persons to their household contacts has also been described. In one study, MRSA was transmitted to the household contacts of 4 (40%) of 10 MRSA-colonized hospital employees *(241)*.

Although individual case reports and outbreak investigations have provided useful information regarding the role of HCP in MRSA transmission, the actual frequency of MRSA transmission from these persons to patients has not been established. A recent review of published studies of MRSA colonization and infection among HCP found that 25% of 106 studies reported strong evidence of HCP-to-patient transmission of MRSA and an additional 49% of the studies had some evidence suggesting that transmission had occurred *(132)*. These findings may overestimate the actual contribution of colonized HCP in the transmission of MRSA within the healthcare system. That is because many of the studies included in the review were performed in settings in which there was strong epidemiologic evidence suggesting HCP involvement in MRSA transmission, a scenario that is somewhat uncommon in facilities in which MRSA is endemic. Regardless, the data suggest that HCP play a significant role in the transmission of MRSA within healthcare settings.

Culturing Nonhealthcare Personnel As previously described, 14.5% to 67% of household contacts of persons with HA-MRSA may become asymptomatic carriers of MRSA *(140–143)*. These asymptomatic carriers may serve as reservoirs for re-exposure and thus contribute to failure of attempts to eradicate MRSA carriage in the index patient *(138)*. Screening household contacts for MRSA carriage, with interventions for those identified as carriers, may be considered when attempts to eradicate carriage in an index case are being made or when an initial attempt to eradicate carriage in an index case fails or when relapse occurs.

Healthcare Animals and Pets Just as MRSA has become a well-recognized colonizing and infecting microorganism in humans, it has also been identified as an emerging pathogen among companion animals and among animals who visit healthcare facilities. Several investigators have reported that clonally related MRSA isolates found to be the cause of human infection and persistent colonization, have been recovered from the household pets of such humans *(242–244)*. These reports suggest that household pets may serve as a contributor to the reservoir for MRSA transmission to humans; however, it has not been possible to determine the direction of such transmission. Since many of the recovered MRSA isolates from pets have been identified by genetic typing to be of hospital origin, most would postulate that the animals first became colonized from their human owners and not from a *de novo* emergence of MRSA from a pet's susceptible *S. aureus*. The prevalence of MRSA colonization among house dwelling companion animals has been reported for a number of species including rabbits, birds, and reptiles, but most appropriate for this discussion are data available for dogs and cats. There are little

data regarding MRSA colonization rates among domestic cats; however, reported colonization rates have generally been low (<5%) for dogs *(245,246)*, most often found among those being admitted to a veterinary hospital for clinical infection. Additionally, risks for MRSA colonization among these animals have not been rigorously investigated, but when assessed have included previous exposure to antimicrobials and contact with the human healthcare system (20,*247)*.

Pet therapy and personal pet visitation have become more common in healthcare facilities; thus, it is important to understand the potential risks for patients posed by such animals entering these facilities. With regards to MRSA, one report of the prevalence of MRSA carriage among resident animals of an LTCF found that among 12 animals (1 dog and 11 cats), two (both cats) were found to be colonized with a healthcare strain of MRSA *(248)*. It was not determined if this strain was seen among the residents of that LTCF; thus, the significance of the colonization among the animals is unknown. Another study reported that an MRSA strain responsible for repeated outbreaks in a Dutch nursing home was recovered from a nurse who worked at the facility, from her infant daughter, as well as from her healthy pet dog *(249)*. All were subsequently treated with anti-MRSA antibiotics and all were successfully "decolonized." One recent cross-sectional study of 102 visitation dogs entering participating hospitals in Ontario, Canada, was conducted to assess the prevalence of several zoonotic agents. Fecal, hair-coat brushing, rectal, aural, nasal, oral, and pharyngeal specimens were sent from each dog, and with regards to MRSA, no animals were found to harbor the microorganism. Further epidemiological studies are required to better describe the nature of MRSA infection and colonization in companion animals as well as in animals who routinely visit healthcare facilities. Additionally, no formal guidelines exist regarding if and when to screen companion animals, but logically it is not indicated in most situations. One would consider screening household pets when there is epidemiological evidence of ongoing transmission between the pet and the owner despite implementation of appropriate infection control measures (20). Guidelines do exist regarding animals participating in animal-assisted interventions in healthcare facilities *(250)*. These guidelines do not recommend routine screening of these animals, but focus more on implementing measures to reduce the risk for transmission should MRSA colonization exist. This includes hand hygiene policies, proper grooming of animals prior to their entry into the healthcare facility, limiting the visiting areas of the animals, properly training animal handlers, and ensuring appropriate environmental cleaning after animal visits. Screening for MRSA may be considered in rare situations when a specific animal (or its handler) is suspected of being involved in transmission of the microorganism through epidemiological investigation. If an animal (or its handler) is screened and is found to have MRSA colonization, most would recommend excluding that animal (and handler) from assisted interventions in healthcare until there is evidence that the animal (or handler) is no longer colonized with the microorganism. Decolonization protocols for animals have been utilized and are beyond the scope of this discussion; however, consultation with a veterinarian is advised.

STRATEGIES TO PREVENT AND CONTROL MRSA

Summary of Existing Guidelines and Recommendations

The emergence of MRSA as one of the most common healthcare-associated pathogens has resulted in a recognized need to establish effective programs to prevent transmission of MRSA within healthcare facilities. The extensive amount of research regarding the epidemiology of MRSA transmission and interventions that can disrupt transmission has allowed several governmental, public health, and professional organizations to develop evidence-based policies, guidelines, and recommendations for the prevention of MRSA transmission (194,251,*252,253*) (Infection Prevention Working Party; www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf). In general, the recommendations provided by these groups are similar, but some differences do exist (Table 29-4). In addition to these policies and guidelines, a number of organizations have developed practical recommendations to assist healthcare facilities in their efforts to implement and measure the results of an MRSA prevention program (194,251).

Basic Practices for Prevention of MRSA Transmission

Develop Necessary Infrastructure Needed to Monitor MRSA A basic MRSA monitoring program should have the ability to identify and track all patients from whom MRSA has been isolated in culture or otherwise identified from clinical specimens and, if available, active surveillance testing. Historically, Infection Prevention and Control programs have typically detected MRSA-colonized or MRSA-infected patients by reviewing daily laboratory result reports. Additional methods of detection are now available in some healthcare facilities through the use of electronic databases and surveillance systems. Identified cases are then tracked using a "line list." At a minimum, the line list or the MRSA database should contain the first MRSA isolate, whether from clinical culture or active surveillance, from each patient. Isolates should be classified as either hospital or community onset using standardized definitions, such as those provided earlier (192). In addition to patients identified by the facility as MRSA-infected or MRSA-colonized, patients known to be colonized or infected with MRSA on the basis of testing performed at another healthcare facility can be included in the line list. A facility may choose to include other information in the line list, such as the date of specimen collection, the patient's physical location at the time of collection, and the site from which the specimen was obtained. The MRSA monitoring program should establish a method to obtain administrative data, such as the number of patient days, admissions, or discharges within specified time periods, so that MRSA data from the line list and other sources may be used to periodically generate MRSA incidence or prevalence reports. A plan for routinely sharing this information with key stakeholders should be developed.

The MRSA monitoring program should also have the capacity to ensure that appropriate actions are taken when a patient is newly identified as MRSA-infected or

TABLE 29-4

Major Recommendations of Published Guidelines and Recommendations for Preventing Transmission of MRSA

Recommendation	*SHEA, 2003 (253)*	*Joint Working Party, 2006 (United Kingdom) (252)*	*CDC, 2006 (USA) (*251*)*	*Infection Prevention Working Party, 2007 (The Netherlands)*[a]	*SHEA/IDSA Practice Recommendations, 2008 (*194*)*
System to identify patients with MRSA colonization or infection	Yes	Yes	Yes	Yes	Yes
Education	Yes	ND	Yes	ND	Yes
Hand hygiene	Yes	Yes	Yes	Yes	Yes
Environmental decontamination	Yes	Yes	Yes	Yes	Yes
Contact Precautions	Yes	Yes	Yes	Yes ("strict isolation")	Yes
Masks	Yes	ND	No	Yes	No
Dedicated equipment	Yes	Yes	Yes	Yes	Yes
Antimicrobial stewardship	Yes	Yes	Yes	ND	ND
Active surveillance testing	Yes	Yes	Yes (in some populations and/or settings)	Yes	Yes (in some populations and/or settings)
Decolonization therapy	Yes (in some populations and/or settings)	Yes (in some populations and/or settings)	Yes (in some populations and/or settings)	Yes	Yes (in some populations and/or settings)
Monitor process measures (e.g., hand hygiene compliance, Contact Precautions compliance)	Yes	ND	Yes	ND	Yes

[a]Infection Prevention Working Party. www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf
ND, not discussed

MRSA-colonized. These actions may include education of the patient about MRSA and the infection control measures that will be implemented, institution of appropriate precautions, and completion of any local or state reporting requirements. As more components, such as surveillance for specific types of MRSA infection or active surveillance testing, are added to the MRSA-monitoring program, sufficient resources must be obtained so that other infection prevention and control activities are not compromised.

Conduct an MRSA Risk Assessment As part of an MRSA prevention and control program, an MRSA risk assessment should be conducted (194). The purpose of the risk assessment is to characterize the burden of MRSA within the facility or population of interest. Currently, there are no validated methods of performing an MRSA risk assessment, although a number of metrics have been recommended for use in monitoring multidrug resistant microorganisms, such as MRSA, in healthcare settings (192). Metrics that may be useful components of an initial risk assessment include the proportion of *S. aureus* isolates from the facility or population that are methicillin resistant, the overall incidence of MRSA (i.e., the number of new cases of MRSA colonization and/or infection that occurs within a given period of time), the incidence of one or more specific types of MRSA infection (e.g., MRSA BSI or MRSA SSI), or point prevalence surveys of MRSA colonization or infection. Data from an MRSA active surveillance program allow for a more accurate assessment of the prevalence and incidence of MRSA within a facility; however, a useful risk assessment can be performed even in the absence of such a program. Process measures may also be included in the MRSA risk assessment. Evaluation of current practices and rates of adherence to hand hygiene policies and the use of Contact Precautions, for example, may allow for a better understanding of potential contributors to the transmission of MRSA within the facility. By allowing an assessment of the overall burden of MRSA within the facility, the risk assessment can inform discussions about the allocation of resources for MRSA prevention and control efforts. In addition, information from the risk assessment, such as the identification of specific populations at increased risk, may

help to prioritize the implementation of specific control measures. The MRSA risk assessment should be repeated periodically and compared with prior assessments in order to evaluate the effectiveness of the prevention and control program.

Hand Hygiene Noncompliance with hand hygiene has been described as the most important modifiable cause of HAI (228,*254–256*), and following suit, compliance with CDC or World Health Organization (WHO) Hand Hygiene guidelines are essential for MRSA prevention and control in healthcare facilities. Evidence-based recommendations regarding how to implement effective hand hygiene programs are readily available *(http://www.who.int/patientsafety/events/05/HH_en.pdf; http://www.ihi.org/IHI/Topics/CriticalCare/IntensiveCare/Tools/HowtoGuideImprovingHandHygiene.htm).* Also, in their 2008 Patient Safety Goals, the Joint Commission requires that as a primary means of preventing hospital infections, there must be compliance with WHO or CDC guidelines *(257)*. Despite this, healthcare facilities continue to struggle with maintaining high rates of hand hygiene compliance with most estimates remaining unacceptably low and reported below 50%. The association between hand hygiene compliance and MRSA rates has been well described. Recently, a time series analysis of the impact of use of an alcohol-based hand disinfectant on the incidence of HA-MRSA infection was conducted over a 58-month time period. The use of ABHR was found to have a significant impact on the monthly incidence of HA-MRSA infections ($p < .001$). Specifically, a 1% increase in the volume of ABHR use was associated with a 5.37% decrease in HA-MRSA infections after a lag time of 3 to 7 months *(119)*. Another recent study that utilized a stochastic mathematical model to simulate the outcome associated with hand hygiene noncompliance demonstrated that this noncompliance was associated with increased MRSA acquisition and infection as well as significant attributable hospital costs *(258)*. In a model that simulated 1 million episodes of noncompliant healthcare workers caring for patients of unknown MRSA status, 143 MRSA colonizations resulting in 42 MRSA infections would have occurred at a mean cost per infection of $47,092 and ultimately a mean cost per noncompliant event of $1.98 (95% CI, $0.91–$3.04). Another model that simulated noncompliant healthcare workers caring for an MRSA patient and a patient of unknown MRSA status estimated that 3,340 MRSA colonizations resulting in 980 MRSA infections at a mean cost of $53,598 per infection and ultimately a mean cost per noncompliant event of $52.53 (95% CI, $47.73–$57.32) *(258)*. Most importantly, the authors estimated that for a 200-bed hospital, an annual cost of $1,779,283 is spent on MRSA-related HAI attributable to noncompliance with hand hygiene and that a mere 1% increase in hand hygiene compliance would result in an annual savings of $39,650.

Several recent studies have also described successful programs to increase hand hygiene in healthcare facilities and have attributed reduced rates of HA-MRSA transmission and infection to these improved hand hygiene practices *(117,121,255,259–262)*. Although encouraging, the long-term impact of these interventions is not known, and many employed these increased hand hygiene efforts as part of a multipronged approach to the control of HA-MRSA including Contact Precautions for colonized and infected patients, cohorting or private rooms for colonized and infected patients, antibiotic stewardship, and active surveillance to identify those with MRSA. Of note, a 2-year prospective, controlled, crossover study by Rupp and colleagues of ABHR use in two medical-surgical ICUs concluded that despite a significant increase in hand hygiene compliance (from 37% to 68% in one unit and from 38% to 69% in the other; $p = .02$), there was no substantial change in the device-associated infection rates or in infections due to multidrug resistant pathogens, including MRSA. The rate of MRSA infection ranged from 1.67 to 2.77 per 1,000 patient days *(263)*. The authors stated that the results of their study did not imply that hand hygiene was not important, but that realistic expectations are needed with regards to the effect that hand hygiene alone can have on HAIs (Table 29-5).

Antibiotic Use The relationship between antibiotic use and rates of MRSA has been explored by many. In separate studies, Crossley and Hershow *(264,265)* reported that patients with MRSA infections had a significantly longer hospitalization before infection and were more likely to have received antimicrobial therapy, and Monnet *(266)* has emphasized the importance of a causal, dose–effect association between antibiotic use and MRSA. Additionally, studies that have analyzed the effect of antimicrobial classes separately on MRSA often found that both cephalosporins and fluoroquinolones increased the risk for acquisition and infection from the microorganism *(267,268)*. However, several studies have not found a significant association between MRSA and previous use of antibiotics *(269,270)*. A recent review systematically described the relationship between antibiotic use and MRSA isolation among more than 24,000 adult patients from 76 studies published between 1976 and 2007 (271). The majority of studies were performed in the United States and Europe, but some were from Asia, Brazil, Australia, and Canada. Compared to those who had not taken antibiotics, the risk of acquiring MRSA was increased by 1.8-fold (95% CI, 1.7–1.9; $p < .001$) in patients who had taken antibiotics. The relative risk for single classes of antibiotics was 3.0 (95% CI, 2.5–3.5) for quinolones, 2.9 (95% CI, 2.4–3.5) for glycopeptides, 2.2 (95% CI, 1.7–2.9) for cephalosporins, and 1.9 (95% CI, 1.7–2.2) for other beta-lactams. Distribution of the relative risk of MRSA acquisition in patients previously treated with antibiotic therapy versus nontreated patients, stratified by definition of cases, showed that the combined risk was 1.9 for infected patients (95% CI, 1.8–2; $p = .001$) and 1.6 for colonized subjects (95% CI, 1.5–1.7; $p = .001$) (271).

The effect of antibiotic therapy on the nasal bacterial load of MRSA has also been reported. A prospective study of patients with MRSA infection or colonization found that patients on beta-lactam or fluoroquinolone therapy have an increased incidence of MRSA colonization, have higher nasal bacterial loads, and appear to spread their MRSA into the near patient environment *(272)*. The median nasal MRSA bacterial load increased significantly from 2.78 to 5.30 $\log_{10}$ cfu per swab ($p < .001$) over 21 days during beta-lactam therapy and increased from 0 to 4.30 $\log_{10}$ cfu per swab ($p = .039$) over 14 days during fluoroquinolone therapy. Median bacterial loads were significantly higher for beta-lactam- and fluoroquinolone-treated patients on

TABLE 29-5

Studies Implementing Activities to Increase Hand Hygiene and Impact on MRSA

Study	*Population*	*Intervention*	*Hand Hygiene*	*MRSA*
Pittet *(255)*	Large university teaching hospital in Geneva Switzerland	Hand Hygiene Campaign of educational posters, wide distribution of individual bottles of 0.5% CHG disinfectant, and performance feedback	Compliance increased from 48% to 66% ($p < .001$) Soap and water compliance did not change (30%) CHG disinfectant compliance increased from 13.6% to 37.0% ($p < .001$)	MRSA infections decreased from 16.9% to 9.9% ($p = .04$) HA-MRSA infections decreased from 0.74 to 0.24 episodes per 10,000 patient days
MacDonald *(259)*	Plastic Surgery unit of a 600-bed general hospital in the United Kingdom	Feedback of hand hygiene compliance and MRSA rates, educational posters, and ABHR dispensers installed outside each isolation room	Hand hygiene compliance before patient contact increased from 20% to 47% Hand hygiene compliance after patient contact increased from 42% to 78%	Newly identified patients with HA-MRSA infections decreased from 23 per 1,211 admissions (1.9%) to 11 per 1,261 admissions (0.9%) ($p < .05$)
Harrington *(260)*	350-bed tertiary referral hospital in Australia	Introduced ABHR, posted signs identifying patients with antibiotic resistant organisms, and provided feedback of MRSA surveillance	32% increased use of hand hygiene product from 78.1 L per 1,000 patient days to 102.7 L per 1,000 patient days	Rate of new MRSA patients in ICU decreased from 9.3 to 6.7 per 100 patient admissions ($p = .047$) Hospital-wide MRSA patients decreased from 3.0 to 1.7 per 100 patient admissions ($p < .001$) MRSA BSI decreased from 0.45 to 0.27 per 100 patient admissions ($p = .02$)
Conrad *(117)*	Tertiary-care University Medical Center in Germany	Hand hygiene campaigns focusing on short educational training sessions	Each hand hygiene campaign resulted in a decrease in hospital acquired MRSA	Greater use of ABHR led to a concomitant decrease in the incidence of HA-MRSA (lag time: 2 months; coefficient: –0.001; *T* statistic: –2.33; $p = .23$)
Sakamoto *(121)*	33-bed NICU of a tertiary-care hospital in Tokyo, Japan	Increased placement of ABHR dispensers (one per bed), and short educational training sessions		The amount of ABHR used for one patient per day was significantly associated with MRSA incidence density (lag time: 0 mo; coefficient: –.052; *T* statistic: –2.62; $p = .011$)
Gagne *(261)*	250-bed community hospital in Quebec, Canada	Education of patients and visitors regarding hand hygiene and instructions to cleanse hands twice daily	Hand hygiene compliance not reported	HA-MRSA infections decreased 51% from 10.6 to 5.2 per 1,000 admissions MRSA mortality decreased 71% from 0.7 to 0.2 per 1,000 admissions
Davis (*262)*	Surgical ward in a UK hospital	Red line taped from entrance to ward to ABHR dispenser on wall with instructional posters	Compliance with ABHR increased from 24% to 62.3% ($p < .0001$)	Two cases of MRSA BSI before intervention compared to none after intervention

CHG, chlorhexidine gluconate; ABHR, alcohol-based hand rub; BSI, bloodstream infection.

days 7, 14, and 21 than controls not receiving antibiotics ($p < .05$). These loads then decreased by 2 to 5 $\log_{10}$ cfu per swab 2 weeks after stopping antibiotics. The environment of patients receiving beta-lactam agents (RR, 3.55; 95% CI, 1.30–9.62; $p = .018$) or fluoroquinolones (4.32; 1.52–12.31; $p = .008$) demonstrated more MRSA contamination than the environment around control patients (0.79; 0.67–0.93; $p = .002$) *(272)*.

Researchers have also studied the effect of antibiotic control and compliance with infection control measures on MRSA rates *(273,274)*. One observational, cross-sectional study used linear regression to model these relationships. There was a strong statistical relationship between macrolide use and MRSA prevalence. Also, use of third-generation cephalosporins, all antimicrobial agents, and all antimicrobial agents except glycopeptides was associated with MRSA prevalence. There was strong evidence that infection control policy recommendations, including use of alcohol-based solutions for hand hygiene and placement of MRSA patients in single rooms, were associated with lower MRSA prevalence rates *(273)*. Another study used time series analysis to evaluate the effect of antimicrobial drug use and infection control practices on HA-MRSA incidence over a 5-year time period in a large general teaching hospital in Northern Ireland. Statistically significant positive relationships were observed for the use of multiple antibiotics with various time lags. Temporal variations in HA-MRSA incidence followed temporal variations in fluoroquinolone use with a mean delay of 1 month with on average, an increase (or a decrease) in fluoroquinolone use by 1 defined daily dose (DDD)/100 bed-days resulting 1 month later in an increase (or a decrease) in the incidence of HA-MRSA by 0.005/100 bed-days. Similarly, third-generation cephalosporin use (average delay: 2 months, variation of HA-MRSA incidence: 0.03/100 bed-days), macrolide use (average delay: 4 months, variation of HA-MRSA incidence: 0.002/100 bed-days) and amoxicillin/clavulanic acid use (average delay: 1 month, variation of HA-MRSA incidence: 0.003/100 bed-days) were temporally associated with HA-MRSA incidence. Additionally, increased infection control activity was associated with decreased HA-MRSA incidence and vice versa. Significant relationships were observed for ABHR use, alcohol-impregnated wipe use, and the number of patients actively screened for MRSA with time lags varying from 2 to 4 months *(274)*.

Results of studies reporting only on antibiotic control, mostly of fluoroquinolone and cephalosporin use, and MRSA rates have been mixed. Charbonneau and colleagues conducted a nonrandomized, prospective, controlled interventional "fluoroquinolone-free" study at four large teaching hospitals in northwest France. During the intervention period, fluoroquinolone use was prohibited in one of the four hospitals (unless no alternative was available). Three other university hospitals with similar pre-intervention MRSA rates were used as controls. During the intervention period, the annual rate of fluoroquinolone use decreased from 54 to 5 DDDs per 1,000 patients per day at the study hospital and remained stable in the control hospitals. At the end of the intervention, the rate of MRSA isolation was significantly lower in the study hospital (32.3% compared with 36.8%; OR, 0.82; 95% CI, 0.69–0.99; adjusted for within-hospital correlation; $p = .036$). In a before–after time series analysis, compared with forecasted rates, there was a significant downward trend in observed monthly rates of MRSA isolation at the study hospital at the end of the intervention *(275)*. Another single-center quasiexperimental time series segmented regression study evaluated whether an intervention to limit fluoroquinolone use was associated with a lower rate of HA-MRSA infection at a VA hospital. A physician-directed computerized intervention to limit the use of fluoroquinolones was initiated, and changes in antibiotic use and HA-MRSA infection rates were tracked. After the intervention, fluoroquinolone use decreased by approximately 34% (levofloxacin by approximately 50%). This decreased fluoroquinolone use was offset by increased cephalosporin, piperacillin–tazobactam, and trimethoprim–sulfamethoxazole use. The HA-MRSA infection rate decreased from 1.37 to 0.63 episodes per 1,000 patient days ($p = .02$), but the rate of infection with gram-negative microorganisms increased. In a separate model, the rate of MRSA infection was negatively correlated with the study intervention ($p = .04$) *(276)*. Another study from Thailand assessed the impact of an education and antibiotic-control program on the antibiotic-prescribing practices, antibiotic consumption, antimicrobial resistance, and cost. After the intervention, there was a 24% reduction in the rate of antibiotic prescriptions (640 vs. 400 prescriptions/1,000 admissions; $p < .001$). The incidence of inappropriate antibiotic use also was significantly reduced (42% vs. 20%; $p < .001$), including that of third-generation cephalosporins (31 vs. 18 DDDs/1,000 patient days; $p < .001$) and glycopeptides (3.2 vs. 2.4 DDDs/1,000 patient days; $p = .002$). Rates of use of cefazolin and fluoroquinolones increased. Significant reductions in the incidence of MRSA infections (48% vs. 33.5%; $p < .001$) were observed with costs savings of $32,231 during the study period *(277)*. How long such restrictions in antibiotic usage can be maintained and what is necessary for long-term control of MRSA remains unclear.

Antibiotic cycling as a means of control has also been reported with regards to MRSA control. Cycling is the scheduled rotation of one class of antibiotics with one or more different classes exhibiting comparable spectra of activity. A 2005 review evaluated the efficacy of this type of intervention and reported that due to multiple methodological flaws and a lack of standardization, the results of studies of the efficacy of antibiotic cycling do not permit reliable conclusions regarding efficacy and that further studies are required to resolve this question *(278)*. One study published after this review evaluated the efficacy of empiric cycling of antibiotics active against gram-positive microorganisms in a before–after intervention in a surgical ICU at a large tertiary-care academic hospital. A strategy where the empiric antibiotic of choice for the treatment of gram-positive infections (linezolid or vancomycin) was changed every 3 months. During the 4 years prior to cycling, 105 MRSA ICU infections were acquired (8.8/1,000 patient days). In the 2 years after implementation of cycling, 11 MRSA ICU infections were acquired (1.8/1,000 patient days; $p < .0001$ vs. noncycling period). The percentage of *S. aureus* infections caused by MRSA declined from 67% to 36% *(279)*.

Contact Precautions for MRSA-Colonized or MRSA-Infected Patients Current guidelines and other recommendations for prevention of transmission of MRSA in acute care facilities recommend the use of Contact Precautions for patients colonized or infected with MRSA (194,251,*252*) (Infection Prevention Working Party; *www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf*). These recommendations are based on the large body of evidence (largely discussed earlier in this chapter) that MRSA is primarily transmitted from one person to another by direct or indirect contact.

Components of Contact Precautions include the use of personal protective equipment, physical separation of the patient from other patients, and, when possible, use of dedicated equipment that is not shared with others. The use of a protective gown and gloves is intended to reduce the risk or severity of contamination of a healthcare worker's hands and clothing and thus reduce the risk of transient or persistent carriage of MRSA by the healthcare worker with its associated risk of subsequent transmission to others. The gown and gloves should be donned prior to entering the patient's room and removed prior to leaving the room. In addition to gown and gloves, some guidelines for preventing MRSA transmission in healthcare facilities recommend the use of surgical masks *(253)* (Infection Prevention Working Party; *www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf*). Surgical masks may serve as physical barriers to reduce the risk of inadvertent contact transmission of MRSA to the anterior nares by a healthcare worker's contaminated gloves and may potentially prevent direct deposition of airborne droplets containing *S. aureus* onto the mucous membranes of the anterior nares and oropharynx. Although the anterior nares is the most common site of *S. aureus* carriage in humans, airborne dispersal of *S. aureus* is thought to occur in only a minority of healthy nasal carriers *(280)*. It has been demonstrated, however, that viral upper respiratory infection and respiratory allergies can substantially increase airborne dispersal of *S. aureus* from some nasal carriers *(239,281,282)*. These so-called cloud babies and cloud adults including healthcare workers, have been implicated in outbreaks of *S. aureus* infection in hospital patients *(239,283,284)*. In some experimental studies of "cloud adults," the use of a surgical mask has reduced airborne dispersal of *S. aureus* by up to 75%. In other studies, the use of a surgical mask was not associated with a reduction in the amount of *S. aureus* dispersed into the air. Thus, if masks are not a routine component of the precautions implemented for the care of patients with MRSA, consideration may be given to the use of masks when caring for MRSA patients with upper respiratory tract infections or allergies that may increase the risk for airborne dissemination of the microorganism.

In addition to the use of personal protective equipment by HCP and others who enter the patient's room, Contact Precautions should also include placement of the MRSA-colonized or MRSA-infected patient in a single room, if feasible. In settings in which a sufficient number of single rooms are not available, patients at greatest risk of transmission of MRSA (e.g., patients with uncontrolled drainage from an infected wound, patients with upper respiratory tract infection) should be given priority for placement in a single room. When a single room is not available, cohorting the patient with another patient with MRSA, preferably of the same genotype or similar antibiotic susceptibility profile, is a reasonable alternative. If a patient with MRSA must share a room with another patient(s) who is not MRSA colonized or MRSA infected, the roommate should ideally be selected from among patients at lower risk of MRSA acquisition and/or lower risk of invasive infection or complications from infection if transmission occurs.

A final intervention that can be considered part of Contact Precautions is dedication of noncritical patient care equipment, such as blood pressure cuffs and stethoscopes, for use with the MRSA patient. Limiting use of the equipment to a single patient reduces the risk of transmission of MRSA to other patients through contact with contaminated equipment. It may not be feasible, however, to dedicate some equipment (e.g., portable electrocardiogram machines) for use with an individual patient. When equipment that has been used for a patient on Contact Precautions must be used for other patients, thorough cleaning and appropriate disinfection prior to its next use can reduce the risk of exposure of other patients.

In LTCFs, implementation of Contact Precautions, and some other strategies that are commonly implemented in acute care hospitals, is associated with a number of challenges. In addition to facility-specific challenges, such as a limited number of single rooms, Contact Precautions may have a more pronounced psychosocial impact in the long-term care setting since these facilities serve not only as healthcare facilities but also as their residents' home. In recognition of these challenges, SHEA and the Association of Professionals in Infection Control and Epidemiology (APIC) have issued a guideline that is focused on infection prevention and control in the long-term care setting *(285)*. Because of the previously mentioned concerns, the guideline prioritizes implementation of Contact Precautions in LTCFs for those at greatest risk of transmitting multidrug resistant microorganisms, such as MRSA, to others, including those residents who are dependent upon HCP for their activities of daily living or whose secretions or drainage cannot be adequately contained. The SHEA/APIC publication provides an excellent review of the epidemiology and prevention of HAI in the long-term care setting.

Contact Precautions are often implemented in conjunction with other control measures, making it difficult to evaluate the individual contribution of Contact Precautions to the interruption of MRSA transmission. In addition, the impact of Contact Precautions in the clinical setting may be limited by poor adherence *(286)* and other factors, such as the presence of unrecognized reservoirs of MRSA (i.e., asymptomatic carriers of MRSA) for whom Contact Precautions are not implemented. Despite these complicating factors, there are data that suggest that Contact Precautions are effective in preventing transmission of MRSA. For example, during an MRSA outbreak in a neonatal ICU, MRSA transmission was found to be reduced 16-fold when colonized infants were cared for with the use of Contact Precautions (287). The effectiveness of Contact Precautions was also suggested in a more recent publication describing control of an outbreak of MRSA in a burn unit *(288)*. In that outbreak, because transmission of MRSA continued to occur despite high compliance with the use of

Contact Precautions for patients known to be colonized or infected with MRSA, empiric use of Contact Precautions for all patients was implemented. This was temporally associated with control of the outbreak and subsequent maintenance of a low MRSA incidence rate. This suggests that transmission of MRSA may have been reduced by preventing opportunities for transmission of MRSA from unrecognized MRSA carriers for whom Contact Precautions had previously not been implemented.

MRSA carriage can be quite prolonged persisting for more than a year in many patients *(289–292)*. In studies that have provided long-term follow-up of HA-MRSA-colonized patients, the median time to clearance has ranged from 8.5 to 40 months *(206,293)*. Factors that have been associated with prolonged carriage of MRSA include chronic skin lesions, the presence of foreign bodies (e.g., gastrostomy tubes, transcutaneous vascular access devices), and having more than one colonized body site *(289,290,293,294)*. Because prolonged carriage is common and asymptomatic carriers can serve as reservoirs for transmission of MRSA, Contact Precautions are typically recommended for the duration of hospitalization in which MRSA is detected (251). Similarly, it is recommended that Contact Precautions be implemented when a known MRSA-colonized patient is readmitted to the hospital. Because it is not possible to predict how long an individual patient will remain a carrier of MRSA, the patient's carriage status should be reassessed prior to discontinuing Contact Precautions. Obtaining samples from known sites of prior MRSA carriage and other common sites of carriage may be useful in assessing a patient's current MRSA carriage status. Obtaining negative results on three or more consecutive surveillance tests obtained in the absence of recent antimicrobial therapy is often considered to be sufficient evidence of clearance of MRSA carriage and indication for discontinuation of Contact Precautions (251).

Several studies have reported a variety of unintended, adverse consequences associated with the use of Contact Precautions *(295–298)*. A recent systematic review of the literature identified four main unintended consequences of Contact Precautions: less patient-healthcare worker contact, changes in systems of care resulting in delays and more noninfectious adverse events (including falls and pressure ulcers), increased symptoms of anxiety and depression, and decreased patient satisfaction *(299)*. In addition, some have found that patients on Contact Precautions have substantial knowledge deficits regarding the rationale for and the components of Contact Precautions, suggesting that insufficient education regarding isolation precautions is provided to these patients *(300)*. Although not all studies have found that patient care or patients' perception of their care is deleteriously affected by the implementation of Contact Precautions, it is important to recognize the potential for these unintended consequences of Contact Precautions to occur. These adverse consequences, however, do not necessarily represent unavoidable effects of the use of Contact Precautions but rather adverse effects due to the healthcare system failing to provide the same level of care to patients on Contact Precautions as provided to those who are not on Contact Precautions. This highlights the importance of ensuring that patients on Contact Precautions are given appropriate information and that they receive care that is equivalent to that received by other patients.

Ensure Cleaning and Disinfection of Equipment and Environment As discussed above, MRSA contaminates the patient's environment and patient care equipment, and exposure to this has been associated with acquisition of the microorganism. Thus, cleaning and disinfection protocols for environmental surfaces should be developed and implemented in healthcare facilities and guidelines have outlined such protocols *(215)*. Routine cleaning and disinfection of the patient environment with EPA-registered hospital disinfectants (e.g., quaternary ammonium compounds, sodium hypochlorite, iodophors, and phenolics) used according to manufacturer's directions (including amount of contact time) is recommended, and protocols should address daily cleaning and terminal cleaning, particularly paying attention to high-touch surfaces such as bed rails, overbed tables, bedside commodes, doorknobs, and sink handles (194). The goal of cleaning and disinfection of the patient care environment is to reduce or eradicate the microbial load in order to reduce the risk for transmission of epidemiologically important microorganisms. The effectiveness of environmental cleaning and disinfection depends on the frequency, the competence of the cleaning staff, as well as the type of cleaner or disinfectant *(225)*. With regards to MRSA, a recent prospective study reported the impact of an environmental cleaning program on the presence of MRSA on surfaces in the ICU. The presence of MRSA and VRE on ICU room surfaces during a 6-week baseline period where routine room cleaning consisted of using a hospital grade quaternary ammonium disinfectant applied according to national standards, was compared to that of a 6-month period where a cleaning intervention was implemented. This consisted of applying the disinfectant via immersion of the cleaning cloth into a bucket instead of via pour bottles, environmental staff education, and feedback regarding the effectiveness of cleaning. Qualitative cultures in 37 rooms at baseline revealed that 45% of them had at least one surface contaminated with MRSA or VRE. During the intervention period, cultures from 44 rooms revealed this had dropped to 27%. Multivariate analysis showed a significant association with reduced environmental MRSA and VRE contamination when cultures were used as the unit of analysis and data were clustered by room *(301)*. Other methods of environmental cleaning have also been shown to reduce MRSA in the environment including high-efficiency particulate air filtration, ultraviolet light, and gaseous decontamination using hydrogen peroxide vapor *(214,215,218)*.

Educate Healthcare Providers and Provide Data to Key Stakeholders Recent guidelines recommend that in order to have an effective control program for MRSA, healthcare worker behavior must be monitored and often modified (194,251). This would include activities such as compliance with hand hygiene, Contact Precautions, environmental disinfection, and active surveillance (194). In order to encourage behavior modification, an educational program should be developed and provided to HCP at all levels (194). This should be evidence-based, include a discussion about the local epidemiology of MRSA,

risk factors for acquisition and infection, how MRSA is transmitted, and the impact that MRSA has on patients and the healthcare system as well as measures for prevention and control. Additionally, data regarding the current compliance rates among different types of HCP should be discussed in the context of how it may relate to local rates or success. Because the healthcare system employs individuals at many levels of educational backgrounds, educational programs need to be presented at appropriate levels dependent on the intended audience. What is appropriate for physicians and nurses may not be appropriate for environmental services or laboratory personnel; however, each group has activities within the facility that will impact the ability to control and prevent MRSA.

The healthcare facility is responsible for ensuring proper support of an infection prevention and control program that works to effectively prevent HAI as well as transmission of epidemiologically important microorganism such as MRSA. This includes support to help properly train individuals to provide education to the providers within the facility. Additionally, senior leadership and administration personnel should develop a system of accountability to ensure that HCP and ancillary staff are competent to perform their job responsibilities as well as compliant with infection prevention and control measures.

Educate Patients and Their Families about MRSA Education of the patient and the patient's family about MRSA is also an important measure a healthcare facility should employ. This may serve not only to enhance the patient's knowledge regarding this important microorganism, but also may increase transparency within the facility, and may help alleviate patient fears regarding being placed into isolation (194,*302*). Newton and colleagues *(303)* conducted a small study to assess patients' perceptions of MRSA as well as the understanding of source isolation. When patients were identified as having an MRSA infection, they were placed into Contact Precautions and visited by an infection control nurse who provided the patient with verbal and written information regarding MRSA and source isolation. Nineteen of these patients agreed to participate in a semistructured interview. MRSA was perceived as an infective agent by the majority (15 of 19), many (6 of 19) attributed their acquisition of MRSA to the healthcare facility, and about half (10 of 19) considered their infection serious. The majority of patients (17 of 19) had little knowledge about the duration of their infection and few (4 of 19) understood why they were placed into isolation *(303)*. This highlights the importance of patient education and a recent paper by Noble provided an excellent example of a script for use by a nurse or other provider in order to communicate MRSA education effectively *(304)*. It includes general information about MRSA, colonization versus infection, the hospital's MRSA prevention program, the components of and rationale for Contact Precautions, and the risk of transmission to family and visitors while in the hospital and after discharge. Methods suggested to facilitate this education process include patient education sheets, patient education channels offered on closed circuit television, web site referrals, and videos. Examples of patient education materials appropriate for use within the hospital environment as well as upon patient discharge are available in several medical journals *(305,306)* as well as through online sources (http://www.shea-online.org/about/patientguides.cfm).

Advanced Practices for Preventing MRSA Transmission

Active Surveillance of Patients The rationale for conducting active surveillance testing for MRSA is based on the understanding that individuals colonized with the microorganism represent a large and important reservoir for spread to other patients and that colonized individuals have an increased risk for developing MRSA infection. Thus, the goals of active surveillance are to (a) identify patients colonized with MRSA in the hospital or other healthcare facility (who would otherwise go undetected unless they happened to have an infection) in order to employ Contact Precautions to halt patient to patient spread and/or to (b) identify patients colonized with MRSA in order to employ decolonization techniques to prevent infection. Active surveillance is recommended to be utilized in combination with other properly designed and executed infection prevention interventions including hand hygiene, Contact Precautions, environmental cleaning and disinfection, as well as prudent use of antimicrobials (Fig. 29-2) (194).

Active surveillance has been described for use under endemic as well as epidemic conditions and has been utilized for all patients admitted to a hospital or a healthcare facility (universal surveillance), or for a high-risk subset of patients (targeted surveillance). It is important to note that controversy exists regarding the effectiveness of active surveillance for prevention of MRSA transmission and infection. Much of this controversy stems from the fact that many of the reports describing active surveillance have been conducted at different types of healthcare facilities, under different circumstances, among different patient populations, in combination with different additional measures of control, as well as utilizing different culturing techniques and different measures of analysis. Recently published guidelines recommend to consider active surveillance in a facility where there is direct or indirect evidence of ongoing MRSA transmission despite adequate implementation of and adherence to hand hygiene, Contact Precautions for those known to harbor MRSA, and environmental cleaning and decontamination (194). Examples of ongoing transmission may include an unacceptably high or increasing prevalence or incidence of HA-MRSA infection or colonization or an increasing proportion of HA-*S. aureus* isolates that are resistant to methicillin. Additionally, CLSI recently released a document dedicated to the topic of surveillance for MRSA, which may serve as a guide for laboratorians, clinicians, epidemiologists, as well as healthcare administrators considering this practice of control (20).

A detailed review of active surveillance for MRSA is beyond the scope of this chapter; however, several recent, well-conducted studies regarding the impact of active surveillance deserve mention. Huang and colleagues assessed the effectiveness of four infection control measures; maximal sterile precautions for central line insertion, ABHR use, hand hygiene campaigns, and active surveillance, introduced over the course of 9 years into their 800-bed academic hospital. Active surveillance was targeted to ICU patients, conducted at the time of admission and then

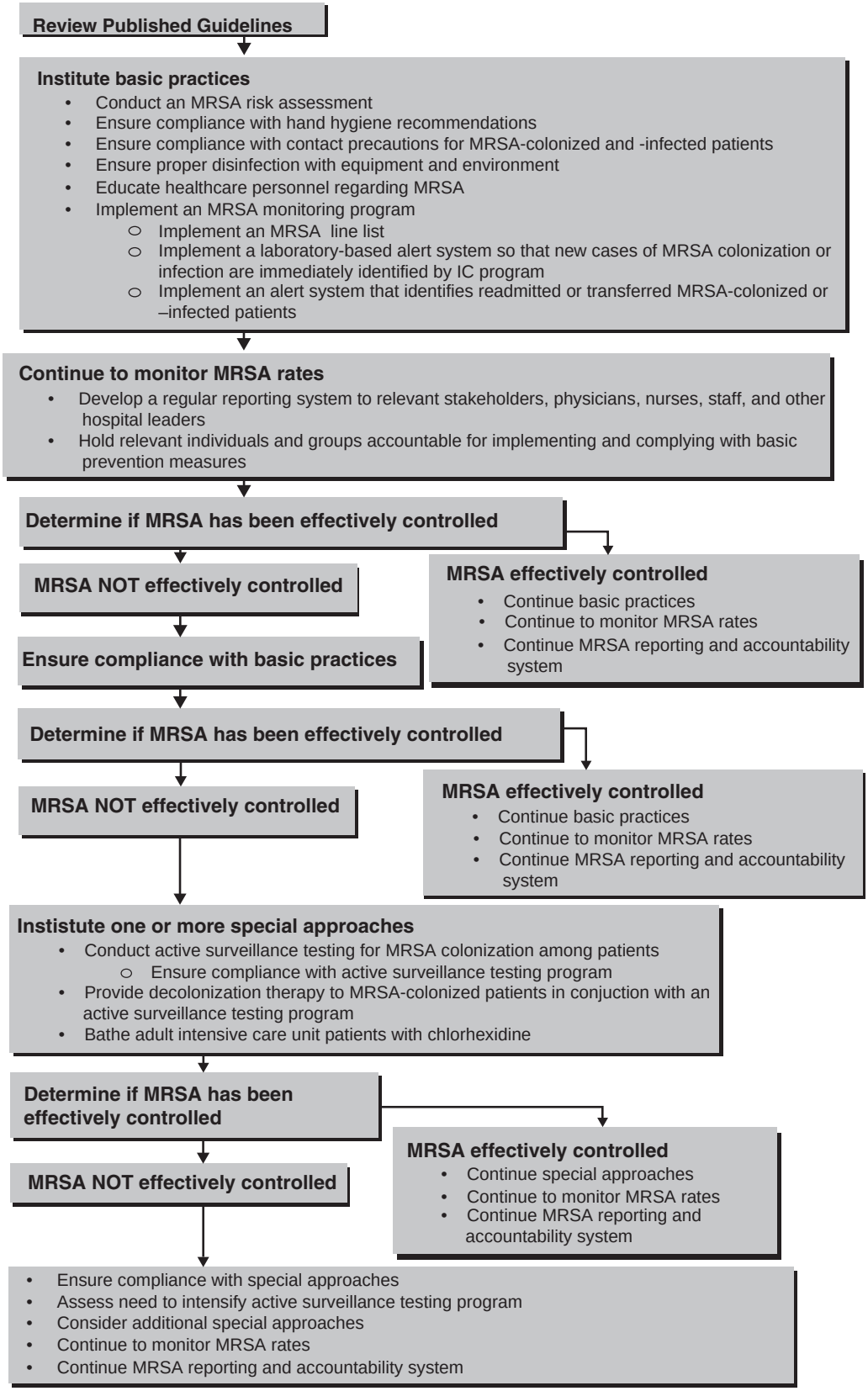

FIGURE 29-2 Approach to control and prevention of MRSA transmission. (Redrawn from Calfee DP, Salgado CD, Classen D, et al. Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals. *Infect Control Hosp Epidemiol* 2008;29(suppl 1):S62–S80, with permission. Copyright © 2008 by The Society for Healthcare Epidemiology of America.)

weekly, and utilized routine culture methodology. MRSA patients were placed into Contact Precautions. Among all the interventions, only active surveillance was associated with a significant decrease in MRSA BSI not only in the ICU but also throughout the general hospital wards. Over the 16 months of active surveillance, MRSA decreased in the ICU by 75% and outside the ICU by 40% ($p = .007$ and .008, respectively). Additionally, there was a significant decrease in MRSA acquisition within the ICU from 43 per 1,000 patients at risk to 23 per 1,000 patients at risk ($p < .001$) *(307)*. In another study from a large Spanish tertiary care hospital, three different infection control measures were assessed with respect to the incidence of MRSA colonization and infection *(308)*. Contact Precautions for all MRSA patients found through clinical cultures were introduced initially followed by identification of high risk MRSA wards where admission and weekly surveillance cultures were conducted among patients and healthcare workers and finally more expanded active surveillance of MRSA patients readmitted as well as those from other healthcare facilities. Routine culture methodology was utilized and of note, MRSA patients received decolonization therapy. Using time series analysis, only after introducing more expanded surveillance was a significant reduction in MRSA achieved. The incidence of colonization or infection due to MRSA and the incidence of BSI due to MRSA decreased by 83% and 80%, respectively. The MRSA rate decreased from 0.56 cases per 1,000 patient days to 0.07 cases per 1,000 patient days, and this has been maintained for more than 8 years *(308)*. Targeted surveillance has also been shown to be effective in a community hospital system. West and colleagues demonstrated that active surveillance on admission and then weekly of ICU patients as well as high risk patients on general wards was associated with significant decreases in MRSA HAIs (BSIs and SSIs) and saved more than 1.5 million dollars over the course of 16 months *(309)*.

However, in a recent cluster-randomized trial, targeted surveillance of ICU patients and use of "expanded barrier precautions" was not effective in reducing the transmission of MRSA. Surveillance was performed in all participating ICUs but the results were only reported to providers in ICUs assigned to the intervention. In these intervention ICUs, MRSA-positive patients were cared for with Contact Precautions and all other patients were cared for with universal gloving until discharge from the unit or until the surveillance culture was reported as negative. The mean ICU-level incidence of MRSA colonization or infection per 1000 patient days at risk did not differ significantly between the intervention and control ICUs (16.0 and 13.5, respectively, p=0.39) and multivariable analysis showed no evidence of an intervention effect overall or a consistent effect over time. The authors concluded that although the intervention was not associated with significant reduction in MRSA, several factors could have contributed to this including, a prolonged turnaround time for reporting of surveillance results (5.2 days), less than optimal compliance with Contact precautions, and a brief intervention period (6 months) (309a).

Robiscek reported the results of an observational study comparing the rates of MRSA clinical disease at baseline, after introducing active surveillance on admission among ICU patients, and then after expanding to universal active surveillance. A rapid PCR method of identification of MRSA was utilized and all MRSA patients were offered decolonization therapy. The baseline MRSA rate was 8.9 per 10,000 patient days, fell only to 7.4 per 10,000 patient days during targeted surveillance of ICU patients, and then decreased significantly to 3.9 per 10,000 patient days after universal surveillance ($p < .001$) (310). Segmented regression found that the aggregate MRSA HAI disease prevalence density significantly decreased 69.6% compared to baseline during the period of universal surveillance ($p = .03$), and this was true for BSI, pneumonias, urinary tract infection (UTI), and SSI. Another recent report described the effect of a comprehensive "MRSA bundle" implemented across all acute care Veterans Affairs hospitals on HA-MRSA infections. The bundle consisted of universal surveillance for MRSA, Contact Precautions for MRSA colonized or infected patients, hand hygiene, and a change in the institutional culture. Compared to baseline, the rates of HA-MRSA infections in ICUs and non-ICUs significantly decreased with implementation of the bundle from 1.64 infections per 1000 patient days to 0.62 per 1000 patient days and from 0.47 per 1000 patient days to 0.26 per 1000 patient days, respectively (P<0.0001 for both) (310a). However, not all have had the same success utilizing universal surveillance. For example, Harbarth and colleagues conducted a prospective cohort study among surgical ward patients in a large Swiss teaching hospital to compare two MRSA control strategies in a crossover design. Rapid screening of all admissions of the nares, perineal area, catheter site, and skin lesions combined with standard infection control measures for MRSA patients was compared to standard infection control measures without surveillance. During the 9-month intervention period, the HA-MRSA infection rate was 1.11 per 1,000 patient days compared to that of 0.91 per 1,000 patient days ($p = .29$). Specifically, there was no decrease in SSI or in the rate of HA-MRSA acquisition. The authors concluded that a universal rapid MRSA admission screening strategy did not decrease HA-MRSA in a surgical department with endemic MRSA but low baseline rates of MRSA infection (311). Additionally, the authors stated that their conclusions were tempered by the fact that 57% of those who developed MRSA infection were known to be MRSA free on admission; thus, there was continued healthcare-associated spread. This could have been the result of poor compliance with standard infection control measures or could have been prevented by the addition of weekly cultures to identify these patients in order to employ control measures. Additionally, there was a delay of almost a day in obtaining the results despite using a rapid identification system, and there was a high colonization pressure incidence over the intervention phase (311).

Some have reported long-term control of HA-MRSA utilizing active surveillance as part of their MRSA prevention and control program *(312,313)*. For example, a large 1,200-bed tertiary care center in the Netherlands has utilized rigorous "search and destroy" approach for many years. This includes active surveillance for high-risk patients, pre-emptive isolation of high-risk patients pending surveillance results, and surveillance of healthcare workers caring for MRSA patients as well as other contacts when feasible. Strict isolation is also employed for any MRSA-positive patient. Over a 5-year period, the average number

of healthcare-associated transmissions was 6.7 per year and five episodes of MRSA bacteremia occurred (0.28 per 100,000 patient days per year) *(312)*. Another study reports the 15-year experience of 38 French hospitals, which have utilized active surveillance of high risk persons (ICU patients and contacts of MRSA patients) with a program of Contact Precautions, hand hygiene, and feedback to key stakeholders since 1993. In acute care facilities, the proportion of MRSA among *S. aureus* significantly decreased from 39.4% in 1993 to 21.6% in 2007 ($p < .001$), and in LTCFs the proportion decreased from 41.0% to 26.6% ($p < .001$). Additionally, in acute care facilities, the incidence of MRSA cases significantly decreased from 1.16 per 1,000 hospital days to 0.57 per 1,000 hospital days ($p = .001$), and this decrease was noted to occur in ICUs, surgical wards, and medical wards. The authors concluded that sustained decreases of MRSA could be obtained at the scale of a large hospital institution with endemic MRSA utilizing an aggressive MRSA control program that included active surveillance *(313)*.

Patient Population(s) to be Screened Selection of the patient population(s) to include in an active surveillance program should be based on the facility's MRSA risk assessment and other facility-specific characteristics (e.g., other infection prevention and control priorities, laboratory resources, information technology support, staffing). Facilities may choose to screen all patients (universal screening), patients with specific risk factors for MRSA carriage, patients admitted to high-risk or high-prevalence locations within the facility, or some combination of these patient populations. There are a number of advantages and disadvantages associated with each of these approaches. Among the screening strategies, universal screening will identify the most MRSA carriers but will also require the greatest amount of laboratory resources. By limiting screening to patients at increased risk of MRSA carriage, screening only those patients with identified risk factors, may optimize laboratory utilization (i.e., may have the fewest negative test results) and may identify a relatively large proportion of the entire population of MRSA-colonized persons *(314)*. Limitations of this approach include potential difficulties identifying which patients meet the screening criteria, especially in the absence of an integrated electronic medical record, and the inability to identify colonized patients who lack the risk factor(s) used in the selection process. Screening patients admitted to high-risk or high-prevalence locations is logistically easier than screening based on patient-specific factors and assessment of adherence to the screening protocol is straightforward. The major limitation of this approach is the inability to identify MRSA carriers admitted to other locations within the facility.

Laboratory Method for Screening As discussed in the earlier section on laboratory detection of MRSA, several methods are currently available for the detection of MRSA in surveillance specimens, including conventional culture-based methods, chromogenic agar-based methods, and molecular techniques. When determining which method of detection will be used in an MRSA active surveillance testing program, a number of factors should be considered. These factors include the test's performance characteristics (e.g., sensitivity and specificity), turnaround time, complexity, and cost as well as the laboratory's capabilities and resources and the volume of specimens to be processed. Culture-based methods have been used in most published descriptions of MRSA active surveillance testing programs. These methods are relatively simple and inexpensive. Results from conventional culture-based techniques, however, are not available for 48 to 72 hours. As compared with conventional culture methods, the recent introduction of chromogenic agars has simplified the laboratory procedure and reduced the turnaround time for culture results. Positive results may be available within 24 hours, and negative results are available within 48 hours.

PCR-based techniques have been demonstrated to be highly sensitive and specific for the detection of MRSA and, because these assays can provide results in as little as 2 hours, have the potential to allow for more rapid detection of MRSA-carriage than is possible with the use of culture-based methods. In clinical practice, however, it may not be practical to process all specimens at the time of receipt by the laboratory. Instead, specimens may be batched and processed during a limited number of runs each day, thus prolonging the turnaround time. Even under these constraints, one study found that when performed only once per day PCR was associated with significantly shorter turnaround times than chromogenic agar for both positive (median: 13.0 vs. 19.5 hours) and negative results (median: 16.5 vs. 42 hours) *(46)*. Reducing the time to a negative test result may be particularly valuable in healthcare facilities in which patients are empirically placed on Contact Precautions pending MRSA testing results. Although PCR-based testing has a number of potential advantages, including high sensitivity and negative predictive values and a rapid turnaround time, the cost of these assays is substantially higher than that of culture-based screening methods. These higher direct laboratory costs may potentially be offset by more effective use of isolation precautions and enhanced prevention of MRSA transmission *(315,316)*, but this has not been observed in all settings *(317)*. The clinical and economic benefits of rapid testing likely vary among populations and settings due to a variety of factors, including the prevalence of MRSA and adherence to infection prevention measures.

Management of Patients with Pending Results When planning an MRSA active surveillance program, a facility must determine how it will manage patients while awaiting the results of the surveillance test. The two major options are implementation of Contact Precautions only for those patients with a positive surveillance test and empiric implementation of Contact Precautions for all screened patients with discontinuation of precautions if the test is negative. The first option is used by the majority of active surveillance programs in the United States. This is likely because it is logistically simpler in many settings, particularly those in which the prevalence of MRSA is low. The major disadvantage of this approach is that it allows opportunities for MRSA transmission during the period between specimen collection and availability of a positive test result. Although this period for potential transmission from unrecognized sources may be minimized by the use of more rapid testing methods *(46)*, such as chromogenic agar or PCR, environmental contamination of the patient's

room has been shown to occur quickly, in many cases prior to the availability of screening test results, even with the use of rapid tests such as PCR *(318)*. Thus, if transmission of MRSA continues in a healthcare facility that is using this approach and another explanation for ongoing transmission cannot be identified, empiric use of Contact Precautions while awaiting the result of surveillance testing could be considered. In fact, empiric use of Contact Precautions has been associated with control of MRSA outbreaks in high prevalence settings *(288)*. The potential benefits of this approach should be considered in the context of the logistic difficulties and resource requirements associated with it. This approach may be logistically quite difficult in facilities or areas of facilities in which single rooms are scarce. In such settings, it may be reasonable to prioritize the available single rooms for those patients with proven infection or colonization with MRSA or other multi-drug resistant microorganisms or with other documented needs for a single room. Similarly, when the number of single rooms is insufficient, patients empirically placed in a single room who are subsequently found to have a negative screening test result will need to be relocated. Such relocations increase the resources needed for room cleaning and may interrupt patient flow in the facility. This approach may be most feasible in facilities or settings (e.g., some ICUs and some newer hospitals) in which a relatively large proportion of patient rooms are single rooms.

Active Surveillance among Healthcare Personnel As described above, testing HCPs for MRSA carriage has been useful in some outbreak investigations, leading to identification and elimination of presumed sources of MRSA transmission. One review of HA-MRSA outbreaks determined that 4.2% of 191 reported outbreaks were attributable to HCPs with MRSA infection and that an additional 1.6% of the outbreaks were attributable to HCPs who were asymptomatic carriers of MRSA *(319)*. The authors concluded that limiting screening to HCPs with evidence of active infection may be a more effective approach to identification of a healthcare worker source than screening all HCPs. A similar review, however, determined that a substantially larger proportion of HA-MRSA outbreaks was attributable to asymptomatic carriage of MRSA by HCPs *(132)*. Current recommendations for the prevention of MRSA transmission in acute-care hospitals from the CDC (251) and other groups (194,*252*) recommend screening HCPs for MRSA colonization if they are epidemiologically linked to new cases of MRSA or in the setting of ongoing transmission of MRSA despite active control measures, regardless of the presence or the absence of signs and symptoms of MRSA infection. In the Netherlands, a country with a very low prevalence of HA-MRSA, screening for MRSA carriage is conducted among HCPs who have had contact with an MRSA colonized or infected patient and those who have been hospitalized in or have worked in a hospital in a foreign country (Infection Prevention Working Party; *www.wip.nl/UK/free_content/Richtlijnen/MRSA%20hospital.pdf*). Routine screening for MRSA among HCPs outside of the outbreak setting, however, has not been included in guidelines and recommendations from countries in which MRSA is endemic within the healthcare system. This is likely due to a lack of strong data indicating that asymptomatic carriers of MRSA play a significant role in MRSA transmission in the endemic setting and a variety of logistic and financial considerations. When screening of HCPs is performed, whether in the outbreak or the endemic setting, specimens should be obtained prior to the beginning of a shift, rather than at the end of a shift, in order to better distinguish between transient and persistent carriage.

Routine Patient Bathing with Chlorhexidine Routine bathing of patients with a chlorhexidine soap has been the focus of recent reports designed to describe the effect of such on acquisition or transmission of MRSA and VRE *(320–322)*, infection rates due to MRSA and VRE *(320,321)*, as well as the incidence of CLABSI due to all microorganisms *(323–326)*. Its use is primarily based on the fact that colonized patients are at risk for developing infection, as well as serve as a reservoir for transmission of microorganisms to other patients via contamination of their surroundings and the hands of HCP. A variety of chlorhexidine products are available for patient bathing and manufacturers' directions should be followed, contact with the eyes and middle ear should be avoided, and the patient should be monitored for adverse skin effects such as fissures, rash, burning sensation, and itching (194). The use of chlorhexidine for routine patient bathing has been primarily studied in the adult ICU population, and primarily for CLABSI prevention *(320,321,323–325)*. For example, routine daily use of 2% chlorhexidine bathing was associated with a decrease in CLABSI in one study among patients of a 22-bed medical ICU by 61% (10.4 BSI per 1,000 patient days among those bathed with soap and water vs. 4.1 BSI per 1,000 patient days among those bathed with chlorhexidine; $p = .01$) *(325)*, and by 87% in another study among patients in a 21-bed medical ICU (5.31 BSI per 1,000 catheter days among those bathed with soap and water vs. 0.69 BSI per 1,000 catheter days among those bathed with chlorhexidine; $p = .006$) *(324)*. Another study among trauma ICU patients found that compared to baseline, when patients did not receive chlorhexidine baths, those bathed with 2% chlorhexidine were significantly less likely to acquire a CLABSI (8.4 vs. 2.1 per 1,000 catheter days; $p = .01$); although there was no difference in the overall rate of VAP between the two time periods, there was a significant reduction in MRSA VAP among patients bathed with chlorhexidine (5.7 vs. 1.6 infections per 1,000 ventilator days; $p = .03$) *(321)*. An additional study using time series analysis to evaluate the use of 2% chlorhexidine baths among patients in a long-term acute care hospital reported that compared to the preintervention period (soap and water baths), by the end of the intervention period (chlorhexidine baths), there was a net reduction of 99% in the CLABSI rate *(326)*.

Data also exist regarding the use of chlorhexidine baths for control of MRSA acquisition and transmission *(320–322,324,326)*; however, in some of these studies, this was not the primary outcome and as such, they were not powered to adequately assess effectiveness *(324,326)*. Climo and colleagues conducted a quasiexperimental multicenter trial where, among other outcomes, the incidence of MRSA colonization and BSI was assessed during a time period where all patients admitted to the participating ICUs received daily bathing with 4% chlorhexidine. The overall rate of MRSA acquisition decreased 32% (5.04 vs. 3.44 cases per 1,000 eligible patient days; $p = .046$), and the

risk of acquiring MRSA was significantly lower for patients bathed with chlorhexidine (p = .024). Furthermore, for patients who were in the ICU longer than 10 days, 4.37% of those bathed with chlorhexidine acquired MRSA compared to 9.93% of those bathed with soap and water (RR, 0.58; 95% CI, 0.351–0.968; p = .02). Time series analysis revealed that by the end of the intervention period there was a 25% decrease in the incidence of MRSA attributable to the use of chlorhexidine bathing. In this study, there was a low rate of MRSA bacteremia over the entire study period that prevented accurate comparisons *(320)*. Similarly, Evans and colleagues reported that during the time period where patients were bathed with 2% chlorhexidine, the rate of MRSA colonization significantly decreased (23.3 vs. 69.3 cases per 1,000 patient days; $p < .001$) and that protection against MRSA colonization was apparent 4 or more days after admission to the ICU. The probability of MRSA colonization was nearly threefold higher in the baseline period compared to the chlorhexidine bathing period (HR, 2.9; 95% CI, 1.4–4.5; p = .02) *(321)*. More often, the use of chlorhexidine baths has been studied as a component of a more comprehensive decolonization protocol, usually with intranasal mupirocin with or without systemic anti-MRSA antibiotic therapy, to eradicate MRSA colonization among patients in healthcare facilities or among patients who are scheduled to have elective surgery to prevent infection. These uses are discussed in the following section.

MRSA Decolonization Therapy for MRSA-Colonized Persons MRSA decolonization therapy has been studied as a means to eradicate, or at least transiently suppress, the MRSA carrier state to assist in prevention of transmission within a healthcare facility or to reduce the risk for MRSA infection among an MRSA-colonized patient. The optimal decolonization regimen has not been determined; however, most of the experience has been with topical administration of intranasal mupirocin with or without chlorhexidine bathing and occasionally with systemic antimicrobials directed toward MRSA.

The effectiveness of topical decolonization therapy on eradication of the carrier state has varied substantially from just 8% to 72.3% depending on the patient population under investigation *(327–329)*. For example, in a randomized, placebo-controlled study designed to evaluate the effectiveness (MRSA free at 30 days) of adding chlorhexidine body washes to nasal mupirocin and chlorhexidine mouth rinse among colonized university hospital and nursing home patients, the effectiveness was only 8% (4 of 48) *(328)*. Multivariate analysis revealed that colonization in the groin, perineum, or at more than one body site was associated with decolonization failure. Robicsek and colleagues reported the success of topical decolonization among colonized patients found through active surveillance in three hospitals in the Chicago area. In a group of 407 patients who were tested for recolonization at the time of a readmission, 47.8% of those who had received any amount of decolonization therapy were still MRSA-colonized compared to 63.2% of those who did not receive any therapy (p = .007) *(327)*. Residence in an LTCF, presence of a pressure ulcer, and high-level mupirocin resistance predicted persistent MRSA colonization. In another study where MRSA colonized patients received topical decolonization therapy and were followed with weekly surveillance cultures, a mean of 72.3% of patients had negative follow-up cultures *(329)*.

The addition of systemic antimicrobials to topical therapy has reported consistently higher decolonization rates ranging from 54% to more than 90% *(330–333)*. A recent prospective cohort study utilizing oral vancomycin and cotrimoxazole along with topical decolonization reported that decolonization was successful in 87% in the intention-to-treat group and in 98% among those in the on-therapy group. Of note, patients could receive repeated courses of therapy as needed if they remained MRSA positive *(331)*. Simor conducted a randomized controlled trial to assess the effectiveness of topical decolonization therapy accompanied by oral rifampin and doxycycline. At the time of 3-month follow-up, 74% who were randomized to therapy remained MRSA negative compared to 32% of those not treated (p = .0001); however, at 8 months only 54% remained MRSA free. Multivariate analysis revealed that mupirocin resistance at baseline was associated with decolonization failure *(333)*.

The use of MRSA decolonization therapy in conjunction with active surveillance has also been reported for prevention of MRSA transmission within a hospital *(322,330,334–337)*. Ridenour and colleagues reported on the use of decolonization therapy (topical only) among patients in a medical/coronary ICU found to be MRSA positive with active surveillance. Incident cases of MRSA colonization or infection decreased by 52% (8.45 vs. 4.05 per 1,000 patient days; p = .048), and no increase in chlorhexidine or mupirocin resistance was found *(334)*. A similar approach was utilized by Gould among ICU patients. By time series analysis, the proportion of patients with MRSA significantly decreased and the authors stated that treatment of 11 patients prevented one clinical case of MRSA *(337)*. Bowler et al. reported on the use of active surveillance and a more complicated decolonization protocol consisting of an initial phase of systemic antibiotics and topical therapy followed by a continuation phase of topical therapy during the first 5 days of the month. After 12 months of utilizing this approach, the prevalence of MRSA colonization in nursing homes decreased from 12% to 4% ($p < .001$), and the incident rate for HA-MRSA infection decreased from 0.64 to 0.32 per 1,000 patient days, ($p < .01$) *(330)*. Another recent prospective study utilizing time series analysis to assess the effectiveness of decolonization therapy and active surveillance on MRSA acquisition of an endemic and an epidemic strain in an ICU population reported an immediate 70% reduction in acquisition of endemic MRSA and an increase in the outbreak MRSA strain. Interestingly though, all of the outbreak strains tested revealed that they had the *qac*A/B gene conferring resistance to chlorhexidine compared to only 5% of the endemic strains *(322)*. Others have reported decreases in HA-MRSA infections with the use of decolonization therapy among neonatal ICU populations *(335)*, and among hospitalized adults *(327)*.

Decolonization therapy has also been used in certain MRSA-colonized patient populations in a direct attempt to reduce the risk of subsequent MRSA infection. This has been successful in preventing CLABSI among hemodialysis patients *(338)* as well as SSI for those undergoing cardiac and orthopedic procedures (*339–342*,343). A recent

Cochrane review found that mupirocin ointment applied to the catheter's exit site at the time of dressing change among colonized hemodialysis patients was protective against CLABSI (RR, 0.17; 95% CI, 0.07–0.43); however, no other decolonization agents such as topical chlorhexidine were studied *(338)*. Jog et al. conducted an observational cohort study of cardiac surgery patients. A rapid PCR test was used preoperatively to screen patients for MRSA colonization and carriers were treated with nasal mupirocin ointment and topical triclosan for 5 days, with single-dose teicoplanin instead of flucloxacillin as perioperative antibiotic prophylaxis. Compared to those who did not receive this decolonization therapy, those who did had a significant reduction in MRSA SSI (RR reduction, 0.77; 95% CI, 0.056–0.95) *(341)*. Rao and colleagues conducted a prospective observational study of patients undergoing elective total joint arthroplasty. Patients were screened preoperatively for *S. aureus* and carriers were decolonized with mupirocin ointment and chlorhexidine baths for 5 days before surgery. Those colonized with MRSA had vancomycin added to their preoperative prophylaxis. All 164 carriers (147 with MSSA and 17 with MRSA) completed the decolonization protocol and had no postoperative *S. aureus* SSIs at 1-year follow-up. In contrast, 1,330 concurrent control patients who did not undergo decolonization had 12 *S. aureus* infections (seven MSSA infections and five MRSA infections) *(342)*.

Widespread use of chlorhexidine to prevent colonization or infection has caused some to speculate on whether there is the potential for the emergence of resistant strains. This has been addressed only rarely in studies evaluating the effectiveness of chlorhexidine use with regards to MRSA control *(322,325)*. Increased minimum bactericidal concentrations (MBCs) to chlorhexidine is thought to occur due to strains with plasmid-borne *qac*A/B genes that code for multidrug efflux pumps. Such strains have two- to fourfold increases in these MBCs, although this seems to be well below the expected concentration of the antiseptic used to treat patients *(322)*. Beasdale reported that among 57 of 64 isolates available for chlorhexidine susceptibility testing, the median chlorhexidine minimum inhibitory concentration was slightly higher for isolates from patients bathed with chlorhexidine compared to those from patients bathed with soap and water (2 vs. 1 μg/mL; $p = .06$), and this was attributed to the less frequent recovery of highly chlorhexidine susceptible, gram-positive bacteria among patients bathed with chlorhexidine for prevention of BSI *(325)*. As mentioned above, Batra and colleagues reported failure to control MRSA using chlorhexidine due to a high prevalence of resistant strains. The authors cautioned the widespread use of chlorhexidine in areas where the prevalence of *qac*A/B is known to be high *(322)*.

As discussed above, decolonization therapy can be successfully utilized as a control measure for MRSA transmission and infection; however, a recent editorial on the subject described the emergence of both low-level mupirocin resistance mediated by a mutation in *ileS* gene and high-level mupirocin resistance mediated by the plasma-encoded *mupA* gene. The author suggested that institutions and investigators considering decolonization protocols with mupirocin should develop a strategy to monitor resistance *(344)*.

SUMMARY

MRSA is a common healthcare-associated pathogen that is capable of causing a variety of infectious disease syndromes often associated with substantial morbidity and mortality. The epidemiology of MRSA in healthcare has recently been further complicated by the emergence of MRSA as a common cause of community-associated infections. Several decades of research, observation, and experience have resulted in the development of a large body of knowledge regarding the pathogenesis, epidemiology, detection, and outcomes of MRSA infection. Similarly, much has been learned about preventing transmission of and infection with MRSA. Reductions in MRSA transmission have been associated with general infection control measures, such as hand hygiene, and with MRSA-specific preventive measures, including active surveillance to detect asymptomatic carriers of MRSA. Prevention of invasive MRSA infection has been associated with the implementation of interventions to prevent device- and procedure-associated infections (e.g., prevention of CLABSI through implementation of the "central line bundle") as well as interventions designed specifically to reduce the risk of MRSA infection among asymptomatic carriers of the microorganism (e.g., MRSA "decolonization" or "suppression" therapy). While numerous studies have demonstrated reductions in the burden of MRSA infection in individual healthcare facilities following the introduction of various preventive measures, data from several Northern European countries and, more recently, the United Kingdom and the United States (345,346) suggest that prevention of MRSA infections is also possible in larger populations. These observations highlight the value of continuing and expanding current efforts to prevent HAI, including those caused by MRSA.

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CHAPTER 30

Coagulase-Negative Staphylococci

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Coagulase-negative staphylococci primarily reside on the healthy human skin and mucosa, and as commensals they are considered to exhibit a low pathogenic potential. Indeed, coagulase-negative staphylococci rarely cause disease in immunocompetent individuals outside of hospitals. In recent decades, however, these bacteria have emerged as common causes of various healthcare-associated infections, preferentially in immunocompromised, long-term hospitalized, and critically ill patients *(1)*. Coagulase-negative staphylococci are regarded as bacteria associated with medical progress as the vast majority of infections are linked to the use of indwelling medical devices such as intravascular and intrathecal catheters systems, pacemaker electrodes as well as urinary tract catheters, and a range of other polymer and metal implants *(2)*. Until the 1970s, coagulase-negative staphylococci did not play a significant role as pathogens. In the National Nosocomial Infections Surveillance (NNIS) report of the Center for Disease Control and Prevention (CDC) in 1979, *Staphylococcus epidermidis*, the predominant coagulase-negative staphylococcal species, accounted for <4% of the pathogens causing healthcare-associated infections *(3)*. From the 1980s onward, this situation changed dramatically and, depending on the site of infection coagulase-negative staphylococci represent now common, if not the most common, healthcare-associated pathogens. Thus, the 2008 annual update of the National Healthcare Safety Network (NHSN) found coagulase-negative staphylococci among the 10 most common pathogens accounting for 84% of all healthcare-associated infections (15% coagulase-negative staphylococci; 15% *Staphylococcus aureus*; 12% *Enterococcus* species; 11% *Candida* species; 10% *Escherichia coli*; 8% *Pseudomonas aeruginosa*; 6% *Klebsiella pneumoniae*; 5% *Enterobacter* species; 3% *Acinetobacter baumannii*; and 2% *Klebsiella oxytoca*) *(4)*. In central-line-associated bloodstream infections (BSI), coagulase-negative staphylococci rank first (*5–7*,8), and second in surgical-site infections *(9)*. Healthcare-associated isolates of coagulase-negative staphylococci exhibit alarmingly high antibiotic resistance rates. In the United States, 89.1% of coagulase-negative staphylococci associated with healthcare-associated infections in intensive care units were found to be methicillin resistant *(10)*. In the United Kingdom and Ireland, methicillin resistance among coagulase-negative staphylococci ranges between 54% and 80% *(11)*, and similar figures have been reported for other countries as well *(12,13)*. As methicillin resistance is strongly associated with resistance against other groups of antibiotics, treatment of coagulase-negative staphylococcal infections is complicated and infections can be expected to increase morbidity and mortality rates and to contribute to the economic burden of healthcare-associated infections in general *(11,14,15)*.

Despite this striking overall impact on healthcare-associated infections, diagnosis of coagulase-negative staphylococcal infections often remains ambiguous and challenging. Due to the ubiquitous nature of coagulase-negative staphylococci as skin and mucosa colonizers, it is often difficult for clinicians to decide whether an isolate represents the causative agent of an infection or a non-specific contamination of a clinical specimen. Also, other than their highly pathogenic cousin *S. aureus*, coagulase-negative staphylococci are often regarded as relatively harmless bacteria and are not taken seriously enough as pathogens in daily routine to prompt immediate action. This may be due to the fact that, in comparison to many other bacterial pathogens, knowledge of coagulase-negative staphylococci virulence-associated factors, pathogenesis, genome evolution, and epidemiology was limited for a very long time. Most recent progress in genome research and molecular epidemiology, however, provided exciting novel insights into the biology of these bacteria. This chapter gives a synopsis on the most common coagulase-negative staphylococcal infections and summarizes, in addition to classical microbiological methods, recent trends in diagnosis, characterization, and typing of coagulase-negative staphylococci. A special emphasis is on the genomics and molecular pathogenesis of coagulase-negative staphylococcal infections as well as current concepts that might help to explain the establishment of these bacteria as successful healthcare-associated pathogens and their spread in hospital settings and beyond.

INFECTIONS CAUSED BY COAGULASE-NEGATIVE STAPHYLOCOCCI

Coagulase-negative staphylococci cause a variety of clinical infections, mainly in the presence of foreign material. Immunocompromised patients, particularly those with

severe neutropenia, are specifically at risk of bacteremia caused by these microorganisms (16). Several studies have demonstrated that colonization of the nasopharynx, rectum, or skin by coagulase-negative staphylococci precedes the development of bacteremia, and chemotherapy-induced breaks of the normal mucosa and skin barriers as well as placement of medical devices often represent typical entry sites for the bacteria *(17)*.

Bloodstream Infection due to Coagulase-Negative Staphylococci

In microbiological surveillance programs, coagulase-negative staphylococci belong together with enterobacteria and *S. aureus* to the most frequently isolated pathogens of BSI and to the leading microorganisms causing healthcare-associated BSI with 30% to 37% of all positive blood cultures being obtained in healthcare settings *(18–21)*. While in outpatients the isolation of coagulase-negative staphylococci is rarely of clinical significance, coagulase-negative staphylococci have emerged in the healthcare-associated setting as a major cause of healthcare-associated bacteremia, especially in immunocompromised patients who have indwelling or implanted medical devices. As coagulase-negative staphylococci and in particular *S. epidermidis* belong to the normal microflora of the skin, they are also often found as contaminants of blood culture specimens. The contamination rate of positive blood cultures is approximately 2% to 3%, and most contaminations are indeed due to coagulase-negative staphylococci *(22)*. To determine whether a coagulase-negative staphylococcal isolate represents a true pathogen causing bacteremia or contamination is often difficult and has also financial impacts. Thus, misdiagnosis of bacteremia due to contaminated blood cultures and subsequent unnecessary treatment of patients were shown to prompt estimated additional costs of $1,000 per patient *(23)*. To date, there is no single criterion with sufficient specificity to predict true bacteremia. Instead, several parameters such as more than one positive blood culture bottle, capability of coagulase-negative staphylococci to produce biofilm, time to positivity of samples, laboratory markers, and clinical signs of septicemia were proposed as predictive markers *(24–27)*. In this regard, fever or other signs of infection in conjunction with detection of coagulase-negative staphylococci in a blood culture sample are of notoriously unreliable discriminating value as presence of the bacteria might both be due to contamination and infection. Therefore, the time to sample positivity and the number of positive blood culture bottles represent better criteria to determine clinically significant BSI. Although some conflicting data have been obtained suggesting that the predictive value of the number of positive blood culture bottles is low *(28)*, most clinical studies use this criterion to discriminate between infection and contamination. Also, the time to positivity of blood culture samples might be helpful in this respect. Thus, it was found that a medium time to positivity of more than 22 hours had a positive predictive value of 87% for diagnosing a contamination *(24)*. This approach is particularly useful in neonates and preterm infants where it is not feasible to obtain more than one blood culture bottle for culturing. In general, blood cultures should be taken using aseptic techniques and, if a central line is present, paired cultures through the central line and through a peripheral vein should be taken (see below). The site and time of sampling should be recorded. Patients with clinical signs of infection, with multiple positive blood cultures and growth within <24 hours have a high likelihood of true bacteremia due to coagulase-negative staphylococci.

Catheter-Related Bloodstream Infections

CRBSI are by far the most common complication in immunocompromised, hospitalized patients. In the United States, each year more than 150 million intravascular devices are purchased and about 80,000 CRBSIs occur. Recently, guidelines for the diagnosis and management of these infections have been revised and published *(29)*. The sources of CRBSI are usually the insertion site, the hub, or both and coagulase-negative staphylococci are the leading pathogens causing CRBSIs *(30)*. Diagnosis of true bacteremia versus contamination in the presence of a central line is extremely difficult and requires a thorough workup. A mathematical model was established to calculate the predictive values for true bacteremia in blood cultures positive for coagulase-negative staphylococci in patients with central venous lines *(26)*. The positive predictive value is 98% if both blood cultures were obtained through a peripheral vein, and 96% if one sample is obtained through the catheter and the other by a vein, and only 50% if both bottles were sampled through the catheter. Thus, in the presence of a central line, it is important to draw blood culture through a peripheral vein (optimal 2×2, but at least 1×2 bottles) in order to diagnose a true BSI. To distinguish between intravascular catheter-associated bacteremia and bacteremia from other sources, the time to positivity from bottles drawn through the catheter and through a peripheral vein can be used. Nowadays, most clinicians take advantage of automated blood cultures systems and use a 2-hour cut-off differential time to positivity of blood cultures drawn from the periphery and the catheter to diagnose CRBSI. The catheter is regarded as the source of positive blood cultures when the catheter blood is positive two or more hours before the peripheral blood *(31)*. If the catheter is removed, a 5-cm segment of the tip should be sent for culture. Growth of more than 15 colony-forming units (CFU) from the catheter tip by semiquantitative (roll plate) culture or growth of more than 10^2 cfu from a catheter by quantitative (sonication) broth culture suggests catheter colonization. When there are positive blood cultures with a 2-hour differential time to positivity between the central line sample and the peripheral blood culture, the diagnosis of CRBSI can be established.

Endocarditis

Coagulase-negative staphylococci are more often found as causative microorganisms in prosthetic valve endocarditis (PVE) than in native valve endocarditis (NVE). However, the number of NVE due to coagulase-negative staphylococci is currently rising, as shown in a recent multicenter study where 8% of NVE were found to be due to these bacteria *(32)*. Patients with a history of healthcare contact are particularly at risk. Coagulase-negative staphylococcal endocarditis on native valves is found in patients receiving long-term hemodialysis or with pacemakers and/or implantable defibrillators, with long-term catheters or with

a history of a recent surgical procedure. Mortality is high (25%), which is probably also associated with the underlying chronic diseases in these patients *(32)*. In PVE, coagulase-negative staphylococci are isolated as causative pathogens in 15% to 40% of the cases. Infections are usually healthcare-associated and occur within 12 months of valve replacement *(33–35)*. Patients present with prolonged symptoms (>1 month) of weakness and low-grade fever. The modified Duke criteria are applied to diagnose infective endocarditis *(36)*, which include, among other factors, positive blood cultures and typical echocardiographic findings.

Infections of Cardiac Devices

Infections of cardiac electrophysiological devices (pacemakers, defibrillators) occur in up to 4% (reviewed in *(37)*) and are in 50% to 60% due to coagulase-negative staphylococci *(38,39)*. Patients present often with pocket site inflammation, mostly within 1 month of insertion but also delays of up to 2 years. Systemic symptoms may be absent. Diagnosis is based on tissue cultures of the pocket, cultures of the devices and multiple blood cultures. In many cases, successful treatment is only possible when the infected device is completely removed and a new device is inserted at a new site.

Sternum Osteomyelitis After Cardiac Surgery

Deep sternal wound infection (DSWI) is an infrequent but severe complication after cardiac surgery with reported incidence rates between 1% and 2% and mortality rates between 10% and 20% *(40–45)*. Clinical manifestations of DSWI are variable. Wound discharge, pain, tenderness, and sternal instability are the most common local signs, whereas fever, sepsis, and elevation of inflammatory parameters are less frequently reported. Most common causative microorganisms are coagulase-negative staphylococci and *S. aureus*, followed by gram-negative bacteria and fungi *(46–48)*. In a recently published study, the causative microorganism of DSWI was identified in 86% of superficial swabs, in 94% of deep swabs, and in 88% of sternal biopsies performed before empirical antibiotic treatment was started. In 60 patients from whom results both of superficial and deep swabs were available, agreement between both specimens was observed in 77% of patients with *S. aureus* and in 68% of those in which coagulase-negative staphylococci were detected *(49)*.

Prosthetic Joint Infections

Prosthetic joint replacement is increasingly used to relieve pain of osteoarthritis and to improve mobility. The average infection rate of joint prosthesis is about 2% (reviewed in (*37*)). Risk factors for infections are previous joint surgery, a perioperative wound complication, and rheumatoid arthritis, the latter being associated with infection rates of nearly 4% *(50)*. The most common microorganisms are coagulase-negative staphylococci, mostly *S. epidermidis* (30%–34%) and *S. aureus* (12%–23%), followed by mixed bacterial infections (10%), streptococci, and other microorganisms *(51)*. Infections associated with prosthetic joint replacement are classified as early (<3 months after surgery), delayed (3–24 months after surgery), or late onset (>24 months after surgery) *(52,53)*. Early- and delayed-onset infections are usually acquired during implantation. In contrast, late-onset infections are mainly due to hematogenous spread of virulent strains such as *S. aureus*, streptococci, or gram-negative bacilli and are rarely caused by coagulase-negative staphylococci. Infections due to coagulase-negative staphylococci can occur early or delayed and manifest with more subtle signs and symptoms. Early infections often present with a history of wound healing complications, purulent secretion at the incision site, and slightly elevated laboratory parameters of inflammation may occur. Delayed infection up to 24 months after surgery may present with persistent joint pain and/or signs of implant loosening, which may be difficult to distinguish from aseptic loosening or with a sinus tract *(51,54,55)*. The diagnosis of prosthetic joint infection is not uniformly established. Detection of coagulase-negative staphylococci may represent either contamination or a true pathogen. Growth of the same microorganism in two or more cultures of synovial fluid or periprosthetic tissues, short time to positivity, a positive Gram stain, the presence of inflammation on histopathological examination, or presence of a sinus tract may help to diagnose an infection *(53)*. Moreover, the recovery of microorganisms can be optimized by sonication of the prosthesis at the time of removal *(56)* and help to verify a true infection (see Chapter 65).

Other Infections

In general, all types of biomaterial or medical devices inserted across the skin or mucous membranes can become colonized and, thereafter, infected by coagulase-negative staphylococci. Thus, meningitis and encephalitis are the most serious complications associated with cerebrospinal fluid shunt implantation *(57–59)*. Other device-related infections that are often caused by coagulase-negative staphylococci and specifically *S. epidermidis* are peritoneal dialysis catheter-associated infections, infections of genitourinary prostheses, and infections of breast implants *(60)*. Since it is not rare nowadays that a patient has, at the same time, for example, a pacemaker, a hip prosthesis, and a vascular graft, it is anticipated that we will observe in the near future a significant increase in device-related coagulase-negative staphylococcal infections.

MICROBIOLOGY

The Genus *Staphylococcus* and Coagulase-Negative Staphylococcal Species

Microorganisms of the genus *Staphylococcus* are nonmotile gram-positive, spheroid bacteria that appear in irregular clusters. They are catalase-positive, lysostaphin susceptible, and have a G + C content ranging between 30% and 40%. Except for a few species that grow exclusively under anaerobic conditions, staphylococci are facultative anaerobes, capable of both aerobic and fermentative metabolism (61). The overall cell wall structure of staphylococci corresponds in general to that of other gram-positive bacteria with some notable characteristics. Thus, in staphylococci, the short peptides that crosslink the heteropolymer glycan chains of the murine, contain glycine residues, which are the targets of the endopeptidase lysostaphin *(62)*. Lysostaphin disrupts the staphylococcal cell wall specifically and the enzyme can therefore be used to distinguish staphylococci from other gram-positive cocci such as micrococci and streptococci (61). The cell wall of many

staphylococcal species is resistant to lysis by lysozyme that normally attacks the β-1,4-glycosidic bonds in the peptidoglycan chains. Lysozyme resistance in staphylococci was found to be based on O-acetylation of the muramic acid of the peptidoglycan, specifically in human pathogens such as *S. aureus*, *S. epidermidis*, and *Staphylococcus lugdunensis (63,64)*. Currently, the genus *Staphylococcus* comprises 47 species and 11 subspecies (Table 30-1). Classification of staphylococci is traditionally based on the production of coagulase, an enzyme that binds fibrinogen and mediates its conversion into fibrin, resulting eventually in blood plasma coagulation. In addition to the major coagulase-positive pathogen *S. aureus*, six other coagulase-positive species have been described that mainly play a role in veterinary medicine (Table 30-1) *(112)*. Among the 41 coagulase-negative species, *S. epidermidis* is the most common one with a broad pathogenic potential causing a wide variety of infections. Other coagulase-negative species involved in human disease are *Staphylococcus haemolyticus*, *Staphylococcus saprophyticus*, *Staphylococcus capitis*, *S. lugdunensis*, *Staphylococcus hominis*, *Staphylococcus warneri*, *and Staphylococcus schleiferii*. The natural reservoir of all staphylococci is the skin and the mucosa of humans and animals where the bacteria mostly reside as harmless and benign commensals. Some species were recovered from processed food or environmental samples and are traditionally used in food industry (e.g., *Staphylococcus carnosus*, *Staphylococcus piscifermentans*). In humans, microbial ecology of staphylococcal species varies individually and also depends on the body site. Thus, *S. aureus* prefers to colonize the anterior nares and the nasopharynx, but only 20% of healthy adults are permanently, and another 60% are transiently colonized by *S. aureus (113)*. In contrast, all human beings are persistently colonized by coagulase-negative staphylococcal species. *S. epidermidis* is the species that occurs in abundance. It colonizes preferentially the upper part of the body, including the nasopharynx, and constitutes over 50% of the resident staphylococci *(114)*. Other coagulase-negative species have adapted to distinct ecological niches and can be recovered from specific parts of the skin (e.g., *S. saprophyticus* from the perineum, *S. capitis* from the scalp, *Staphylococcus auricularis* from the external ear, *S. haemolyticus* and *S. hominis* from the axilla as well as the pubic and the perineal region, respectively).

TABLE 30-1

The Genus *Staphylococcus* and Its Species

Species/Subspecies	*Origin/Reservoir*	*Reference*
Coagulase-positive species		
S. aureus		
S. aureus subsp. *aureus*	Human	*(65)*
S. aureus subsp. *anaerobius*	Human	*(66)*
S. delphini	Dolphins	*(67)*
S. hyicus	Pigs	*(68)*
S. intermedius	Dogs	*(69)*
S. lutrae	Otters	*(70)*
S. pseudintermedius	Various animals (dogs, cats, horses, parrots)	*(71)*
S. schleiferi subsp. *coagulans*	Dogs	*(72)*
Coagulase-negative species		
S. arlettae	Animals	*(73)*
S. auricularis	Human	*(74)*
S. capitis		
S. capitis subsp. *capitis*	Human	*(75)*
S. capitis subsp. *urealyticus*	Human	*(76)*
S. caprae	Goats	*(77,78)*
S. carnosus		*(79)*
S. carnosus subsp. *carnosus*	Food	*(79)*
S. carnosus subsp. *utilis*	Food	*(80)*
S. chromogenes	Cattle	*(81)*
S. cohnii		*(82)*
S. cohnii subsp. *cohnii*	Human	*(82)*
S. cohnii subsp. *urealyticus*		*(83)*
S. condimenti	Food	*(80)*
S. croceolyticus	Human	*(84)*
S. devriesei	Cattle	*(85)*
S. epidermidis	Human	*(86,87)*
S. equorum	Horses	*(73)*
S. equorum subsp. *equorum*	Raw milk cheese	*(73)*
S. equorum subsp. *linens*		*(88)*

(*Continued*)

TABLE 30-1

The Genus *Staphylococcus* and Its Species

Species/Subspecies	*Origin/Reservoir*	*Reference*
S. felis	Cats	*(89)*
S. fleurettii	Goat's milk cheese	*(90)*
S. gallinarum	Poultry	*(78)*
S. haemolyticus	Human	*(82)*
S. hominis		*(75)*
S. hominis subsp. *hominis*	Human	*(75)*
S. hominis subsp. *novobiosepticus*	Human	*(91)*
S. kloosii	Animals	*(73)*
S. leei	Human (gastric mucin)	*(92)*
S. lentus	Goat	*(93)*
S. lugdunensis	Human	*(94)*
S. massiliensis	Human	*(95)*
S. microti	Voles	*(96)*
S. muscae	Flies	*(97)*
S. nepalensis	Goats	*(98)*
S. pasteuri	Human, animal, food	*(99)*
S. pettenkoferi	Human	*(100)*
S. piscifermentans	Fermented fish	*(101)*
S. pseudolugdunensis	Human	*(102)*
S. rostri	Pigs	*(103)*
S. saccharolyticus	Human	*(104)*
S. saprophyticus		*(105)*
S. saprophyticus subsp. *bovis*	Cattle	*(106)*
S. saprophyticus subsp. *saprophyticus*	Human	*(105)*
S. schleiferi		*(94)*
S. schleiferi subsp. *schleiferi*	Human	*(72)*
		(94)
S. sciuri		*(93)*
S. sciuri subsp. *carnaticus*	Cattle	*(107)*
S. sciuri subsp. *rodentium*	Rodents	*(107)*
S. sciuri subsp. *sciuri*	Squirrels	*(93)*
S. simiae	Monkeys	*(108)*
S. simulans	Human	*(75)*
S. simulans biovar staphylolyticus		*(62)*
S. stepanovicii	Small wild mammals	*(109)*
S. succinus	Amber	*(110)*
S. succinus subsp. *casei*	Food	*(88)*
S. succinus subsp. *succinus*		*(110)*
S. vitulinus	Food	*(111)*
S. warneri	Human	*(82)*
S. xylosus	Human	*(82)*

Species Identification of Coagulase-Negative Staphylococci

In the early days of microbiological diagnostics all non-*S. aureus* staphylococci were referred to as *Staphylococcus albus*. Later, these isolates were differentiated into *S. epidermidis* and *S. saprophyticus*, a diagnosis that was mainly based on the novobiocin resistance of the latter. All other coagulase-negative species were subsumed as *S. epidermidis*, as the diversity of the genus was largely unknown at that time. Only upon introduction of phenotypic typing schemes in the late 1960s and early 1970s, the situation changed and a large number of novel species were identified in the following years *(75,82)*. However, coagulase-negative staphylococcus species definition was still reserved to specialized laboratories and was rarely performed in routine diagnostics. Nowadays, staphylococcal species determination is based on combinations of various phenotypic and genotypic tests that are widely available to most laboratories. However, depending on the clinical situation, an exact species determination is not always performed. A coagulase-negative species is only reported as such when the appropriate tests have been performed. All other isolates are referred to as "coagulase-negative staphylococci." Species identification in the routine laboratory

TABLE 30-2

Genotypic Methods for Species Identification of Coagulase-Negative Staphylococcal Species

	Target(s)	*Reference*
PCR-based methods		
Amplified-fragment length polymorphism analysis (AFLP)	Whole genome; specific amplification of restriction fragments	*(119,120)*
Ribotyping	16S, 5S, 23S rRNA loci and flanking DNA	*(121)*
tDNA-ILP analysis	tRNA intergenic spacer DNA	*(122–124)*
DNA sequencing of housekeeping genes and loci		
Ribosomal RNA loci	16S rRNA locus	*(122)*
Heat-shock protein 60	*cpn60*	*(125)*
Heat-shock protein 40	*dnaJ*	*(126)*
Superoxide dismutase	*soda*	*(127–129)*
Elongation factor Tu	*Tuf*	*(115)*
β-Subunit of RNA polymerase	*rpoB*	*(130,131)*

initiates with a variety of phenotypic tests, first of all to differentiate between coagulase-negative staphylococci and *S. aureus*. Slide-agglutination tests are performed to detect *S. aureus*–specific clumping factor, and other cell wall–associated proteins of *S. aureus*. As slide agglutination occasionally provides ambiguous results, the classical coagulase test mentioned above may be performed as well. Putative coagulase-negative staphylococcal species are then further examined for their colony morphology, growth requirements, oxidative and fermentative utilization of carbohydrates, novobiocin susceptibility, and various enzymatic activities (e.g., nitrate reductase, alkaline phosphatase, urease, ornithine decarboxylase, arginine dehydrogenase, etc.) (61). A variety of commercial test kits such as the API 20 Staph and API ID32 Staph systems (bioMerieux), the Staph-Zym (Rosco) or the Vitek system (bioMerieux) are available that combine detection of most of these phenotypic properties and allow for a rapid and convenient identification in the routine diagnostic laboratory. However, phenotypic tests have an inherent weakness as they rely on the expression of the phenotypic characteristic in question, and in coagulase-negative staphylococci these properties may vary within isolates belonging to the same species (115,*116,117*). Thus, DNA-based genotyping methods become increasingly important for an expression-independent species identification of coagulase-negative staphylococci *(118)*. These methods target highly conserved species-specific DNA loci and genes that are PCR-amplified and subjected to either DNA-fragment pattern comparison or DNA sequencing. PCR-based approaches include ribotyping, amplified-fragment-length-polymorphism (AFLP), and tRNA-locus-interspacer-length-polymorphism (tDNA-ILP) analyses (Table 30-2). DNA sequencing of amplified 16S rRNA DNA loci is the most common method for species identification across many bacterial genera *(122)*. Due to the close relatedness of some coagulase-negative staphylococcal species, the method may not have, in all cases, sufficient discriminatory power *(126)*. Therefore, DNA sequencing of a range of housekeeping genes has been implemented to complement 16S rRNA locus analysis (see Table 30-2 for details and references). In general, genotyping methods are considered to be superior to mere phenotyping for coagulase-negative *Staphylococcus* species definition. With the increasing availability and cost effectiveness of molecular techniques in diagnostic laboratories, accurate species identification of coagulase-negative staphylococci can be anticipated to become a routine procedure. This most welcome development in microbiological diagnostics will surely shed more light on the association of specific coagulase-negative staphylococcal species with distinct infection processes.

Antibiotic Resistance among Coagulase-Negative Staphylococci

Coagulase-negative staphylococcal isolates recovered from hospital-acquired infections are notoriously antibiotic resistant, and in many medical facilities multiresistance rates exceed those of *S. aureus*. Figure 30-1 exemplifies the steady increase of multiresistance rates among coagulase-negative staphylococci in Europe in the period from 1990 to 2007, and similar numbers have been reported from other countries worldwide *(10–12,132)*. The classical antistaphylococcal β-lactam antibiotic penicillin G, which inhibits cell wall synthesis by binding to penicillin-binding proteins, is practically no longer suitable to treat staphylococcal infections as approximately 90% of all isolates are nonsusceptible to the antibiotic. Penicillin G resistance is caused by enzymatic destruction of the antibiotic through a staphylococcal β-lactamase that is mostly plasmid encoded and now widespread among staphylococci. But resistance rates toward alternative antibiotics such as methicillin/oxacillin, gentamicin, macrolides, and fluoroquinolones are also alarmingly high (Fig. 30-1). The molecular and genetic basis of resistance against some of these compounds is briefly discussed here.

Methicillin Resistance Methicillin and oxacillin are β-lactam antibiotics that withstand the action of staphylococcal β-lactamases. They were introduced into clinical practice in the early 1960s to overcome β-lactamase-producing *Staphylococcus* strains. However, methicillin/oxacillin

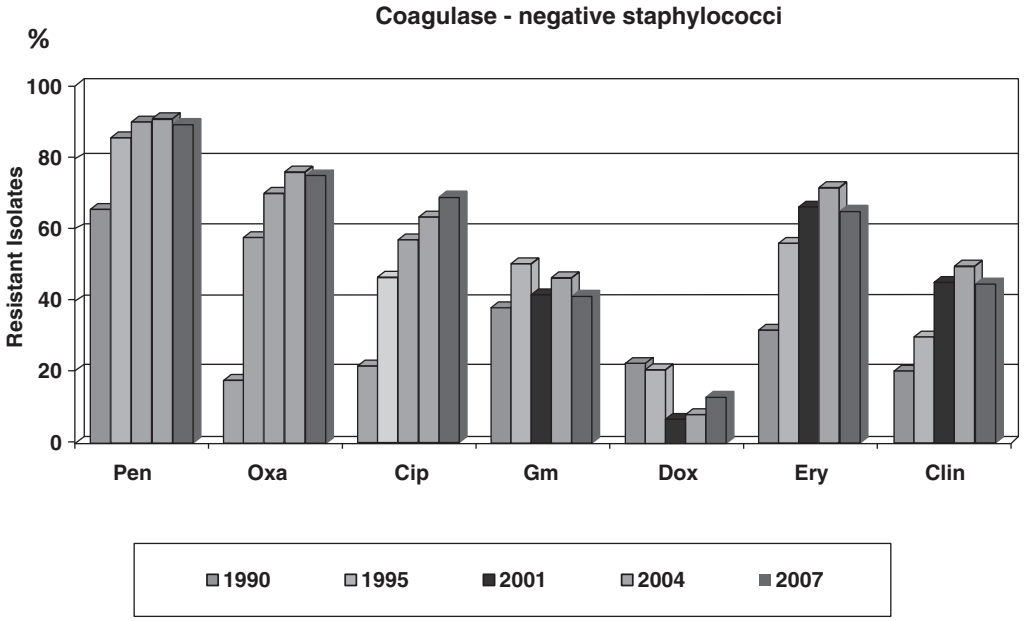

FIGURE 30-1 Antibiotic resistance development among healthcare-associated coagulase-negative staphylococci in Central Europe from 1990 to 2007. Oxa, oxacillin/methicillin; Cip, ciprofloxacin; Gm, gentamicin; Dox, doxycycline; Ery, erythromycin; Clin, clindamycin. (Data obtained from Antibiotic resistance situation among clinically relevant pathogens in Germany and Central Europe. Multicenter study report of the working group 'Susceptibility testing & resistance' of the Paul-Ehrlich-Society for Chemotherapy for the year 2007. [database on the Internet] 2009. Available at *http://www.p-e-g.org/ag_resistenz/main.htm.)*.

resistance emerged very soon, and resistance rates are nowadays as high as 70% to 90% among coagulase-negative staphylococci. Methicillin resistance is mediated by the *mecA* gene complex that is located on a unique molecular vector called the staphylococcal chromosome cassette (SCC*mec*) (133). *mecA* encodes the additional low-affinity penicillin-binding protein PBP2a that enables cell wall synthesis in the presence of β-lactam antibiotics. SCCmec cassettes represent large chromosomal DNA fragments that may harbor, in addition to *mecA*, a great variety of accessory genes, for example restriction modification systems, metabolic genes, integrated plasmids, transposons, insertion sequence (IS) elements, and many more. A characteristic feature of SCCmec cassettes is the presence of recombinase genes that confer mobility and mediate the site-specific integration of the elements into a highly conserved locus of the *Staphylococcus* chromosome (i.e., *orfX*). SCC*mecs* have an independent evolutionary history and eight major SCC*mec* types have been described to date (133,*134*). They are considered to be transferred into *S. aureus* from a coagulase-negative species *(135,136)*. However, the evolutionary origin of SSC*mecs*, the mechanism of SCC*mec* acquisition, and the factors that favor or limit their spread are still poorly understood. Interestingly, SCC cassettes cannot only carry *mecA* and mediate methicillin resistance. A number of SCCs has been identified that are devoid of *mecA*, but carry other genes instead *(135,137)*. Therefore, SCCs are regarded as effective vectors to spread useful genes among staphylococci *(138)*.

Aminoglycoside Resistance Aminoglycoside antibiotics inhibit protein synthesis by irreversible binding to the bacterial small ribosomal subunit (i.e., the 16S rRNA). Aminoglycoside resistance among coagulase-negative staphylococci is common (40%) and is mostly due to enzymatic inactivation of the antibiotic by acetyltransferases, adenylyltransferases, and phosphotransferases *(139)*. Table 30-3 lists the genes and enzymes that mediate aminoglycoside resistance in staphylococci. These determinants are often located on mobile genetic elements such as plasmids and transposons. The most widespread mechanism is resistance through the bifunctional phosphotransferase-acetyltransferase enzyme AAC(6)-APH(2) that confers resistance to a broad range of aminoglycoside compounds (Table 30-3). The corresponding *aacA-aphD* gene is located on composite transposon Tn*4001* that harbors two IS*256* copies at its ends. In *S. epidermidis*, Tn*4001* and IS*256* have been shown to be associated with biofilm formation in isolates obtained from device-related healthcare-associated infections *(141)*.

Macrolide-Lincosamide-Streptogramin Resistance Resistance toward the lincosamide clindamycin and the macrolide erythromycin among coagulase-negative staphylococci ranges between 20% and 70% and may vary by region. Although being structurally diverse, macrolide, lincosamide, and group B streptogramin antibiotics share overlapping binding sites on the large subunit of the bacterial ribosome, and are therefore often considered together. In addition to efflux pumps, inactivating enzymes, and point mutations, which are not discussed here, resistance against macrolides, lincosamides, and group B streptogramins is mainly mediated by rRNA methylases that modify the binding sites in the 23S rRNA molecule. In staphylococci, rRNA methylases are encoded by the *ermA*, *ermB*, *ermC*, *ermF*, and *ermQ* genes, most of them being located on plasmids and transposons *(142,143)*. The so called MLS_B cross-resistance

TABLE 30-3

Aminoglycoside Resistance Genes in Staphylococci (140)

Enzyme	*Gene*	*Localization (Plasmid/ Chromosome/Transposon)*	*Resistance Profile*
Adenylyltransferases			
ANT(4′)-I	*ant(4′)-I*	Chromosome	Tobramycin, amikacin
ANT(9)-I	*aad(9)*, *spc*	Tn*554*	Spectinomycin
Phosphotransferases			
APH(3′)-III	*aph(3′)-IIIa*	pAT4	Gentamicin, kanamycin, neomycin, amikacin
Bifunctional enzymes			
AAC(6′)-APH(2″)	*aacA-aphD*	Tn*4001*	Gentamicin, tobramycin, amikacin, netilmicin, kanamycin

phenotype depends on the expression status of the respective *erm* genes. In staphylococci, *ermA* and *ermC* can be expressed either constitutively or inducibly *(144,145)*. Constitutive expression results in cross-resistance against all three antibiotic classes. In contrast, strains with inducible *erm* expression display *in vitro* resistance to 14- and 15-membered ring macrolides, which also represent inducer molecules, while retaining susceptibility toward clindamycin and group B streptogramins. Although clindamycin is not able to induce *ermA* or *ermC* expression directly, exposure of *erm*-inducible staphylococcal isolates to clindamycin may result in complete MLS_B cross resistance both *in vitro* and *in vivo*. This phenomenon is attributed to the selection of preexisting constitutive *erm* mutants *(144)*. As clindamycin is an alternative drug for the treatment of some staphylococcal infections, detection of the inducible MLS_B resistance phenotype is of clinical relevance and should be performed when required by the D-test (Fig. 30-2) *(146)*.

Glycopeptide Resistance The glycopeptide antibiotics teicoplanin and vancomycin inhibit cell wall synthesis of gram-positive bacteria by interfering with the terminal D-alanine-D-alanine residues in the interpeptide side chains of the peptidoglycan. With the rise of multiresistance, glycopeptides gained significant importance in the treatment of infections due to gram-positive cocci in the late 1980s and 1990s. In enterococci, transmissible high-level glycopeptide resistance is a matter of concern in healthcare-associated isolates, and the resistance mechanism has been elucidated in molecular detail (*147*,148). Resistance in enterococci is mainly based on the modification of the glycopeptide binding site by replacement of one of the terminal D-alanine residue in the interpeptide side chain by D-lactate. The enzymes and regulators required for that process are transposon and plasmid encoded. Although being transferable from enterococci into staphylococci, high-level glycopeptide resistance through this mechanism is still rare among staphylococci *(149–152)*. However, some staphylococcal species exhibit an intrinsically diminished susceptibility toward glycopeptides, and in *S. aureus* and coagulase-negative staphylococci distinct subpopulations can develop intermediate resistance upon exposure to the antibiotics *(153–155)*. These intermediate or heterogeneous resistance phenotypes differ from the resistance mechanism described above for enterococci and are mainly attributed to an altered cell wall synthesis turnover and thickening of the peptidoglycan *(156,157)*. Glycopeptide resistance in coagulase-negative staphylococci was first reported in 1986 in *S. haemolyticus (158)*. *S. haemolyticus* displays often less susceptibility toward teicoplanin, while vancomycin is still effective. Glycopeptide resistance

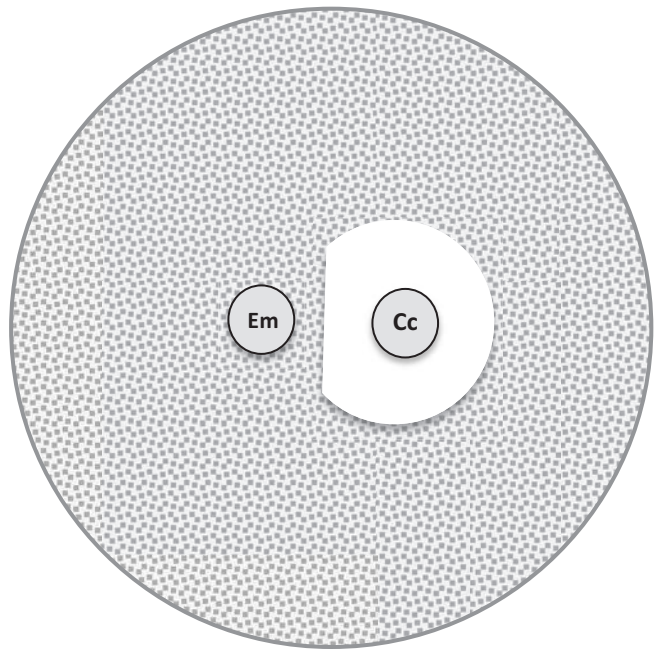

FIGURE 30-2 Scheme illustrating a positive D-test for detecting inducible MLS_B resistance in staphylococci. Erythromycin- and clindamycin-containing disks are placed onto an agar plate on which a staphylococcal strain was spread and grown overnight. Lack of an inhibition zone around the erythromycin disk indicates erythromycin resistance of the isolate. In case of clindamycin susceptibility, an O-shaped inhibition zone would be present around the clindamycin disk. However, the zone is blunted on the side facing the erythromycin disk where the diffusion zones of the two antibiotics meet. The typical D-shaped inhibition zone is due to the induction of clindamycin resistance by erythromycin in the colonies growing in this region. (Modified from Woods CR. Macrolide-inducible resistance to clindamycin and the D-test. *Pediatr Infect Dis J* 2009;28(12):1115–1118, with permission.)

has been reported for a number of other coagulase-negative staphylococcal species as well (e.g., *S. epidermidis*, *S. warneri*), and it is therefore necessary to perform careful antibiotic resistance testing to avoid treatment failure *(153,155,159,160)*.

TYPING OF COAGULASE-NEGATIVE STAPHYLOCOCCI

Typing of infectious agents aims at the elucidation of clonal relationships between single isolates of a species. It plays a major role in the detection of reservoirs of disease-associated bacteria and their transmission routes. Typing is therefore an indispensable tool in infection surveillance and outbreak control. In coagulase-negative staphylococci, due to the ubiquitous nature of the bacteria as commensals, typing is specifically important in order to distinguish between specimen contamination and true infection as well as for the recognition of outbreak situations. Repeated isolation of one and the same strain from various clinical samples or from different patients within a hospital unit makes it more likely that the isolate in question represents indeed the cause of an individual infection or an outbreak, respectively. Typing methods comprised in the past mainly classical microbiology approaches such as the comparison of antibiotic resistance patterns, the analysis of enzymes and metabolic properties as well as phage typing. However, in coagulase-negative staphylococci, these approaches proved to be unreliable and of insufficient discriminatory power. They were therefore largely replaced by genome-based molecular typing methods, which are briefly described here.

DNA Fingerprinting by Pulsed-Field Gel Electrophoresis

Pulsed-field gel electrophoresis (PFGE) is based on the comparison of DNA restriction fragment length polymorphism (RFLP) patterns of microorganisms upon separation in an agarose gel. For PFGE, the bacterial genome is fractionated into large DNA fragments through digestion by rarely cutting restriction enzymes, which is in contrast to classical RFLP comparisons where a high number of small DNA fragments are generated. In PFGE, the resulting large DNA molecules (usually 10–20) are separated in an agarose gel electrophoresis unit that allows for the separation of high-molecular weight DNA fragments by applying an alternating electric field (Fig. 30-3). PFGE has been established for a great variety of bacterial pathogens, including *S. aureus* and coagulase-negative staphylococci *(161,162)*. The method has an excellent discriminatory power and has been proven to be highly reproducible *(163)*. Using appropriate gel visualization and evaluation software, PFGE can also be employed to generate phylogenetic trees and to establish the relatedness of different strains *(164)*. A disadvantage

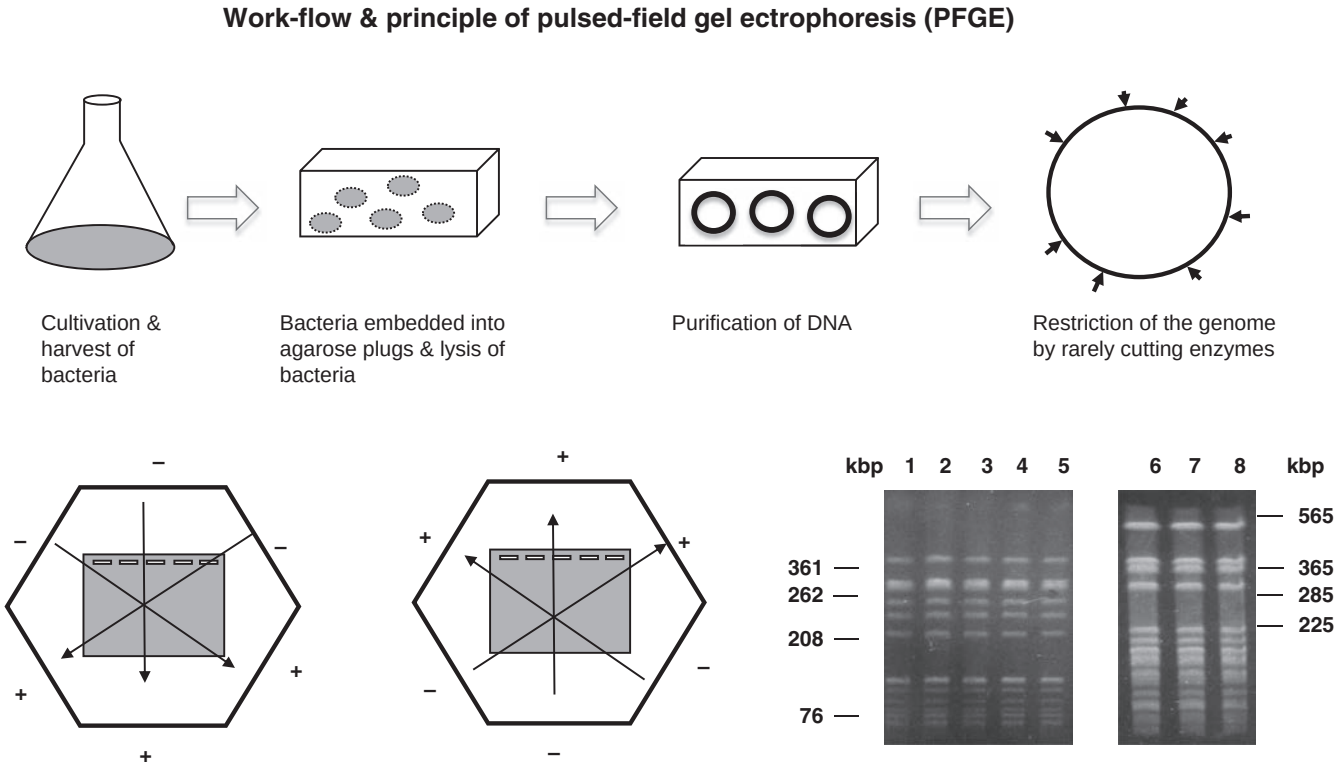

FIGURE 30-3 Principle and workflow of PFGE. Bacteria are grown, harvested, and subsequently embedded into agarose plugs. To mechanically stabilize the genomic DNA, the bacteria are lysed *in situ* within the plugs. The DNA is purified and restricted using rarely cutting restriction enzymes that provide 10 to 20 DNA fragments of a relatively large size (15–500 kbp). The agarose plugs are placed into an agarose gel and the DNA fragments are separated in a pulsed-field apparatus by applying an alternating (pulsed) electric field. Results can be visualized by ethidium bromide staining of the DNA under UV light.

of the approach is that it is technically demanding and relatively time consuming. Moreover, as with all gel-based visual typing methods, data storage and comparability over time and between laboratories is difficult. Although still being the gold standard for local outbreak control and surveillance, PFGE is therefore increasingly complemented or replaced by nucleotide sequence–based methods that generate more portable data formats.

Multilocus Sequence Typing

Multilocus Sequence Typing (MLST) analyzes nucleotide sequence variations in a set of housekeeping genes (usually seven) and identifies strains by their unique allelic profiles (165). For this purpose, the housekeeping genes are PCR-amplified and subjected to nucleotide sequencing. Sequences that differ at least in one nucleotide from a reference sequence are regarded as an allele that is numbered. Most importantly, identical alleles get identical numbers resulting in an unambiguous assignment of a nucleotide sequence. Applying the procedure to all seven housekeeping genes provides an allelic profile as a numeric code, which can be compared to that of other isolates. Allelic profiles are numbered as well and assigned as sequence types (ST). Allele definition does not consider the number of nucleotide exchanges, and no weighting is performed of a single nucleotide difference that arose from a point mutation or multiple sequence variations that might have been generated by a single recombination event or through the accumulation of multiple point mutations. In fact, the relatedness of strains is determined by the pairwise comparison of allelic profiles using the BURST (Based Upon Related Sequence Type) or eBURST algorithms *(166)*. Allelic profiles being very similar and differing in a maximum of two loci are likely to be derived from a common ancestor and displayed in a dendrogram. The ST exhibiting the highest number of single locus variants (SLVs) within a dataset is defined as the common ancestor and placed into the center of the dendrogram, while SLVs and DLVs (double locus variants) appear in a second and third circle or line, respectively, emanating from the center (Fig. 30-4). Related STs displayed in this way are called a clonal complex (CC), which is often named according to its common ancestor. MLST has proven to exhibit a high discriminatory power and is, facilitated by the recent technical progress in high-throughput sequencing, widely used for strain typing. The data are portable and primers, protocols, allele sequences and profiles held in publicly approachable databases (e.g., www.mlst.net), which can be queried online via the internet. MLST schemes have been established for numerous human pathogens including *S. aureus* and *S. epidermidis (167–169)* (Fig. 30-5). The technique has turned out to be an excellent tool not only for tracking the geographical and temporal spread of hypervirulent and antibiotic-resistant strains, but also for the population and evolutionary analysis of pathogenic bacteria *(172,173)*.

Multiple Loci Variable Number of Tandem Repeat Analysis

Multiple loci variable number of tandem repeat (VNTR) analysis (MLVA) is a typing method based on the length analysis of tandem repeat DNA sequence stretches present in most bacteria and also eukaryotes *(174)*. VNTRs

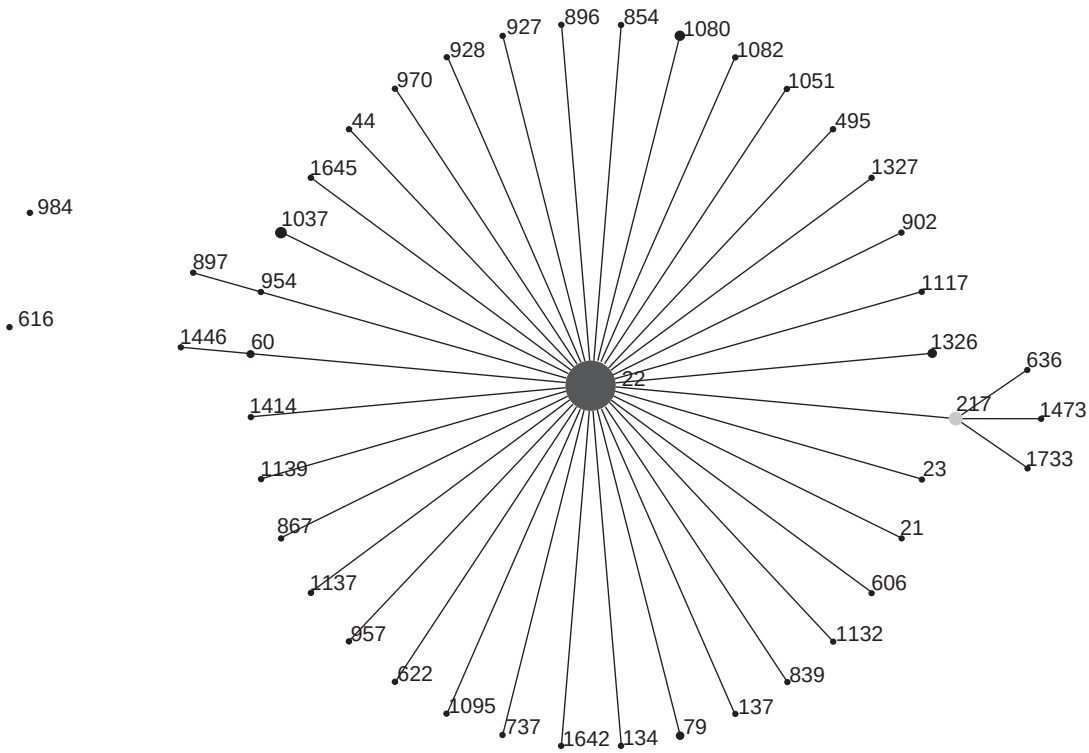

FIGURE 30-4 Example of an eBURST dendrogram. The figure was generated using the *S. aureus* MLST dataset on www.mlst.net by employing the eBURSTv3 algorithm available on this website. CC22 of *S. aureus* is shown with sequence type ST22, the common founder, being placed in the center of the diagram. Numbers represent STs and lines emanating from the center and from the circles display SLVs of the respective ST (see text for details). Circle diameters represent the number of isolates within the dataset that exhibit a particular ST.

arcC	*aroE*	*glpK*	*gmk*	*pta*	*tpi*	*yqiL*	ST	Wisplinghoff *et al.*, 2003
7	1	3	1	1	1	1	ST27	Kozitskaya et al., 2005
arcC	***aroE***	***gtr***	***mut S***	***pyr***	***tpi***	***yqiL***	**ST**	Thomas *et al.*, 2007
7	1	2	2	4	1	1	ST2	Miragaia*et al.*, 2007

FIGURE 30-5 MLST alleles used in two different *S. epidermidis* MLST typing schemes. The respective allelic profile of the most widespread healthcare-associated epidemic *S. epidermidis* clonal lineage (170,*171*) is shown when applying the scheme suggested by Wisplinghoff et al. *(169)* (ST27) and Thomas et al. *(168)* (ST2), respectively.

are usually scattered around a bacterial genome and they have been proven to be suitable for strain identification and typing in many human pathogens. In staphylococci, VNTRs typically occur in genes encoding surface-associated proteins carrying repeat units that mediate interactions with host matrix proteins. Thus, MLVA schemes for *S. aureus* and *S. epidermidis* preferentially target cell wall–associated protein genes, but other tandem repeat units such as the CRISPR loci (clustered regularly interspaced short palindromic repeat) would be adequate for MLVA as well. In the *S. epidermidis* MLVA scheme, currently five gene regions containing tandem repeats and the *mecA* gene are amplified in a multiplex PCR reaction *(175)*. The resulting PCR fragment patterns are resolved and displayed using microcapillary electrophoresis and are automatically assessed by computer-aided cluster analysis. The approach was demonstrated to have a similar discriminatory power as PFGE or MLST *(176)*. A major advantage of the technique is that it only comprises a single (multiplex) PCR reaction and does not require subsequent DNA sequencing. The computer-based pattern analysis makes the data portable, albeit data comparison between laboratories is not that convenient as with the MLST approach. Nevertheless, the technique is rapid and cost efficient and might therefore be suitable for the high-throughput analysis of large numbers of isolates in the routine laboratory.

SCCmec Typing

Although SCCmec typing does not represent a method suitable for strain identification, it will be discussed here as the classical typing methods described above are often complemented by the determination of SCCmec types detectable in clinical staphylococcal isolates. As already mentioned in the antibiotic resistance paragraph of the chapter, SCCmec elements consist of conserved and variable DNA regions encoding methicillin and other antibiotic resistance traits, the *ccr* mobility genes and so called J regions encoding accessory functions. Obviously, a great (unidentified) variety of SCC elements with and without the methicillin resistance conferring *mecA* gene do exist, specifically among coagulase-negative staphylococci *(177)*. For the routine praxis, a typing scheme has been implemented for eight major SCCmec types that carry *mecA* and are common among *S. aureus* and coagulase-negative staphylococci *(134,178–181)*. SCCmec elements typically consist of region J1 forming the left end of the element, followed by the recombinase complex *ccr*. Region J2 separates *ccr* from the *mec* gene complex, while region J3 borders the element at the right end, giving rise to the overall structural organization J1-*ccr*-J2-*mec*-J3. Typing is performed by a multiplex PCR reaction using 10 primer sets that target regions, which are, alone or in combination, specific for each of the SCCmec types. The resulting PCR amplification patterns are visualized either by classical agarose or automated capillary gel electrophoresis, the latter approach making the data more portable. SCCmec multiplex PCR typing is constantly evolving and updates with new primer sets targeting newly identified SCCmec types are continuously added to the typing scheme.

GENOMICS

Deciphered Coagulase-Negative Staphylococcal Genomes

With the recent progress in sequencing technology, bioinformatics, and database management, genome sequencing of microbes has become widely available and is currently revolutionizing the field of bacteriology and our understanding of infectious diseases in general. So far, representatives of all notable human bacterial pathogens have been sequenced, and from some species genome sequences of a number of several strains have been identified *(182)*. Thus, in July 2010, the genome sequences of as much as 64 distinct *S. aureus* strains were available in established databases (http://www.ncbi.nlm.nih.gov). The number of available coagulase-negative staphylococcal genomes is considerably lower, but constantly growing as well. Genome sequencing projects are completed for the most common coagulase-negative staphylococcal pathogens *S. epidermidis*, *S. haemolyticus*, *S. saprophyticus* as well as for the apathogenic species *S. carnosus*. Incomplete or provisional genome sequences exist currently for *S. hominis*, *S. capitis*, *S. warneri*, and *S. lugdunensis (183)*. Staphylococcal genome sequences represent a unique source of information. They provide a basis for molecular typing of strains and epidemiology, but give also invaluable insights into mechanisms of genome evolution, similarities and differences between strains and species, and the resulting molecular pathogenesis of coagulase-negative staphylococcal infections. The main characteristics of some coagulase-negative staphylococcal genomes are summarized in the following paragraphs.

Staphylococcus Epidermidis *S. epidermidis* was the first coagulase-negative staphylococcal genome to be sequenced and analyzed *(184)*. To date, two finished and another five incomplete genomes are available for the species *(184,185)*. The two completely sequenced strains

comprise *S. epidermidis* ATCC 12228, which is a commensal isolate widely used as a reference strain for antibiotic susceptibility testing, and *S. epidermidis* RP62A, a pathogenic isolate originally obtained from a blood culture associated with a catheter-associated septicemia *(186)*. *S. epidermidis* RP62A is also known as ATCC 35984 and serves as a reference strain for biofilm production among coagulase-negative staphylococci *(187)*. Whole genome analysis of both strains revealed a genome size of approximately 2.499 Mbp for ATCC 1228 and 2.616 Mbp for RP62A, respectively. Variation in genome size and gene content is mainly due to the insertion of a *Bacillus* prophage in *S. epidermidis* RP62A and differences in terms of other mobile elements such as genomic islands (see below), transposons, and ISs. Direct comparison of the *S. epidermidis* RP62A and ATCC 12228 sequences indicates over a broad extent a very uniform overall genome organization, except a region around the origin of replication. This DNA region is inverted in RP62A and harbors, in addition to the insertion site for the SCC*mec* elements (i.e., *orfX*), a number of genes involved in adhesion and biofilm formation. Most strikingly, the *ica* gene complex, involved in polysaccharide intercellular adhesin (PIA)-mediated biofilm formation, is present in the RP62A strain at the left-hand border of the inverted region, while this gene cluster lacks in ATCC 12228. *Ica* operon-mediated biofilm formation has been associated with invasive *S. epidermidis* isolates and was suggested as a discriminating marker between pathogenic and commensal isolates, at least in device-associated BSI (*141*,188,189–*193*). In both genomes, a number of genomic islands were detected that carry resistance or virulence-associated traits. Genomic islands are understood as genetic elements on the bacterial chromosome that have been acquired by horizontal gene transfer. They often differ in their GC content from the surrounding DNA, carry mobility genes, and are inserted in highly conserved regions of the chromosome such as tRNA loci. Most genomic islands are derived from mobile genetic elements. Thus in *S. epidermidis*, the νSe1 and νSe2 genomic islands originate from integrated plasmids. νSe1 was detected in RP62A and encodes a cadmium resistance gene complex, while νSe2 is a large DNA fragment specific to ATCC 12228 carrying among others two surface-associated proteins, which suggests specific interactions of this strain with host structures. A third island, νSeγ, is present in both *S. epidermidis* genomes at the same site and encodes β1 phenol soluble modulins (PSMs), which are known to interact with the human innate immune system *(194)*. The two strains differ with respect to their SCCmec islands. While strain RP62A harbors an SCCmec type II cassette, *S. epidermidis* ATCC 12228 contains an unusual SCC element (named SCC*pbp4*) that encodes, instead of the *mec* complex, the penicillin-binding protein gene *pbp*4 *(137,185)*. Compared to *S. aureus*, *S. epidermidis* does not carry superantigen and toxins genes, which might explain the more subacute and chronic course of *S. epidermidis* infections. However, the species contains a range of genes encoding proinflammatory cytolysins and other secreted exoenzymes such as lipases, esterases, and proteases, which are likely to be involved in invasion, evasion of host defense, and recruitment of nutrients through the destruction of host structures. A surprising result of the *S. epidermidis* genome sequencing project, however, was the strong evidence for an ongoing horizontal gene transfer across species and even genus borders. Thus, *S. epidermidis* RP62A was found to contain the *cap* operon that encodes a poly-gamma-glutamate (PGA) capsule and represents a major virulence factor in *Bacillus anthracis*. Presence of the *Bacillus* phage SPβ and detection of identical SCCmec cassettes both in *S. epidermidis* and *S. aureus* are further hints that coagulase-negative staphylococcal genomes are shaped by the uptake and incorporation of foreign DNA.

Staphylococcus Haemolyticus *S. haemolyticus* ranks second after *S. epidermidis* as a coagulase-negative staphylococcal species associated with BSIs and is capable of causing a wide range of infections including peritonitis, septicemia, otitis, and urinary tract infections. The species is known for its intrinsic and acquired antibiotic resistance, and as a consequence it seems logical that its genome sequence was revealed shortly after that of *S. epidermidis (195)*. Genome sequencing was undertaken in strain *S. haemolyticus* JCSC1435, a highly glycopeptide-resistant isolate that frequently generated mutants that had spontaneously lost resistance and metabolic traits upon subcultivation in antibiotic-free medium. The *S. haemolyticus* JCSC1435 genome size is similar to that of *S. epidermidis* and *S. aureus*, and a large proportion of open reading frames were identified that are conserved in their sequence and gene order in all three species. Differences were mainly detected in a region around the origin of replication. This region, named the "oriC environ," corresponds to the region around the origin of replication described above for *S. epidermidis* and contained most of the species-specific genes of *S. haemolyticus*. For example, genes encoding *S. haemolyticus*-specific metabolic pathways (e.g., mannitol utilization) are located in that region. Also, a putative capsule synthesis gene cluster, likely to be involved in pathogenesis, was detected in the oriC environ. Other putative virulence-associated genes such as three *S. haemolyticus*-specific hemolysin genes, a number of cell wall-associated adhesin genes, and PGA capsule synthesis enzyme genes are scattered around the genome. *S. haemolyticus* harbors, like *S. epidermidis*, a number of genomic islands that carry mostly genes of so far unknown function. Intact integrase genes on the islands point to a possible mobility of these structures. A characteristic and unexpected feature of the *S. haemolyticus* genome, however, is the unusually high number of mobile genetic elements. Thus, the genome carries two prophages, two integrated and another three free plasmids, three transposons, five genomic islands (including SCCmec) and, most notably, as much as 82 IS elements from which 60 were found to be intact and active. The complex mobile genetic elements (i.e., phages, plasmids, transposons, SCCmec) mostly carried antibiotic resistance genes, which explains the multiresistance phenotype of the isolate. The IS elements, however, which only encode functions for their own mobility, are suggested to play a role in the observed genome instability of the isolate *(195)*.

Staphylococcus Saprophyticus *S. saprophyticus* is a coagulase-negative staphylococcal species commonly involved in uncomplicated urinary tract infections, preferentially in young female outpatients. Genome sequencing of

the type strain ATCC 15305 revealed some specific features and mechanisms that shaped this species as a uropathogen *(196)*. Thus, *S. saprophyticus* has a number of additional sets of transporter systems involved in osmoprotection, which probably evolved by paralogue expansion *(196)*. Staphylococci are relatively salt tolerant, which is accomplished by the import of osmoprotective compounds such as proline, choline, and betain. The additional genes in *S. saprophyticus*, which were both chromosomally and plasmid-encoded, are likely to reinforce this mechanism and enable the bacteria to survive under the high ion conditions in urine. Also, the urease activity identified in the species might help the bacteria to thrive in this very special environment *(197)*. Other staphylococcal species harbor a great variety of cell wall–anchored adhesins, which interact with host matrix proteins and mediate adhesion to tissues and surfaces (198,*199*). In *S. saprophyticus*, only one such protein was predicted *(196)*, and this adhesin exhibited hemagglutination and adherence to human bladder cells suggesting again a highly specialized adaptation of the species to its environment *(200–203)*. Like the other staphylococcal genomes, *S. saprophyticus* harbors a range of mobile genetic elements, but their number is considerably lower than that of *S. haemolyticus*. Thus, *S. saprophyticus* ATCC 15305 contains one prophage, two complete IS elements and nine putative transposases as well as two SCC cassettes, one genomic island encoding streptomycin resistance, and two free plasmids carrying some of the osmoprotecting genes discussed above. Interestingly, the two SCC cassettes do not harbor *mecA*, but encode a capsule gene cluster and a restriction modification system, respectively.

Staphylococcus Carnosus In contrast to other coagulase-negative staphylococci, *S. carnosus* is a completely apathogenic species. The bacterium is classified as a GRAS (generally regarded as safe) microorganism and used as meat starter culture in dry sausage production and as a cloning vehicle for gram-positive bacteria *(204)*. Genome analysis of strain *S. carnosus* TM300 is an interesting project, not only because of the importance of the bacterium for the food industry, but also for understanding staphylococcal genome organization and pathogenesis by comparing the *S. carnosus* genome with those of pathogenic staphylococcal species. The *S. carnosus* TM300 genome is of similar size as other coagulase-negative staphylococcal genomes, but somewhat smaller than the *S. aureus* genomes *(205)*. *S. carnosus* encodes a series of metabolic pathways that obviously play a role when the bacterium is employed as a meat starter culture (e.g., nitrate/nitrite reduction, various sugar degradation pathways, osmoprotection systems, etc.). *S. carnosus* harbors also an *oriC* environ, which is inverted in comparison to *S. aureus* and carries some of the species-specific genes, while other genes of this class are scattered around the genome. The most intriguing feature, however, is that the *S. carnosus* genome does not contain intact mobile genetic elements such as plasmids, transposons, SCCs, IS elements, or any other repetitive sequence stretches. Lack of these elements is attributed to a relative stability of the *S. carnosus* genome and a low tendency for horizontal gene exchange with other bacteria. In addition to one prophage, only one genomic island with an integrase-like gene was detected, while other putative genomic islands only stood out as such by an aberrant GC content and integration into tRNA loci.

Mobile Genetic Elements of Coagulase-Negative Staphylococci

Mobile genetic elements are indispensable structures of nearly all bacterial genomes. They are characterized by their ability to move between different strains as well as between bacteria of various species and even genera. Mobile genetic elements in bacteria comprise plasmids, bacteriophages, transposons and IS elements, as well as genomic islands such as SCC elements or pathogenicity islands, carrying virulence factors. Mobile genetic elements often encode antibiotic resistance, metabolic or virulence-associated genes whose acquisition might be of benefit for the recipient bacterium. Therefore, horizontal gene transfer by mobile genetic elements has a major impact on enhancing the biological fitness of bacteria, but also contributes to the generation of genetic diversity within a species and the evolution and adaptation of the bacterial genome. Coagulase-negative staphylococci harbor a great diversity of mobile genetic elements. Table 30-4 lists a range of selected staphylococcal mobile genetic elements.

Plasmids The class I to III plasmids occur both in *S. aureus* and coagulase-negative staphylococci and confer resistance not only to antibiotics, but also to heavy metal ions or other toxic compounds *(206)*. Especially the large complex class II and III plasmids play an important role in the development of multiresistance in staphylococci. However, staphylococcal plasmids do not only carry resistance genes. They may also encode metabolic factors useful for the adaptation under specific external conditions as exemplified by two plasmids detected in *S. saprophyticus* that mediate salt tolerance *(196)*.

Genomic Islands Plasmids occasionally integrate into the bacterial chromosome where they can lose their replicative function and become a stabilized and integral part of the chromosome and form genomic islands such as νSe1 and νSe2 in *S. epidermidis*. The same applies to bacteriophages. All coagulase-negative staphylococcal genomes sequenced so far harbor at least one prophage, some of them likely to be defective. In *S. aureus*, prophages gave rise to the evolution of pathogenicity islands, which represent genomic islands carrying toxin and superantigen genes *(219,220)*. It is an intriguing feature of coagulase-negative staphylococci that they are devoid of toxin-encoding genomic islands. Instead, their phage-derived genomic islands carry antibiotic resistance genes or genes of so far unknown functions. Genomic islands often become hot spots for recombination events and the further uptake and integration of foreign DNA. The evolution of novel SCC elements, which obviously takes place preferentially within the coagulase-negative staphylococcal population, is a good example for the ongoing evolution of genomic islands in these bacteria *(138,221)*.

Transposons and IS Other important players in shaping staphylococcal genomes are transposons and IS elements (Table 30-4). Transposons and IS are DNA sequences capable of moving from one site within a genome to another.

TABLE 30-4

Selected Mobile Genetic Elements in Staphylococci

Element	*Phenotype/Distribution*	*Reference*
Antibiotic resistance plasmids		
Class I		*(206)*
pT181	Tc^r	
pUB112	Cm^r	
pS194	Sm^r	
pUB110	Km^r, Bl^r	
pOX6	Cd^r	
pE194	Em^r	
Classes II & III		
pI524	Pc^r Cd^r Pb^r Hg^r Om^r Asa^r Asi^r Sb^r	
pI258	Asa^r Em^r	
pII147	Pc^r Cd^r Pb^r Hg^r Om^r Asa^r	
pI9789	Cd^r Pb^r Hg^r Om^r Asa^r Asi^r Sb^r	
pGO1	Gm^r Tp^r Eb^r Qa^r	
Transposons		
Tn*4001*	Gm^r Km^r Tob^r	*(207)*
Tn*4003*	Tp^r	*(208)*
Tn*552*	Pc^r	*(209)*
Tn*554*	Em^r Spc^r	*(210)*
Tn*916*-family	Tc^r	*(211)*
Tn*5385*	Tc^r Em^r Gm^r Pc^r Sm^r Hg^r	*(212)*
IS elements		
IS*Sep1*	*S. epidermidis (2/38)*, *S. aureus*	*(184)*
IS*Sep2*	*S. epidermidis (14/3)*, *S. aureus*	*(184)*
IS*Sep3*	*S. epidermidis (3/3)*, *S. aureus*	*(184)*
IS*Shae1*	*S. haemolyticus (28)*	*(195)*
IS*256*	*S. epidermidis*, *S. haemolyticus*, *S. aureus*, Tn*4001*	*(213)*
IS*257*/IS*431*	*S. epidermidis*, *S. aureus*, *S. saprophyticus*, Tn*4003*	*(208)*
IS*1181*	*S. aureus*, *S. epidermidis*	*(214)*
IS*1182*	*S. aureus*, *S. haemolyticus*	*(215)*
IS*1272*	*S. haemolyticus*, *S. epidermidis*, *S. aureus*	*(215)*
Bacteriophages of coagulase-negative staphylococci		
ΦTM300	*S. carnosus TM300*	*(205)*
39.3-kb prophage remnant	*S. saprophyticus* ATCC 15305	*(196)*
ΦSh1	Tn*552* (Pc^r)/ *S. haemolyticus*	*(195)*
ΦSh2	Hg^r/ *S. haemolyticus*	*(195)*
ΦSPβlike	Nuclease/*S. epidermidis* RP62A	*(185)*
ΦPH15	*S. epidermidis*	*(216)*
ΦCNPH82	*S. epidermidis*	*(216)*
ΦIPLA5	*S. epidermidis*	*(217)*
ΦIPLA6	*S. epidermidis*	*(217)*
ΦIPLA7	*S. epidermidis*	*(217)*
Φ812	*S. aureus* and coagulase-negative staphylococci (broad host-range phage)	*(218)*

While IS encode exclusively genes necessary for their own mobility, transposons encode additional factors as well, usually antibiotic resistance genes. Many transposons in staphylococci mediate resistance to standard antibiotics such as penicillin (Tn*552*), aminoglycosides (Tn*4001*, Tn*554*), trimethoprim (Tn*4003*), macrolides (Tn*554*), and tetracyclines (Tn*916*) (Table 30-4). More recently, large composite transposons have been described where one or more transposons along with IS elements and other DNA stretches have been inserted into another transposon forming new multidrug elements *(222–224)*. Most interestingly, these structures contain DNA fragments specific to both staphylococci and enterococci suggesting horizontal gene exchange between these bacteria.

IS-Mediated Genome Flexibility IS can be found in all three kingdoms of life and there is hardly any microorganism that is devoid of these elements. Coagulase-negative staphylococci harbor, with the notable exception of *S. carnosus*, a large number of various IS in their genomes (Table 30-4). IS exert a significant influence on expression of the genetic material and are important elements in genome organization. Thus, IS are capable of inactivating genes by active transposition to new insertion sites, but they can also trigger gene expression of neighboring genes through intrinsic promoter structures. In contrast to transposons, identical IS elements often occur in multiple copies within a bacterial genome, thereby influencing the genome structure more passively by their mere presence. Thus, multiple copies of the same IS form repetitive DNA sequence stretches that serve as crossover points for homologous recombination events. Depending on the orientation of two identical elements to each other, inversions or deletions of the enclosed DNA fragment will occur. The number of IS within a bacterial genome therefore also reflects the dynamics of the genetic material and its capacity for rearrangements and the generation of genetic diversity. *Staphylococcus* species differ to some degree with respect to the number and nature of IS elements residing in their genomes. *S. aureus* strains contain on average 10 to 20 IS, while this number is considerably higher in coagulase-negative species involved in infections. The highest number (i.e., 82 IS) can be found in *S. haemolyticus*, and the two *S. epidermidis* genomes sequenced so far harbor up to 54 IS copies. IS-mediated genome flexibility was recently suggested to play a role in the infection process, and specifically the IS*256* element detected in *S. epidermidis* RP62A and in other biofilm-forming isolates was shown to be involved in the generation of phenotypic and genotypic diversity. Details of this phenomenon are discussed in the "Pathogenesis" section of this chapter.

Mechanisms of Horizontal Gene Transfer and Its Limitation

Coagulase-negative staphylococci have an extraordinarily high capacity to exchange genetic material among each other and even across genus borders. This finding was rather unexpected and coagulase-negative staphylococci are now recognized as a genetic reservoir for the evolution and spread of novel antibiotic resistance and virulence-associated genes. Transformation, conjugation, and transduction are the main mechanisms of horizontal gene transfer in bacteria. Other than *Neisseria*, streptococci or *Haemophilus*, staphylococci are not naturally competent, which means that they are unable to be transformed by naked DNA directly. So, mechanisms of horizontal gene transfer are mainly restricted to conjugation and phage transduction.

Conjugation Conjugation is the transfer of genetic material by direct contact of a donor and a recipient bacterium, and conjugationally proficient staphylococcal plasmids are mobilized by this mechanism *(225)*. However, conjugation can also mediate the exchange of certain transposons. While classical transposons and IS only move within their host genome, the so called conjugative transposons can be mobilized to another cell *(226,227)*. They transpose from an insertion site by excising as a single-stranded circular DNA intermediate, which is then either inserted into another site of the genome or transferred to a new host bacterium in a similar manner like a conjugative plasmid. Conjugative transposons were first detected in gram-positive bacteria, but are widespread in many other bacteria as well. In staphylococci, members of the Tn*916* family are the most common conjugative transposons *(211)*. They have a significant capacity to accumulate accessory genes and to form composite transposons, making them important vectors for the dissemination of genetic material among a great variety of commensal and pathogenic bacteria *(223)*.

Transduction Another important mechanisms for the spread of antibiotic resistance and virulence genes is transduction by bacteriophages *(228)*. As outlined above, coagulase-negative staphylococci harbor a range of prophages inserted in their genomes. Once activated and entering the lytic cycle, bacteriophages can accidently pack or incorporate host genetic material and transfer it to another recipient cell. Due to their specificity for certain species and strains, staphylococcal phages were in the past widely used for strain typing *(229)*. More recently, a number of novel phages, mainly from *S. epidermidis*, have been identified and for some of them the genome sequence was established *(216,217)*. Interestingly, among coagulase-negative staphylococci and also in *S. aureus*, broad-host range phages were identified capable of infecting a number of various species *(218)*. In *S. aureus*, such phages were even shown to transfer superantigen genes into *Listeria* species, suggesting that phage transduction contributes more to horizontal gene transfer and genome evolution of pathogenic bacteria than originally anticipated *(230)*.

CRISPR Loci and Limitation of Horizontal Gene Transfer From the evolutionary point of view, intensive exchange of genetic material, as observed in coagulase-negative staphylococci, does not necessarily represent an advantage *per se*. There is also a certain risk for taking up too much or nonbeneficial DNA leading to the generation of less fit and nonviable variants. Classical factors of self-protection are restriction modification systems, which recognize and eventually degrade invading foreign DNA *(231)*. A range of restriction modifications systems are present in staphylococci, and some of them are localized on genomic islands such as SCC elements *(137)*. In addition to restriction modifications systems, *S. epidermidis* has adopted another fascinating mechanism to limit horizontal gene transfer and to prevent specifically the repeated uptake of elements that have already been acquired. Clustered, regularly interspaced, short palindromic repeat (CRISPR) loci were recently detected in the multiresistant clinical strain *S. epidermidis* RP62A. (232,*233*). CRISPR loci are widespread in bacteria and archaea *(234–236)*. In *S. epidermidis*, they were shown to confer acquired immunity against the invasion of phages and conjugative plasmids *(*232*,233)*. CRISPR-mediated immunity is based on sequence matches between the invading mobile DNA element and short spacer DNA stretches that separate the CRISPR repeats. These spacer regions are highly dynamic

and evolve rapidly upon contact with a novel mobile genetic element. The CRISPR repeats are regularly linked to a cluster of genes, *cas* (CRISPR-associated genes) encoding a sophisticated machinery of proteins involved in CRISPR adaptation and interference with invading DNA. The spacers along with parts of the conserved CRISPR sequence encode small untranslated RNAs that target the invading DNA in a sequence-specific manner by blocking it by direct base pairing *(237)*. The mechanism is regarded as a kind of adaptive immune system of bacteria, which acts as an important factor to limit the spread of antibiotic resistance traits.

Genome Evolution of Coagulase-Negative Staphylococci

Another result of the numerous *Staphylococcus* genome sequencing projects was the finding that coagulase-negative staphylococci have imbalanced genomes (*195,205*). All circular bacterial chromosomes exhibit two replicores: replicore 1 is the DNA strand spanning clockwise from the origin of replication *oriC* to *terC*, the terminus of replication, while replicore 2 spans counterclockwise the rest of the genome from *oriC* to *terC*. Replication of bacterial circular chromosomes initiates at *oriC* and runs in both directions. It terminates at *terC* where the two replication forks meet. In all *S. aureus* genomes sequenced so far and in many other genomes, *terC* is located 180 degrees from *oriC* ensuring that the two replication forks have to cover an equal distance until termination. Such genomes are called balanced genomes. In contrast, in all sequenced coagulase-negative staphylococcal genomes, *terC* significantly deviates from the 180-degrees position. The biological consequences of this imbalance for coagulase-negative staphylococci are currently poorly understood. However, it is hypothesized that genome imbalance is a result of the accumulation of exogenous DNA by horizontal gene transfer and its incorporation mainly into the *oriC environ* of the staphylococcal chromosome. The staphylococcal *oriC* environ is defined as the region around the *oriC* in which <45% of the genes encode common staphylococcal genes, and indeed, most of the species-specific as well as accessory genes of coagulase-negative staphylococci are localized in this region. It seems to be the most dynamic part of the staphylococcal chromosome in which the establishment of genetic diversity and delineation of strains and species are most likely to occur, however, at the cost of generating an imbalanced genome. It is tempting to speculate that the frequent inversions, deletions, and rearrangements observed in this region represent attempts to (re)establish the physical balance of the genome (*293*).

PATHOGENESIS

Infections due to coagulase-negative staphylococci are of typical opportunistic nature. They are favored when the fine-tuned balance between commensalism and pathogenicity is disturbed either by the presence of distinct bacterial virulence factors or by a transient or permanent weakness of the host defense. Indeed, coagulase-negative staphylococcal infections predominantly occur in immunocompromised patients and when the integrity of the skin barrier is disturbed. Often, the bacteria make use of indwelling medical devices such as intravenous catheters as vehicles to enter the host *(238)*. In the last decade, numerous studies were performed to identify bacterial factors that might help to distinguish commensal isolates from those being able to cause infections. In *S. epidermidis*, the most common coagulase-negative staphylococcal pathogen, two putative virulence-associated determinants were identified in invasive isolates. One is the *ica* gene cluster mediating polysaccharide-dependent biofilm formation and the other is presence of IS*256*, an IS element supposed to influence genome flexibility and adaptation of gene expression during an infection (*141*,188,*189–193*). The role of these and other factors in the pathogenesis of coagulase-negative staphylococcal infections will be discussed here.

Bacterial Factors Involved in Colonization and Biofilm Formation

As typical skin and mucosa commensals, coagulase-negative staphylococci have evolved surface structures mediating the contact to epithelial cells and matrix proteins of their hosts. MSCRAMMs (microbial surface components recognizing adhesive matrix molecules) are cell wall–associated proteins interacting with matrix proteins such as collagen, fibrinogen, vitronectin, and many others *(239)*. Most MSCRAMMs are covalently linked to the staphylococcal cell wall, and they have been detected in nearly all coagulase-negative staphylococcal species. MSCRAMMs are considered as key factors that guarantee the commensal lifestyle of the bacteria by maintaining contact to the host. As matrix proteins rapidly cover abiotic surfaces of indwelling medical devices, MSCRAMMs are also important for the colonization of implants and the initialization of device-associated infections by coagulase-negative staphylococci (198,*199*,*240*,*241*) (see Chapter 31). Initial attachment to a surface is often followed by the multiplication of the bacteria *in situ* and the formation of microcolonies. When growing into larger, mushroom-like structures with the development of channels for water, ion, and nutrient exchange, these microcolonies may give rise to the accumulation of a bacterial biofilm. Biofilms are, by definition, communities of microorganisms that stick to each other and/or to a surface, mostly by the production of a self-produced extracellular matrix *(242)*. The biofilm lifestyle has fascinating consequences for both the single bacterial cell and the population as a whole, and details of this phenomenon are discussed comprehensively elsewhere in this volume. Most strikingly, bacteria organized within a biofilm exhibit much higher resistance against antibiotics than their planktonically living peers *(243)*. In staphylococci, two different modes of biofilm formation have been described. Thus, biofilm formation can be accomplished by production of a PIA, a slimy matrix which is also known, according to its structure, as poly-*N*-acetylglucosamine (PNAG) *(244)*. The enzyme complex responsible for PIA/PNAG synthesis is encoded by the *icaADBC* operon (245). It is noteworthy that in *S. epidermidis* this gene cluster is preferentially found in epidemic, healthcare-associated clonal lineages, while it is rarely detectable in commensal *S. epidermidis* isolates recovered outside of medical facilities (*141*,170,188,*189–192*). The *ica* gene cluster has been detected in other staphylococcal species as well, but due to the low number of isolates analyzed no clear association

between presence of the genes and invasiveness has been deduced so far *(246–248)*. *S. epidermidis* biofilm formation can also be PIA/PNAG independent. Thus, *icaADBC*-negative strains have been described in which biofilm formation was found to be mediated by proteins such as the accumulation associated protein Aap and the biofilm associated protein Bap/Bhp, respectively *(249–252)*. More recently, it was shown that wall teichoic acids and extracellular DNA are also part of the biofilm matrix and contribute to biofilm formation, most likely as stabilizing factors through their polyanionic nature *(253–255)*.

Evasion of Host Defense

The formation of biofilms is one strategy to evade the host defense, as biofilms represent an efficient physical barrier for cells and soluble factors of the immune system. However, PIA/PNAG itself was also shown to have direct effects on the innate immune system by inhibiting phagocytosis and killing through polymorphonuclear leukocytes as well as by increasing resistance toward host-derived antimicrobial peptides (AMPs) *(256)* (see Chapter 31). Another exopolymer with similar effects is the PGA capsule of *S. epidermidi,s* which was demonstrated to protect from major components of the innate immune system as well and is obviously present in many coagulase-negative staphylococcal genomes *(257)*. Also, *S. epidermidis* is able to sense AMPs in the environment by dedicated signaling systems (*258*,259*,260*). AMPs are produced by eukaryotes and are in the first line of defense against many pathogens *(261,262)*. Staphylococci, notably coagulase-negative staphylococci, are known to be notoriously resistant to AMPs, which is accomplished by the upregulation of genes that decrease susceptibility to these peptides or facilitate their export from the staphylococcal cell *(263,264)*. Other small molecules interacting with the immune system are the PSMs, which are encoded by genomic islands or the *agr* quorum-sensing system (see below) *(194)*. PSMs were demonstrated to have proinflammatory and cytolytic effects on eukaryotes and one compound, the PSMγ (delta-toxin), is supposed to play a role in biofilm detachment and re-initiation of the process at other sites *(265–267)*.

Regulation of Gene Expression and Cross talk within the Ecological Niche

Successful establishment and survival of a bacterium within an ecological niche requires coordinated gene expression and adaptation according to nutrient supply, influence of the host immune system, and other external conditions. Staphylococci employ a number of various regulatory networks to accomplish this sophisticated task. Thus, staphylococcal gene regulators comprise, for example, alternative sigma factors such as SigB, which is involved in the control of stress response, numerous DNA-binding transcription factors, classical two-component signaling systems, and most interestingly, the quorum-sensing system Agr (accessory gene regulator) *(268)*. Agr is present in all staphylococcal species. It contains a two-component signal transduction system consisting of the sensor-histidine kinase AgrC and the response regulator AgrA as well as AgrD and AgrB responsible for the synthesis, export, and posttranslational modification of small pheromone peptides *(269)*. The Agr pheromone peptides vary in their sequence between staphylococcal species, and various subgroups have been detected within a single species *(270)*. Interestingly, these pheromones show self-induction of their own Agr system, while nonself-pheromones cross-inhibit expression of the locus *(271,272)*. The actual Agr effector molecule is a regulatory RNA (RNAIII) that interacts with the target mRNAs of Agr-controlled genes and that additionally encodes the PSM delta-toxin *(273–275)*. Agr is known to adapt staphylococcal physiology to postexponentially growth when nutrients start to become short in supply *(276)*. It activates a range of virulence-associated genes such as extracellular proteases, lipases, and other exoenzymes that might help to degrade host tissue structures and immune components. Moreover, it is involved in the general stress response of staphylococci, including the control of detoxifying enzymes *(276)*. Also, Agr seems to facilitate detachment of *S. epidermidis* biofilms most likely through the action of extracellular proteases and the detergent effect of delta-toxin *(265,277)*. Moreover, the system has a major impact on the central metabolism of staphylococci, thereby influencing indirectly staphylococcal physiology and biofilm formation (278). Agr-mediated quorum-sensing control of gene expression has therefore consequences for the protection from the innate immune system and metabolic adaptation of coagulase-negative staphylococci, but also for the mutual crosstalk of the bacteria on the skin and the suppression of unwanted neighbors and their displacement from the ecological niche (*269*,*279*).

Heterogeneous Gene Expression and Genome Instability as an Adaptive Strategy

Coagulase-negative staphylococci are known for their pronounced variability and heterogeneity, which can often be observed in clinical samples. Primary cultures from clinical specimens grown on agar plates frequently differ in colony morphology, size, color, hemolysis, and other properties suggesting, on first glance, a mixed bacterial population. Phenotypic differences may also affect the expression of metabolic traits, which in turn, hampers the correct identification of the species by metabolic tests. Other typical features subject to phenotypic and genetic instability are biofilm formation and methicillin resistance. Thus, early studies on *Staphylococcus* biofilm formation report a high variability of biofilm expression with the regular and spontaneous generation of biofilm-negative variants arising from a biofilm-forming population *(*188*,280)*. Alongside with biofilm formation, methicillin resistance was often found to be affected as well in such variants, and there is growing evidence to suggest that the IS element IS*256* plays a crucial role in these processes (*59*,281,*282*). IS*256* is present in multiple copies in the genomes of certain *S. epidermidis* clonal lineages preferentially associated with healthcare-associated infections, and the element is therefore regarded as a marker for invasive isolates. As IS*256* also forms the ends of composite transposon Tn*4001*, conferring aminoglycoside resistance, the element is detected in other multiresistant coagulase-negative staphylococcal strains and species as well (e.g., *S. haemolyticus*) *(283)*. When active, IS elements transpose from one insertion site within a genome to another, and IS*256* was shown to insert spontaneously into biofilm-associated genes and global regulators of staphylococcal gene expression (*141*,*190*,*193*,281,*284*). IS*256*

has also the capacity to activate the expression of genes through the formation of strong hybrid promoters when the element inserts into the neighborhood of genes and operons *(285–287)*. As a result, a heterogeneous bacterial population is generated in which virulence, metabolic, and antibiotic resistance genes are differentially expressed. It is tempting to speculate that the presence of IS*256* is an advantage in the infection process by facilitating the emergence of a variety of well-adapted variants that can readily cope with the very different environments on the skin and within the bloodstream, respectively. Biofilm formation seems to be particularly prone to variation and IS*256* was shown to impair *S. epidermidis* PIA expression by insertion into the *icaADBC* operon (281). The process is reversible and precise IS*256* excisions from an insertion site are mediated by an illegitimate recombination event that does not require the element's transposase *(288)*. While switch-off of PIA-production through IS*256* insertions occurs with a frequency of approximately 10^{-6} per cell, and generation, restoration of PIA-dependent biofilm formation by precise IS*256* excision was found to be an extremely rare event (10^{-11} per cell and generation). Interestingly, it was demonstrated that strains with a dysfunctional *ica* operon are able to induce biofilm formation, after repeated passages, by proteins (289). This ability to switch between different modes of biofilm formation obviously occurs *in vivo* and seems to play a critical role in pathogenesis. Thus, in a recently described clinical case of a fatal *S. epidermidis* septicemia, a number of consecutive isogenic isolates were obtained, which differed with respect to biofilm formation and oxacillin resistance (16). Isolates from the beginning of the infection produced a weak protein-mediated biofilm, while isogenic isolates from a later stage of the infection were strong PIA-expressing biofilm formers. It is generally thought that biofilm switching is of biological relevance in the highly dynamic course of a device-associated infection. Thus, PIA synthesis is known to be a costly, energy-, and resources-consuming process, which is not necessary and even detrimental when the bacteria live as commensals on the skin (290). In contrast, when the bacteria are translocated into the bloodstream, PIA production is required and indispensable for survival as the polysaccharide protects the bacteria efficiently from antibiotics and the action of the host immune system (291). The molecular mechanism of biofilm mode switching is currently poorly understood, and it remains to be investigated whether or not active IS*256* transpositions, into so far uncharacterized regulators controlling biofilm formation and/or the metabolism of the staphylococcal cell, are involved in this process.

In addition to active transposition, multiple genomic IS copies are supposed to serve as crossover points for homologous recombination events, and therefore to play an important role in genome flexibility and adaptation of bacterial genomes. In disease-associated *S. epidermidis* strains and in the course of an infection spontaneous IS*256*-mediated chromosomal DNA fragment deletions may occur that encompass, among many metabolic genes, the *ica* operon and large parts of the methicillin/oxacillin-resistance conferring SCC*mec* elements (16,*59*). *S. epidermidis* genome analyses indicates that both the *ica* genes and the SCC*mec* elements are colocated in a region of high recombination in the oriC environ of the chromosome suggesting a joint genetic instability of these traits *(292)*. This phenomenon is obviously not restricted to *S. epidermidis*, but has also been described in *S. haemolyticus*, a species that typically harbors a large number of IS elements in its genome *(293)*. Thus, upon drug-free passage of the multiresistant clinical isolate *S. haemolyticus* JCSC1435 large chromosomal rearrangements and deletions occurred, which were due to the action of multiple copies of IS*Sha1*, an IS that formed composite transposons, and which mediated the excision and self-integration of large chromosomal fragments in the oriC environ *(293)*.

Taken together, coagulase-negative staphylococci are highly versatile bacteria that can adapt their gene expression patterns very efficiently to rapidly changing environmental conditions. This flexibility is particularly pronounced in clinical isolates and recent research suggests that the number and activity of mobile genetic elements present in the genomes of coagulase-negative staphylococci play a crucial role in this process, which may critically determine pathogenesis, disease progression, and outcome of coagulase-negative staphylococcal infections.

MOLECULAR EPIDEMIOLOGY AND INFECTION CONTROL

Identification of Disease-Associated *S. Epidermidis* Clonal Lineages

Due to the ubiquitous nature of *S. epidermidis* as commensals, it was thought for a long time that any isolate residing on the skin of a patient can cause disease and that *S. epidermidis* infections are therefore likely to be polyclonal. In support of this idea, molecular typing by PFGE demonstrated indeed a striking diversity among *S. epidermidis* isolates *(294–297)*. However, at the same time, transmission of strains between patients, wards, and hospitals were also reported suggesting an epidemic spread of *S. epidermidis* strains *(298–303)*. These apparently conflicting data were even more difficult to interpret when it became clear that, as comprehensively described in this chapter, *S. epidermidis* genomes readily undergo rearrangements, sometimes with such aberrations being generated within an isolate in the course of one and the same infection (16,*59*,*304*,*305*). The high resolution power of the PFGE approach detects these genomic differences, suggesting a much higher degree of genetic diversity within the *S. epidermidis* population than genuinely present. The problem was eventually overcome by introducing MLST as a tool in *S. epidermidis* epidemiology. Thus, an MLST scheme introduced by Wisplinghoff et al. *(169)* revealed, for the first time, distinct related clones of *S. epidermidis* that were implicated in infections, but were recovered independently from patients in various geographic locations and over a long period of time. Employing the same MLST scheme, another study, which aimed at the clonal relatedness of biofilm-forming and non–biofilm-forming *S. epidermidis*, eventually revealed that the majority of disease-associated isolates belong to one sequence type, ST27, which was detected in various hospital settings in Europe and the United States (170). *S. epidermidis* ST27 strains were found to harbor in their

genomes the biofilm-mediating *ica* operon along with various SCC*mec* cassettes and multiple IS*256* copies. These findings were further backed and detailed by a more recent study, applying an improved MLST scheme to establish the overall population structure of the species *S. epidermidis* (*168*,*171*) (Fig. 30-5). MLST analysis of a representative collection of *S. epidermidis* isolates from various spatiotemporal and clinical origins revealed a high degree of genetic diversity within the species, but identified also nine epidemic clonal lineages that were disseminated worldwide. The most widespread clone was ST2, with isolates being identified in as many as 13 different countries on three continents. ST2 is the founder sequence type of CC2 and a particular high recombination frequency was recorded within this CC giving rise to further expansion of the clone *(171)*. Re-typing of the ST27 isolates identified in the study by Kozitskaya et al. 2005 revealed that ST27 corresponds to ST2 according to the revised MLST scheme (Kozitskaya and Ziebuhr, unpublished data) (Fig. 30-5). Using one or the other MLST schemes, ST2 (ST27) strains have meanwhile been detected in many geographic regions, suggesting that this clonal lineage is evolutionarily highly successful and able to disseminate worldwide (*169–171*,306–*308*). In general, *S. epidermidis* is now regarded as an epidemic species with a few well adapted clonal lineages emerging upon a background of a highly diverse and recombining population *(171)*. In the light of these findings, PFGE can still be regarded as the most appropriate and powerful tool for the short-term surveillance of *S. epidermidis* outbreak situations, but it has its limitations when it comes to long-term evolutionary analyses or the surveillance of the geographic dissemination of *S. epidermidis* clonal lineages. For these purposes, MLST, MLVA, or a combination of PFGE with other methods such as SCC typing are more suitable and recommended *(309)*.

Coagulase-Negative Staphylococci as a Reservoir of Antibiotic Resistance Genes

While occurrence of methicillin-resistant *S. aureus* (MRSA) in medical facilities immediately prompts action to contain their spread, there are hardly any infection control measures in place to fight methicillin-resistant *S. epidermidis* or methicillin-resistant coagulase-negative staphylococci. Numerous studies, however, demonstrate an ongoing evolution of novel SCC*mec* elements within the coagulase-negative staphylococcal population *(177,221,297,310,311)*. Notably, in *S. epidermidis* it was shown that epidemic, healthcare-associated clones readily acquire SCC*mecs* and that these acquisitions had occurred independently from each other many times *(171)*. Thus, among coagulase-negative staphylococci, a great variety of SCC elements can be found, many of them being novel, nontypable variants, suggesting that *S. epidermidis* and other coagulase-negative staphylococci are specifically prone to take up these mobile genetic elements (*169–171*). A recent study addressing the molecular epidemiology of commensal coagulase-negative staphylococci colonizing patients and staff in a nursing home with high MRSA colonization rates identified a great variety of novel SCC types (with or without *mecA*) among coagulase-negative staphylococci *(312)*. Most interestingly, many of these SCC elements were found to be shared with *S. aureus* strains recovered from the same nursing home. These and other data provide growing evidence that coagulase-negative staphylococci represent a reservoir and genetic background for the evolution of novel SCC*mec* elements and other resistance traits that might be transferable into *S. aureus*.

Prevention and Infection Control

The new insights gathered on genetics and epidemiology of coagulase-negative staphylococci during the last decade demonstrate that distinct isolates with very special properties have established in the hospital environment, causing the majority of infections. These isolates are characterized by multiresistance toward antibiotics, the ability to form biofilms on medical devices, and an extraordinary phenotypic and genetic flexibility and adaptation to changing external conditions. Moreover, these healthcare-associated multiresistant coagulase-negative staphylococcal populations have been recognized as a gene pool and reservoir for the evolution and spread of novel resistance genes which might be transferred into more pathogenic species such as *S. aureus*. At the moment, multiresistant and biofilm-forming coagulase-negative staphylococci are not targeted by any hospital infection control measures. However, in the light of the recent findings, it would be interesting to see whether consideration of these bacteria in future infection prevention plans could lower the number of device-associated infections by coagulase-negative staphylococci and, in the very long run, also decrease the burden of multiresistant *S. aureus* in medical facilities. Thus, studies would be desirable to detect biofilm-forming multiresistant coagulase-negative staphylococci in the environment of intensive care units, transplantation and cancer treatment centers, as well as other facilities with a high risk and incidence of coagulase-negative staphylococcal infections. Screening should specifically aim at strains colonizing the skin of staff and patients, and based on the experiences with MRSA control, it is tempting to speculate that a targeted "search and destroy policy" along with a meticulous hand hygiene regime might be effective to prevent individual infections and to stop the further spread of putative pathogenic strains within a medical setting.

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CHAPTER 31

Mechanisms of Biofilm Formation in the Staphylococci

Paul D. Fey

As documented in other chapters of this text, both *Staphylococcus aureus* and *S. epidermidis* are a cause of significant infections in both the community and the hospital environment. Most likely due to their ability to colonize mucous membranes and skin of humans, data from the National Nosocomial Infection Surveillance (NNIS) system demonstrate that *S. aureus* and *S. epidermidis* are the most common cause of healthcare-associated infections including catheter-related infections *(1)*. One particularly onerous aspect of staphylococcal pathogenesis is the ability of most staphylococcal species to form biofilm on foreign medical devices (2). Despite the documented function of biofilm in the context of staphylococcal disease, our understanding of molecular mechanisms fundamental to biofilm formation is incomplete. It is clear that bacteria within a biofilm have a unique and heterogeneous metabolism compared to planktonic cells (3). Consequently, bacterial biofilms are inherently resistant to antibiotics and the innate immune system leaving clinicians little choice but to remove the infected device. Staphylococcal biofilm is defined as a heterogeneous mixture of cells, usually bound to a foreign body, encased in an extracellular matrix consisting of protein, extracellular DNA (eDNA), and polysaccharide (2,4). Recent data from a variety of investigators have clearly shown that extracellular matrix differs between strains; in fact, the composition of the extracellular matrix within a particular isolates biofilm may change depending upon the extracellular niche *(5–7)*. In an attempt to organize the data, this chapter will focus on the four identified stages of *S. aureus* and *S. epidermidis* biofilm synthesis (a) initial attachment, (b) accumulation, (c) maturation processes, and (d) dispersion. However, in some cases, particular factors clearly function in multiple stages of biofilm formation (i.e., initial attachment and accumulation). Particular biofilm components may have been studied in the context of either *S. aureus* or *S. epidermidis* biofilm, and this will be noted.

STAPHYLOCOCCAL ATTACHMENT TO A FOREIGN BODY

Both *S. aureus* and *S. epidermidis* have multiple factors that function to mediate adherence to foreign biomaterials. After insertion into a host, foreign medical devices are rapidly coated by serum proteins including fibrinogen, fibronectin, collagen, and vitronectin. Staphylococci have the capability to bind these serum proteins, and thus the biomaterial, through the interaction with MSCRAMMs (*M*icrobial *S*urface *C*omponents *R*ecognizing *A*dhesive *M*atrix *M*olecules) *(8–10)*. Although the number of MSCRAMMs encoded by a particular strain differs, *S. aureus* (~20) typically encodes more MSCRAMM-like proteins than does *S. epidermidis* (~12) *(8,11)*. MSCRAMMs have a common structure including a surface-exposed-binding domain, a cell wall-spanning domain, and a peptidoglycan-binding domain that is typically covalently attached through an LPXTG motif by sortase A *(12,13)*. *S. aureus* MSCRAMM examples include the fibronectin/fibrinogen/elastin-binding proteins FnBpA and FnBpB *(14)*, two unique fibrinogen-binding proteins ClfA and ClfB *(15,16)*, and the collagen-binding protein Cna *(17)*. Other staphylococcal MSCRAMMs found in both *S. aureus* and *S. epidermidis* include a family of proteins containing extensive serine-aspartate (SD) repeats *(8)*. One extensively studied MSCRAMM in *S. epidermidis* and *S. aureus* is SdrG, a molecule that binds fibrinogen through a "dock, lock, and latch" mechanism *(12)*. Evidence also suggests that (GehD), a cell wall-associated protein that does not encode an LPXTG motif, is a bifunctional enzyme that also binds collagen in addition to its activity as a lipase *(18)*.

In addition to binding specifically to serum proteins, staphylococci, especially *S. epidermidis,* have the unique ability to bind plastic polymers (e.g., catheters). Heilmann and colleagues found this binding property is linked to the autolysin AtlE in *S. epidermidis (19)*. It was subsequently shown that *atlE* mutants of *S. epidermidis* were less virulent in a rat vascular catheter model *(20)*. Further work demonstrated that both AtlE bind vitronectin whereas a separate autolysin, Aae, binds fibrinogen, fibronectin, and vitronectin in a dose-dependent manner *(19,21)*. Thus, autolysins of staphylococci have the ability to bind both polymers (through an unknown mechanism) and serum proteins. Somewhat complicating the interpretation of the autolysin mutant phenotype, however, is the recent finding of the importance of bacterial extracellular DNA (eDNA) in the establishment of a staphylococcal biofilm *(22,23)*. eDNA provides structure that is important for both initial adherence and biofilm accumulation; thus, bacteria that are unable to lyse effectively (*atlE* or *aae* mutants) would be defective in eDNA release and thus be less adherent.

Thus, autolysins may have multiple roles in biofilm formation including the release of eDNA, initial adherence to polymers, and specific binding to serum proteins.

STAPHYLOCOCCAL BIOFILM ACCUMULATION

Defining the multiple mechanisms of staphylococcal biofilm accumulation and its clinical relevance has been an extremely exciting avenue of recent investigation. Recent data have suggested that *S. epidermidis* biofilm accumulation is mediated mostly by polysaccharide intercellular adhesin (PIA) and is sensitive to polysaccharide-dispersing enzymes such as dispersin B but resistant to proteases, whereas the converse is true for *S. aureus* biofilms *(24)*. However, there is increasing evidence demonstrating that clinical isolates of *S. epidermidis* produce proteinaceous biofilms (i.e., accumulation associated protein [Aap]) *(5)*. Furthermore, antibodies against PIA (or PNAG; poly-*N*-acetyl glucosamine) are protective in animal models of *S. aureus* infection suggesting expression of PIA/PNAG *in vivo (25)*. Therefore, the available data suggest that multiple proteins and PIA/PNAG may function to mediate biofilm accumulation within staphylococci, and their expression may depend on the nutritional state of the bacterium and/or niche. It is unknown whether the expression of these unique accumulation molecules exhibits any clinical significance in regards to clinical management of the biofilm-mediated infection or whether the metabolism differs in a PIA/PNAG-dependent biofilm in comparison to a proteinaceous-sensitive biofilm. Understanding these and other questions is fundamental to the rational design of new antibiotics and/or biofilm inhibitors. This section will summarize the molecules known to mediate biofilm accumulation; transcriptional regulation of these determinants will be discussed if known.

Polysaccharide Intercellular Adhesin/ Poly-*N*-Acetylglucosamine

Staphylococcal biofilm accumulation has been most well studied in the context of polysaccharide intercellular adhesin (PIA) or poly-*N*-acetylglucosamine (PNAG) synthesis. PIA is a β-1,6 linked poly-*N*-acetylated glucosamine and its synthesis is directed by enzymes encoded by the *icaADBC* operon (26,27). An identical molecule has been identified from *S. aureus* and is termed PNAG *(28,29)*. All four open reading frames (ORFs; *icaA*, *icaD*, *icaB*, and *icaC*) are required for PIA/PNAG synthesis *(30,31)*. Utilizing UDP-*N*-acetylglucosamine as a substrate, IcaAD acts as an *N*-acetylglucosaminyl transferase; IcaC, a membrane protein, most likely functions to transfer the growing polysaccharide outside of the bacterium to the cell wall. IcaB is a secreted deacetylase that functions to deacetylate PIA/PNAG; 15% to 43% of glucosamine residues are deacetylated *(29,32)*. Vuong and colleagues found that a 1457 *icaB* mutant was unable to form functional biofilm and exhibited reduced virulence in a foreign body infection model demonstrating the importance of deacetylation in PIA/PNAG-mediated biofilm accumulation *(33)*. Utilizing *icaADBC* mutants, several studies have demonstrated the importance of PIA in virulence of *S. epidermidis* using relevant animal models of infections; these studies found that PIA-deficient strains of *S. epidermidis* 1457 and O-47 have reduced virulence in comparison to isogenic PIA positive strains (*20,34,35,*36). Furthermore, PIA/PNAG inhibits neutrophil-dependent killing and mediates biocide resistance *(37,38)*. However, it is important to note and as will be detailed below, multiple clinical strains of *S. epidermidis* do not encode the *icaADBC* operon (*39–41*,42,*43*) and, even when encoded, *icaADBC* can be highly repressed (unpublished observations from the author). Similarly, most studies have found *icaADBC* encoded in almost all *S. aureus* isolates *(30,39,44)*, but the operon is highly repressed and is dispensable for biofilm formation *in vitro (39,45–48)*. However, *icaADBC* expression is upregulated in *S. aureus* during infection demonstrating that *icaADBC* expression is strain dependent and contains multiple layers of transcriptional and/or translational regulation *(47,49)*. Transcriptional regulation of *icaADBC* is very complex and published reports have documented 14 unique direct or indirect regulatory elements (Fig. 31-1).

σ^B—The first regulatory element identified as a member of the *icaADBC* regulon was σ^B, the alternative sigma factor in staphylococci *(50)*. Insertion of Tn*917* into the *S. epidermidis* 1457 *rsbU* gene, a positive regulator of σ^B expression, led to significantly decreased biofilm and PIA synthesis. Further work demonstrated that σ^B functions in an indirect manner to repress expression of *icaR,* a transcriptional repressor of *icaADBC (51)*; inactivation of

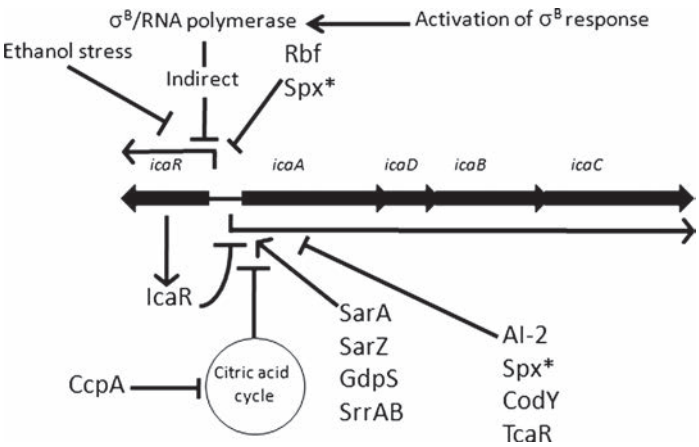

FIGURE 31-1 *icaADBC* regulatory circuit. Regulatory proteins known to function as activators of either *icaADBC* or *icaR* transcription are indicated with an *arrow*. Those that are known to repress transcription of *icaADBC* or *icaR* are indicated by a *blunt arrow*. (*) Spx is known to repress *icaR* transcription in *S. aureus* but represses *icaADBC* in *S. epidermidis*.

σ^B led to increased expression of IcaR and thus, decreased *icaADBC* transcription *(52,53)*. Ethanol pressure is also known to repress *icaR* transcription, however, this regulatory pathway is σ^B independent *(54)*.

IcaR/TcaR—icaR, a member of the TetR family of transcriptional regulators, is divergently transcribed from *icaADBC* (Fig. 31-1) and negatively regulates *icaADBC* transcription *(51)*. IcaR functions as a dimer and binds cooperatively to a 28-bp region upstream of *icaADBC (55)*. Cerca and colleagues recently found that in *S. aureus*, in contrast to *S. epidermidis*, *icaR* transcription is SarA and σ^B dependent, and IcaR is not required for activation of its own transcription suggesting that *S. aureus* and *S. epidermidis* regulate *icaR* transcription differently *(56)*. Utilizing the *ica* promoter region as a target in pull-down assays, Jefferson and colleagues identified a second regulator, TcaR, which has recently been shown to bind specifically to three separate regions in the *icaADBC* promoter region *(57,58)*. Interestingly, similar to IcaR, antibiotics bind to TcaR and inhibit their binding to the promoter region thus activating *icaADBC* transcription and PIA/PNAG production *(55,57)*.

Rbf—Rbf (*R*egulator of *B*iofilm *F*ormation) was first identified as a locus that regulated biofilm formation in response to glucose and sodium chloride in *S. aureus (59)*. Rbf has homology to the AraC/XylS family of transcriptional regulators and functions in an indirect manner to regulate *icaADBC* transcription by repressing *icaR* transcription *(60)*. As predicted, inactivation of *rbf* led to decreased virulence of *S. aureus* in a mouse model of foreign body infection due to decreased PIA/PNAG synthesis, although the effect was strain dependent *(61)*.

SarA/SarZ—The Sar family of DNA-binding proteins is a group of transcriptional regulators that function to activate or repress a large number of genes within the staphylococci, many of which are virulence genes including biofilm formation *(62)*. SarA has consistently been noted as a factor absolutely required for biofilm formation in both PIA/PNAG-dependent and PIA/PNAG-independent biofilms in *S. aureus* and *S. epidermidis (52,63–67)*. SarA is a positive regulator impacting *icaADBC* transcription in an *icaR*-independent manner *(65,66)*, although its function in regulating biofilm formation in PIA/PNAG biofilms is not clear but may involve protease production *(64)*. Furthermore, SarZ also acts as a positive activator of *icaADBC* transcription in *S. epidermidis* apparently independent of SarA *(68)*, although others have observed a relationship between SarA and SarZ expression and their interaction on biofilm formation in *S. aureus (69)*.

GdpS—The synthesis of cyclic dimeric GMP (c-di-GMP) is an important signaling molecule and regulator of biofilm formation in multiple Gram-negative bacteria *(70)*. However, only one protein in staphylococci, GdpS, contains a conserved GGDEP domain (diguanylate cyclase motif) *(71)*. Inactivation of *gdpS* resulted in a loss of biofilm formation and *icaADBC* transcription in media supplemented with sodium chloride; however, no c-di-GMP activity was detected in staphylococci suggesting that GdpS regulates biofilm formation in a c-di-GMP-independent pathway *(71)*. Further work has found that GdpS functions to regulate other virulence factors in *S. aureus* including proteases, fibrinogen-binding proteins, and protein A *(72)*.

SrrAB—Early studies on staphylococcal biofilm formation found that *icaADBC* transcription was induced when both *S. aureus* and *S. epidermidis* were grown under anaerobic conditions *(46)*. Later studies tied this observation to SrrAB, a two-component regulatory system homologous to ResDE in *Bacillus subtilis (73)* that is hypothesized to respond to environmental oxygen *(74)*. Studies from Ulrich and colleagues indicated that *icaADBC* transcription and PIA/PNAG synthesis in an *srrAB S. aureus* mutant was not induced under anaerobic growth conditions in an IcaR-independent manner *(74)*. In addition, the *srrAB* was less resistant to PIA/PNAG-mediated resistance to nonoxidative host response *(74)*. Induction of *icaADBC* in *S. aureus* grown under anaerobic conditions further suggests a function of PIA/PNAG in host resistance to the innate immune response.

Spx—Regulation of protein degradation in the staphylococci is mediated in part by ClpXP *(75)*. Two separate studies have indicated that ClpXP protease functions to regulate biofilm formation in both *S. aureus* and *S. epidermidis (75,76). clpX/clpP* mutants accumulate the transcriptional regulator Spx, known to function in multiple metabolic processes in *B. subtilis* including thiol homeostasis *(77)* and organosulfur metabolism *(78)*. Two recent studies have published conflicting data (see Fig. 31-1) demonstrating that accumulation of Spx in *clpXP* mutants increased *icaADBC* transcription through an IcaR-dependent process in *S. aureus (79)*; however, overexpression of Spx in *S. epidermidis* decreased *icaADBC* transcription in an IcaR-independent manner *(80)*. Further work is required to determine if the observed phenotype differences between *S. aureus* and *S. epidermidis* in regards to Spx are strain-dependent differences or conserved aspects within the species.

AI-2—It is proposed that the quorum-sensing molecule AI-2, which is synthesized from *S*-adenyolsylmethionine by LuxS, functions as a bacterial interspecies communication molecule. Multiple Gram-negative and Gram-positive species encode *luxS,* which was first identified as a locus required for bioluminescence in *Vibrio harveyi (81)*. However, the function of LuxS in the staphylococci is not known. Studies by Xu and colleagues found that insertional inactivation of *luxS* caused increased transcription of *icaADBC* and biofilm concomitant with an increase in metastatic disease as measured by a rat catheter model *(82)*. Microarray studies recently demonstrated that *luxS* mutants of *S. epidermidis* were deficient in amino acid, nitrogen, nucleotide, and carbohydrate metabolism *(83)*.

Central metabolism—Several early reports found that biofilm synthesis is regulated or induced by several environmental conditions such as anoxic growth conditions, iron limitation, glucose concentration, and subinhibitory concentration of antibiotics leading Somerville and colleagues to hypothesize that PNAG/PIA synthesis was linked to tricarboxylic acid (TCA) cycle activity *(46,84–87)*. Inactivation of aconitase led to increased *icaADBC* transcription and PIA synthesis suggesting that derepression of *icaADBC* is mediated by regulatory proteins that respond to the metabolic status of the bacterium *(88)*. Two global regulatory proteins involved in the carbon and the nitrogen metabolism cycles in Gram-positive bacteria are CcpA and CodY; both are linked to the TCA cycle (89). Seidl and colleagues demonstrated that an allelic replacement mutant of *ccpA* in

S. aureus increased *icaADBC* and PIA transcription; it was postulated that this was due to repression of the TCA cycle (*citA* and *citB*) *(90)*. Furthermore, CodY, which detects nutrient status of the bacterium by binding branched chain amino acids and GTP, represses *icaADBC* transcription under nutrient replete conditions *(91,92)*. Therefore, although the direct relationships regulating *icaADBC* transcription have not been identified in all cases, PIA/PNAG synthesis is linked to the metabolic status of the cell including TCA cycle activity and the regulatory circuit governed by CcpA and CodY.

Biofilm-Associated Protein

As previously mentioned, an increasing amount of evidence supports the notion that many clinical isolates of both *S. epidermidis* and *S. aureus* produce proteinaceous accumulation molecules and do not produce a detectable amount of PIA/PNAG. Biofilm-associated protein (Bap) was first identified as a proteinaceous adhesin that functioned in biofilm accumulation *(93)*. An orthologue exists in *S. epidermidis* and is termed Bhp *(11)*. Bap is closely linked to *S. aureus* isolates obtained from a bovine source and is quite rare in human isolates *(94)*; a recent study found that *bap* was not found in 262 *S. aureus* clinical isolates from various human and animal sources *(95)*. Depending on the study, *bhp* is encoded in approximately 15% to 45% of *S. epidermidis* human isolates *(5,96). bap* is associated with a pathogenicity island in *S. aureus* termed SaPIbov2, but *bhp* does not seem to be encoded on a mobile element in *S. epidermidis* RP62A *(11,94,97)*. Transcriptional analyses have shown that *bap* transcription is SarA and σ^B dependent in *S. aureus*, and formation of a Bap-dependent biofilm is sensitive to the σ^B-dependent proteases Aur and SspA that are overexpressed in a σ^B mutant *(98,99)*.

Accumulation-Associated Protein/ *Staphylococcus aureus* Surface Protein G

Aap (encoded by *S. epidermidis*) and its *S. aureus* orthologue *S. aureus* surface protein (SasG) are LPXTG proteins containing an N-terminal A domain and a B domain containing a variable number of 128-bp repeats *(100–103)*. SasG and Aap have no known binding affinity for extracellular matrix proteins; however, biofilm accumulation is mediated by Zn^{2+}-dependent dimerization utilizing the B domains of bacteria within the immediate vicinity of one another *(104)*. Furthermore, the A domain is known to bind specifically to corneocytes *(105)*. Interestingly, Aap is secreted in a nonfunctional form and is further processed by both host and bacterial proteases into a fibrillar protein *(100,103)*. Although Aap-dependent biofilms have been isolated from clinical *icaADBC*-negative *S. epidermidis* isolates *(5)*, the function of Aap in a PIA-dependent biofilm is unknown. Sun and colleagues found that inhibition of Aap by polyclonal antibodies in *S. epidermidis* RP62A inhibited a PIA/PNAG biofilm by 87% suggesting a function for Aap in both PIA/PNAG-dependent and PIA/PNAG-independent biofilms *(106)*. In addition, although the *aap* gene is found in approximately 90% of *S. epidermidis* isolates, recent data demonstrate that a functional Aap protein cannot be detected in some isolates when the gene is present *(96,107)*.

Extracellular Matrix-Binding Protein

Through enrichment experiments, Christner and colleagues isolated a biofilm-positive variant (1585v) of the PIA/PNAG negative *S. epidermidis* strain 1585 that produced a 460-kDa truncated isoform of Embp *(108)*. Extracellular matrix-binding protein (Embp) in strain 1585v was able to bind fibronectin but also mediates the accumulation phase of biofilm synthesis in addition to inhibition of phagocytosis *(108)*. Although most strains of *S. epidermidis* encode Embp, it is unclear how many clinical isolates of *S. epidermidis* express the appropriate isoform that is able to mediate biofilm accumulation.

Fibronectin-Binding Proteins A and B

The discovery demonstrating that FnbpA and FnbpB function to mediate *S. aureus* biofilm accumulation was reported independently by two laboratories *(109,110)*. Accumulation required both FnbpA and FnbpB and was independent of their ability to bind extracellular matrix proteins *(109)*. FnbpA and FnbpB accumulation was stimulated by mildly acidic growth media (due to glucose catabolism) or sodium citrate and is thus linked to TCA cycle activity *(109,110)*. Shanks et al. also determined that sodium citrate stimulation of biofilm accumulation was *icaADBC* independent, and, in fact, repressed *icaADBC* transcription as would be predicted by work from Sadykov et al. *(88,110)*.

Protein A (Spa)

Utilizing proteomic techniques, protein A was identified as an essential component of proteinaceous *S. aureus* biofilm *(111)*. Surprisingly, protein A-mediated accumulation was not dependent on anchoring of protein A to the cell surface as exogenously added protein A stimulated biofilm development *(111)*. Furthermore, competition studies indicated that protein A proficient wild-type strains (*S. aureus* Newman) outcompeted the *S. aureus* Newman *spa* mutant in a mouse foreign body infection model further demonstrating the fundamental role of Spa in proteinaceous biofilm accumulation *(111)*.

STAPHYLOCOCCAL BIOFILM MATURATION

Maturation is the most understudied aspect of biofilm development within the staphylococci. It is clear, however, that biofilm is composed of multiple metabolic niches with unique nutrient and oxygen concentrations (3). For example, using pulse-labeled DNA, oxygen probes, and green fluorescent protein (GFP) labeling experiments, Rani and colleagues found that *S. epidermidis* biofilms consisted of aerobically growing cells, cells that were utilizing fermentation to acquire ATP, dormant, and dead cells *(112)*. Several microarray studies have confirmed these data demonstrating that, in comparison to *S. aureus* or *S. epidermidis* growing under exponential phase, bacteria growing within a biofilm exhibit traits of microaerobic or anaerobic metabolism including amino acid catabolism *(45,113,114)*. In addition, microarray studies have indicated that additional genes are induced as a biofilm matures in flow cell systems (authors' unpublished data). Two genes induced

in a staphylococcal biofilm that have been studied include the arginine–ornithine transporter ArcD and succinate dehydrogenase (*sdhCAB*) *(115,116)*. Although a striking biofilm phenotype was not observed or reported when allelic replacement experiments were performed with both *arcD* or *sdhCAB,* the data strongly suggest that amino acids are utilized as a carbon source within biofilms. ArcD is part of the arginine deiminase operon that catabolizes arginine to form ATP and ammonia; succinate dehydrogenase functions within the TCA cycle that is required for catabolism of many amino acids. Further work is required to determine if inhibition of biofilm maturation processes is a viable target for antibiofilm treatment modalities.

STAPHYLOCOCCAL BIOFILM DISPERSAL

Similar to biofilm maturation, bacterial dispersal from staphylococcal biofilms is not well understood, but models are beginning to emerge. The difficulty in obtaining a model is due to the plurality of biofilm accumulation molecules (e.g., PIA/PNAG, Aap, eDNA, etc.). Detachment from *S. epidermidis* PIA/PNAG-dependent biofilms is accessory gene regulator (*agr*) dependent as *agr* mutant biofilms are thicker and *agr* activity has been detected on the surface of both *S. aureus* and *S. epidermidis* biofilms *(117,118)*. The detergent-like activity of phenol-soluble modulins and δ-toxin has been proposed to detach PIA/PNAG-mediated *S. epidermidis* biofilms; phenol-soluble modulins and δ-toxin are *agr*-dependent virulence factors *(119)*. A functional *agr* system is required for functional detachment of *S. aureus* proteinaceous biofilms where addition of autoinducing peptide (AIP; *agr* quorum sensing peptide) causes dramatic biofilm detachment (120). It is hypothesized that activation of *agr* on the outer surface of the biofilm activates transcription of certain proteases (e.g., Aur metalloprotease and SplABCDEF serine proteases) and nucleases that function to degrade the proteinaceous accumulation molecules including the eDNA (120,121).

CONCLUSIONS

An emerging theme in staphylococcal biofilm biology is the multitude of adherence and accumulation molecules that are used to form functional biofilms. Two recent reports found that both *S. aureus* and *S. epidermidis* clinical isolates have the ability to alternate between PIA/PNAG and proteinaceous biofilms *(6,7)*. These data suggest that staphylococci with particular accumulation molecules are selected under certain conditions/niches. Further investigation of biofilm development and maturation should yield novel antimicrobial therapies effective against all aspects of biofilm development (e.g., attachment, accumulation, maturation, and dispersion).

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CHAPTER 32

Streptococci

Kent B. Crossley

Microorganisms of the genus *Streptococcus* were a major cause of healthcare-associated infection in the preantibiotic era. During the last half-century, they have been associated with occasional outbreaks of infection in hospitals.

The most frequent streptococcal species encountered as causes of healthcare-associated infections are group A β-hemolytic streptococci (*Streptococcus pyogenes*) (GABHS), group B β-hemolytic streptococci (*Streptococcus agalactiae*) (GBS), and *Streptococcus pneumoniae*. This chapter discusses healthcare-associated infections caused by these microorganisms and by other streptococci (e.g., group C and G streptococci). Healthcare-associated infections caused by enterococci are considered in Chapter 33.

Streptococci were first described in material recovered from wound infections by Billroth in 1874 and 5 years later by Pasteur in the blood of a patient with puerperal sepsis *(1)*. Until the introduction of sulfonamides, streptococci (particularly GABHS) were common causes of healthcare-associated infection. Puerperal sepsis was a major concern in the first third of the 20th century *(2)*. The mortality rate from bacteremic group A streptococcal infections at Boston City Hospital in the 1930s was 72% *(3)*.

Although antimicrobials have markedly reduced the frequency of these infections, streptococci continue to cause healthcare-associated disease. In a recent study of bloodstream infections, 10.3% were caused by Streptococci. *S. pneumoniae* accounted for half followed by GABHS and viridans Streptococci in decreasing frequency *(4)*.

GROUP A β-HEMOLYTIC STREPTOCOCCI

GABHS are relatively uncommon causes of healthcare-associated infection *(5)*. A review of invasive GABHS infections in Ontario between 1992 and 2000 found that 12.4% were healthcare-associated *(6)*. Surgical site and postpartum infections accounted for two-thirds of these cases. Interestingly, 70% of the hospital outbreaks involved nonsurgical, nonobstetric patients (7). Of severe cases of GABHS disease in Europe in 2003 to 2004, 4.3% were noted to be healthcare-associated (8). GABHS tend to cause small outbreaks of burn wound, puerperal, and neonatal infection that persist and that are difficult to evaluate and control.

GABHS may be serogrouped on the basis of protein antigens, designated as M and T antigens. For the last decade, sequencing of the *emm* gene, which specifies filamentous M protein, has been more widely used *(9)*. This method has also been used for large population-based studies *(10)*. Random amplified polymorphic DNA (RAPD) and pulse field gel electrophoresis are also occasionally used *(11)*.

Surgical Site Infection and the Epidemiology of GABHS Infection

GABHS are common causes of community-acquired pharyngitis and skin infection. These microorganisms may also be carried in the throat, on the skin, and in the rectum and vagina of asymptomatic people *(12–15)*. Somewhat <1% of normal individuals have positive anal or vaginal cultures for group A streptococci *(14,16)*. Anal carriage in children with group A β-hemolytic streptococcal pharyngitis appears to be somewhat more frequent; in one study, 6% of children with documented GABHS pharyngitis had the same microorganisms recovered from anal swabs *(13)*.

Wu et al. *(12)* reported that 12.3% to 18.4% of hospital employees with pharyngitis had throat cultures positive for GABHS. It is curious that, despite frequent carriage of this microorganism in the respiratory tract of healthcare workers, very little healthcare-associated transmission from this source has been documented. Only five small outbreaks of infections appear to be directly the result of pharyngeal carriage of GABHS *(17–21)*. In one of these outbreaks, the same strain that infected the patients and an anesthesiologist was also recovered from a member of the physician's family *(17)*.

Although GABHS may be carried on unbroken skin *(15)*, outbreaks resulting from cutaneous sources in healthcare workers have primarily been traced to individuals with clinically evident infection. Bisno et al. *(22)* described a patient who developed GABHS bacteremia from an intravascular catheter inserted by a physician who had an identical *Streptococcus* isolated from a healing wound on the dorsum of his hand. Mastro et al. *(23)* reported an outbreak of 20 postoperative surgical site infections that occurred over 40 months. This outbreak was eventually traced to an operating room technician who had the identical type of GABHS cultured from psoriatic lesions on his scalp. This individual worked in the operating rooms only before operations were performed.

Asymptomatic rectal or vaginal carriage of GABHS is the most commonly reported source of outbreaks of healthcare-associated surgical site infection. Schaffner et al. *(24)* described an outbreak that resulted from anal carriage of streptococci by an anesthesiologist. His throat culture was negative, but an M nontypeable group A *Streptococcus* similar to that recovered from nine patients with infection was cultured from an anal swab. McKee et al. *(25)* reported an outbreak of 11 cases of infection associated with a medical attendant who was a rectal carrier. The same microorganism was also cultured from two of four family members. In this study, after the carrier exercised in an 8-ft by 11-ft examining room, settle plates yielded GABHS. A similar outbreak involving four patients was reported by Richman et al. *(26)* and resulted from carriage by a surgeon. Kolmos et al. *(21)*, in a review of surgical site infections causally tied to healthcare workers, noted that anal carriage appeared to be associated with rectal ulcers, hemorrhoids, and other rectal pathology.

Viglionese et al. *(27)* described an outbreak of postpartum infections traced to an obstetrician who was an anal carrier of GABHS. Of 34 patients delivered vaginally by this physician, 6 (18%) were infected. The obstetrician was treated with penicillin, rifampin, and hexachlorophene; surveillance cultures were negative 1 week, 1 month, and 3 months later. Subsequently, however, four additional cases occurred 14 months after the end of his treatment, and he was again found to be colonized with the same microorganism. One additional case occurred during the next 19 months. This is the only published report that suggests recurrent outbreaks might be caused by one healthcare worker who continues to carry or becomes recolonized with the same GABHS. We have had a similar experience with a vaginal carrier of GABHS. After treatment with erythromycin and rifampin, additional infections occurred, and she was found again to be colonized. Some experts recommend use of settle plates as a sensitive method to assess ongoing shedding of GABHS by carriers during an outbreak *(28)*.

Vaginal carriage has been documented as a source of surgical site infections less often than rectal carriage. Berkelman et al. *(29)* reported postoperative surgical site infections that occurred on two occasions, 5 months apart, associated with a nurse with both vaginal and rectal carriage of GABHS. (In this case, the two outbreaks involved serologically different streptococci.) Stamm et al. *(16)* reported another outbreak involving 18 patients. The source was a nurse with vaginal colonization with GABHS.

Based on evidence presented by Berkelman et al. *(29)* and Mastro et al. *(23)*, it seems most likely that aerosolization of GABHS with motion or activity followed by contamination of the surgical site is the usual mode of transmission. In the outbreaks described by Stamm et al. *(16)* and Schaffner et al. *(24)*, cases occurred in operating rooms adjacent to the one in which the source employee worked. Rutishauser et al. *(30)* reported two patients who developed streptococcal toxic shock after exposure to a surgeon who had nasal (but not pharyngeal) GABHS colonization. An outbreak involving three patients (two of whom died) was reported to be associated with a surgeon believed to be colonized with GABHS *(31)*. A recent outbreak of 28 cases of GABHS infection was associated with care from a hospital wound care team. Although vaginal, rectal, and pharyngeal cultures of members of the team were negative, cases recurred a year later and a carrier was then identified *(32)*.

Nearly all of the approximately 20 reported outbreaks of GABHS surgical site infection have been small, relatively chronic, and associated with an infected or colonized healthcare worker who is not immediately identified as the source. Occasional outbreaks not associated with an identified source have been reported. Webster et al. *(33)* described an outbreak of infection in seven patients on a plastic and maxillofacial surgery ward and in one patient on an adjacent psychiatric ward in London. The source of the outbreak was unclear, and it ended with the closure of the unit before its move to a new building.

GABHS may also be recovered from dust in the environment, and it is possible (but unlikely) that microorganisms disseminated by a carrier could contaminate hands or other surfaces and then be transmitted to a patient.

There are several reported outbreaks in which clusters of healthcare employees have acquired GABHS in an outbreak. Ramage et al. *(34)* reported three patients and six nurses who had developed infection; the nurses (three of whom were not cultured) all had developed pharyngitis. Kakis et al. (35) described transmission of the identical GABHS strain to 24 healthcare workers. Transmission occurred within 25 hours following exposure to this individual, and all 24 healthcare workers developed symptoms of pharyngitis within 4 days of contact with the source patient.

Two recent reports document transmission from a patient with pneumonia to two nurses (36) and from a patient with necrotizing fasciitis to a respiratory therapist who developed pneumonia and toxic shock syndrome *(37)*. A 2006 report noted transmission from a patient with necrotizing fasciitis to two operating room staff; both developed pharyngitis *(38)*. The last two papers recommended more careful infection control precautions when caring for patients with large open wounds infected with GABHS.

Although a very uncommon event, foodborne GABHS illness may occur. A recent Japanese report described an outbreak among students at a university hospital. After eating boxed lunches, some 65% of the group had GABHS isolated from a throat culture (39).

Burn Wound Infection

GABHS were important pathogens in burn units before the introduction of routine penicillin prophylaxis for patients with thermal injuries. They continue to cause occasional burn wound infections and outbreaks.

In 1984, Whitby et al. *(40)* reported an outbreak that began in a burn center and eventually spread to involve an intensive care unit in an associated hospital. Of the eight patients in the burn unit who were colonized with GABHS, two developed clinical evidence of infection and one additional patient became bacteremic. The outbreak apparently resulted from admission of a patient who carried GABHS in his pharynx. Burnett et al. *(41)* described an outbreak involving four patients, six relatives of the index case, and four staff members in Sheffield. The source was a child with burns who had streptococcal pharyngitis. GABHS infection developed in four nurses (cellulitis in two, a facial pustule and an infected whitlow in one each). The outbreak was

controlled by treatment with penicillin V. In the index case, the burn wounds did not clear with oral antibiotic therapy alone but were cured after mupirocin was applied to the burn wounds. The authors believed that the use of short-sleeved isolation gowns was related to the occurrence of the lesions on the forearms of two of the nurses. Allen and Ridgway *(42)* reported a small outbreak of *S. pyogenes* infection in a burn unit in Liverpool. The source was apparently GABHS pharyngeal colonization in a patient admitted to the burn unit. The outbreak persisted despite treatment of cases and careful hand washing. Prophylaxis of all uninfected patients on the unit and all new admissions with penicillin V, 500 mg each day, terminated the outbreak.

Two papers have questioned the need for prophylaxis of GABHS in patients with burn wound infection. Sheridan et al. compared two cohorts of children (treated in 1992–1994 and 1995–1997, respectively) with and without penicillin prophylaxis *(43)*. There was no difference in the frequency of GABHS infection during the two time periods. Bang and others did a similar study and reached a similar conclusion *(44)*.

Puerperal and Neonatal Infection

The communicable nature of puerperal fever was well understood by 1840 *(45,46)*. The careful observations of Alexander Gordon in Aberdeen and Semmelweis in Vienna made prevention possible *(47)*. Semmelweis noted that an obstetric service staffed by midwives had little puerperal infection. On an adjacent ward, the service run by physicians (who also participated in autopsies on patients who had died) experienced three to five times the number of infections. He also observed that, in hospitals in which obstetric units were distant from autopsy rooms (and here he compared Dublin and Vienna), puerperal infection was uncommon. In May 1847, he introduced chlorine water hand rinses to the first obstetric clinic in Vienna and documented a dramatic decrease in the frequency of puerperal infections *(48)*.

Despite the significant reduction in the occurrence of these infections through hand washing, major outbreaks were relatively common until effective antimicrobials became available *(2)*. Isolated outbreaks of puerperal infection caused by GABHS have continued to occur. Data from the Active Bacterial Core surveillance program from 1995 to 2000 suggest about 220 cases of GABHS postpartum infection occur annually in the United States. Clusters of infections caused by microorganisms of the same *emm* types suggested common source outbreaks occurred (49). Most outbreaks are small (i.e., one or two cases). While postpartum infections account for only about 2% of invasive GABHS infections in the United States, 3.5% of healthy women with GABHS postpartum infections die of their infection (49).

Van Beneden and others recently assessed knowledge of obstetricians and gynecologists about prevention and management of healthcare-associated GABHS infections *(50)*. Of the respondents, >70% were unaware of Centers for Disease Control and Prevention (CDC) recommendations. Most (86%) reported not routinely culturing postpartum infections.

Small outbreaks of infections in newly delivered neonates are also well recognized. Studies published in the last 30 years include an outbreak caused by a tetracycline-resistant strain of GABHS that was isolated from both adults and neonates *(51)*. The outbreak was terminated by closing the implicated ward and administering penicillin prophylaxis or treatment to all of the mothers and infants. Tancer et al. *(52)* reported an outbreak involving 11 infants, 2 postpartum mothers, 3 nurses, and another hospital employee. This outbreak was temporally related to episodes of pharyngitis in a newly delivered mother and an elevator operator in the maternity wing of the hospital. Neither of these individuals was cultured. Ogden and Amstey *(53)* described five patients with puerperal GABHS infection. These cases were characteristic of the clinical presentation of puerperal GABHS infection. All of the mothers experienced uterine tenderness and then developed fever spikes associated with recovery of these microorganisms from the lochia. McGregor et al. *(54)* reported a similar-sized outbreak. A labor room nurse had mild eczema on her hands, and these lesions grew GABHS and *Staphylococcus aureus*. The microorganism was serologically identical to that recovered from the patients. In two studies, evidence has suggested that outbreaks were related to contamination of inanimate objects. In one, a handheld showerhead was seen as a possible route of transmission; in the other, use of a communal bidet was implicated *(55,56)*. GABHS were shown by Claesson and Claesson *(55)* to remain viable on a metal surface for more than 9 days.

Outbreaks of GABHS infection also have involved neonates. In these episodes, microorganisms have primarily contaminated the umbilicus. Transmission between infants has apparently occurred with nursing care. In the two outbreaks described by Geil et al. *(57)*, penicillin was administered to all of the infants in the nursery on both occasions. This regimen was successful in the first of their two outbreaks. However, in the second outbreak, it was not successful without the additional application of bacitracin ointment to the umbilical stumps of the infants. Bygdeman et al. *(58)* reported an outbreak in Stockholm in which 67% of infants had umbilical colonization with GABHS. Pharyngitis was documented among family members of neonates. Five of sixty-nine mothers who had nose and throat cultures for GABHS yielded this microorganism. Presumably, this outbreak resulted from introduction of an epidemiologically virulent strain by a mother or healthcare worker. Transmission at the time of delivery could also have been responsible, although the authors did not perform vaginal or rectal cultures.

An outbreak described by Isenberg et al. *(59)* involved 10 newborn infants over a 2-month period. Nineteen percent of the infants in the nursery were found to be carriers of streptococci. Again, umbilical infection was most frequent. Only 1 of the 10 infected infants had GABHS isolated from throat cultures.

Infections Associated with Nursing Homes

GABHS has been reported to cause outbreaks of infection in various healthcare settings notably in facilities for the elderly *(60–62)*. Over the last 20 years, a number of outbreaks of GABHS infections have been reported in long-term care units (LTCF) in the United States. These reports have occurred during a period in which GABHS disease has been caused by strains of apparent increasing virulence *(63,64)*.

The CDC described outbreaks in four nursing homes during the winter of 1989 to 1990, each in a different state *(65)*. Infection occurred in 18 residents, with slightly over half [(10 of 18 (56%)] of the residents dying. Pneumonia and cutaneous infection were most common. Culture surveys to identify pharyngeal carriage in each of the four nursing homes revealed that 11 of 312 residents (3.5%) and 4 of 297 staff members (1%) had asymptomatic pharyngeal carriage of GABHS. These isolates were found to be the same serotype as the strains causing infection in each of the homes. The outbreaks were controlled following antimicrobial prophylaxis or therapy (Fig. 32-1).

Data about long-term care facility (LTCF) associated GABHS infection from the Active Bacterial Core surveillance program from 1998 to 2003 were recently reviewed (66). Invasive GABHS infections were six times more common among LTCF residents when compared with community-living elderly. Death was also 1.5 times more frequent among the LTCF residents. Bacteremia without a focus, pneumonia, and cellulitis were the most common infections in both groups of patients.

A review of invasive GABHS infection in Minnesota for the years 1995 to 2006 found that 7% of cases occurred in nursing home residents. Of the 134 cases, 34 were part of 13 clusters of infection (67). In two of these outbreaks, 2.7% and 6.2% of throat cultures from staff grew GABHS. In the same facilities, 5.9% and 4.5% of throat cultures of residents were positive. Carriage rates documented in a Georgia outbreak were 9% among staff and 10% among residents (68).

A more recent LTCF outbreak in Georgia involved six cases that occurred in a 104-bed facility in March and April 2004. As also documented in the other Georgia outbreak, presence of nonintact skin was associated with this cluster. Although 16.5% of residents carried the implicated strain, only 2.4% of employees were colonized with this microorganism. These authors suggested the importance of training both employees and visitors in hand hygiene and infection control *(69)*.

Another outbreak occurred in a Nevada nursing home in late 2003 *(70)*. The authors reported that about a third of employees did not always wash their hands between patient contacts.

Schwartz and Ussery *(71)* reviewed reports to the CDC of invasive GABHS infections in nursing homes and described five other outbreaks that were primarily associated with noninvasive infection. Outbreaks of noninvasive disease tended to last longer, were associated with more cases, and characteristically involved patients who were more physically impaired than those infected in the invasive outbreaks.

In all of these nursing home outbreaks, there was no clear proof that healthcare workers were sources of the microorganism. (The positive pharyngeal cultures suggest possible introduction of these microorganisms, but obviously the healthcare workers might have been colonized by exposure to the nursing home patients.) In two of the nursing home outbreaks investigated by the CDC, extensive environmental culturing yielded only one positive culture for GABHS. This would suggest that these microorganisms are uncommonly transmitted by fomites *(65)*.

Critical Care Units

Several outbreaks of GABHS have been described in intensive care units in teaching hospitals. In a review of clusters of GABHS, Schwartz et al. *(72)* describe family and healthcare-associated clusters and outbreaks within nursing homes. All five healthcare-associated clusters reported to the CDC occurred in intensive care units. The index patient in each had streptococcal toxic shock syndrome.

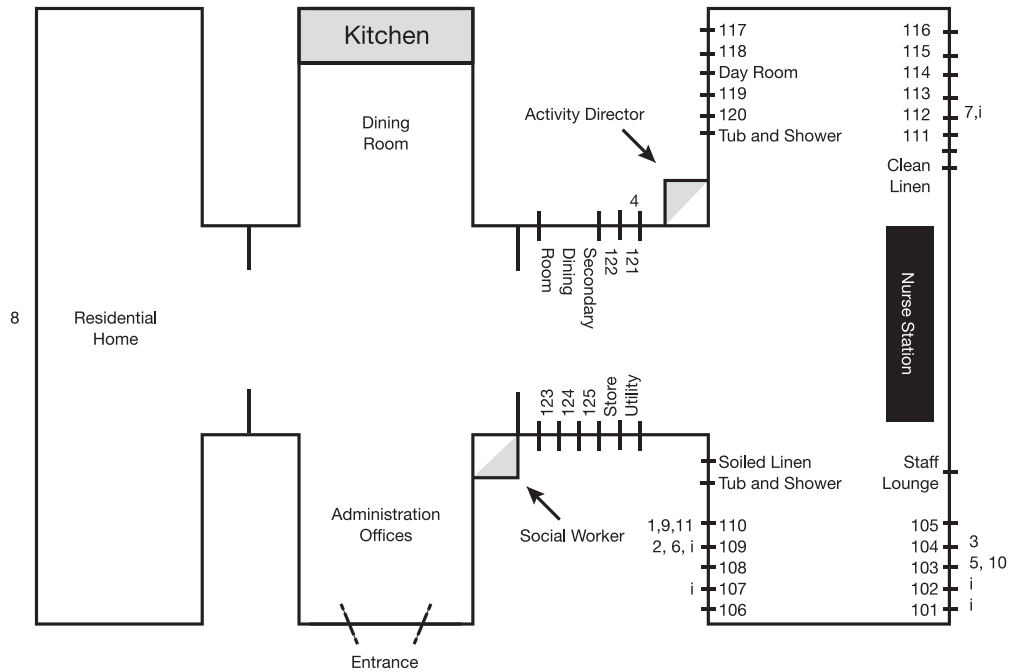

FIGURE 32-1 Distribution of cases of GABHS infection in a North Carolina nursing home. Spatial clustering of infections in one wing of the nursing home is evident. (Adapted from Auerbach SB, Schwartz B, Williams D, et al. Outbreak of invasive group A streptococcal infections in a nursing home. Lessons on prevention and control. *Arch Intern Med* 1992;152:1017–1022.)

Types of infections included cellulitis, paronychia, and pharyngitis. In three of the four outbreaks in which the causal microorganisms were typed, a serotype M1 strain was identified. This serotype has often been associated with invasive infection and the streptococcal toxic shock syndrome *(73,74)*.

Lannigan et al. *(75)* described a cluster of five cases that followed the admission of a patient with necrotizing fasciitis to a Canadian hospital. The microorganism was serotype M1. Two nurses developed cellulitis (superimposed on underlying dermatitis), and three patients had GABHS isolated from endotracheal secretions. Both of the isolates from the nurses and one of the three isolates from endotracheal secretions were the same M and T type as the index patient's microorganism; in two of the patients, sputum isolates were not typed. Transmission by contamination of the nurses' hands seemed most likely. A similar outbreak, involving two patients with isolates of the same M and T type, occurred following admission of a patient with facial cellulitis to an intensive care unit *(76)*. The two patients who acquired the microorganism had endotracheal tubes in place and developed pneumonia and bacteremia.

A recent outbreak involving two healthcare workers that developed febrile pharyngitis was described by Chandler et al. *(38)*. Both individuals had prolonged contact with the open wound of a patient with GABHS pharyngitis and necrotizing fasciitis in an operating room.

Control of Infections in Hospitals and Long-Term Care

Whether a GABHS outbreak occurs in an acute care hospital or a nursing home (and no matter the types of infection), much of the process of evaluation and control is the same (Table 32-1). Most outbreaks of GABHS are small; a single case that is apparently healthcare-associated should warrant an investigation.

After developing appropriate case definitions, determining the time course of the outbreak, and examining basic epidemiologic data, it is appropriate to look for patients or healthcare workers who might be carrying GABHS. Rectal and/or vaginal carriage is at least as frequent as pharyngeal carriage. Use of settle plates may be very helpful in determining if colonized staff continued to shed microorganisms *(28)*. Penicillin alone has not been effective in eliminating pharyngeal, rectal, or vaginal colonization in a number of carriers. Recommendations for chemoprophylaxis from CDC are summarized in Table 32-2 (77). (See also Chapter 8.)

Prompt culturing and treatment of individuals who have clinical manifestations of streptococcal infection is appropriate. Although penicillin remains uniformly effective against GABHS, resistance to alternative agents (e.g., the macrolides or tetracycline) occurs in 10% to 15% of isolates. Before erythromycin is used in place of penicillin to treat a carrier or for prophylaxis, susceptibility of the isolate to this drug should be determined. In some settings—especially in long-term care—antibiotic treatment has been given to all of the patients on a ward or a unit. Although this has not been done in a controlled fashion, outbreaks have usually ended after this intervention *(71,78)*.

In settings other than operating rooms, GABHS infections are occasionally spread by the respiratory route or, more often, by contamination of hands of healthcare workers. Appropriate infection control intervention will, therefore, require emphasis on careful hand washing. Interruption of respiratory spread (by use of a mask) in individuals who are known or suspected to be infected or colonized with GABHS before antibiotic administration is also necessary. In acute care hospitals, these are relatively easy interventions, but in nursing homes, limited hand washing facilities and infection control resources may make it difficult to take appropriate control steps. Most homes do not pay employees when they are ill. Thus, workers with streptococcal pharyngitis or cutaneous infections may often be providing care while they are infectious.

Especially when patients are infected with large numbers of microorganisms (e.g., burn wound infections), control may require awareness of the potential of airborne transmission and the possible (although unlikely) role of fomites. GABHS are very resistant to desiccation, and reports of infections in operating rooms adjacent to those in which colonized surgeons or anesthesiologists have worked indicate that airborne transmission may occur *(24,26,29)*.

TABLE 32-1

Steps in the Management of an Outbreak of GABHS Infection

More than one case of apparent institutionally acquired infection should initiate an outbreak investigation
Develop case definitions (*definite* infection if culture positive for GABHS, *probable* if symptoms and signs compatible with streptococcal infection but no culture done)
Examine susceptibility of isolates and treat cases appropriately
Make an effort to determine likely sources for the outbreak by examining data about contacts between patients and healthcare workers
Attempt to identify healthcare workers and patients who might be sources (by examining for dermatitis and by asking about skin infections and sore throat)
Do vaginal, rectal, and pharyngeal cultures (and cultures of areas of dermatitis) of healthcare workers or patients who may be potential sources
Arrange for serotyping of isolates
Isolate apparent sources and patients until appropriately treated (see text)
Reculture source of outbreak at 1 week and at 1 and 3 months after treatment

GROUP B β-HEMOLYTIC STREPTOCOCCI

S. agalactiae (β-hemolytic streptococci belonging to Lancefield group B) was originally described as a cause of mastitis in cattle *(79)*. Since the mid-1960s, GBS have become a common cause of puerperal and neonatal

TABLE 32-2

Recommended Regimens for Elimination of Asymptomatic Group A Streptococcal Colonization

Drug	*Dosage(s)*	*Comment(s)*
BPG plus rifampin	BPG. 600,000 U i.m. in 1 dose for patients weighing <27 kg or 1,200,000 U i.m. in 1 dose for patients weighing ≥27 kg; rifampin; 20 mg/kg/d po (max. daily dose, 600 mg) in 2 divided doses for 4 d	Not recommended for pregnant women because rifampin is teratogenic in laboratory animals. Because the reliability of oral contraceptives may be affected by rifampin therapy, alternative contraceptive measures should be considered while rifampin is being administered
Clindamycin	20 mg/kg/d po (max. daily dose, 900 mg) in 3 divided doses for 10 d	Preferred for healthcare workers who are rectal carriers of GAS[a]
Azithromycin	12 mg/kg/d po (max. daily dose, 500 mg/d) in a single dose for 5 d	Pregnancy category B: human data reassuring (animal positive) or animal studies show no risk[a]

All regimens are acceptable for nonpregnant persons who are not allergic to penicillin, BPG, benzathine penicillin G; GAS, group A streptococci; max., maximum.

[a]Clindamycin or azithromycin is acceptable for persons allergic to penicillin. If administered to healthcare workers implicated in an outbreak or to their colonized household contacts, susceptibility testing should be performed.

(From The Prevention of Invasive Group A Streptococcal Infections Workshop Participants. Prevention of invasive Group A streptococcal disease among household contacts of case patients and among postpartum and postsurgical patients; recommendations from the CDC. *Clin Infect Dis* 2002;35:950–959.)

infections, some of which are healthcare-associated *(80)*. In one recent population-based study, 22% of GBS infections were healthcare-associated *(81)*. Other studies suggest that about 25% of cases of GBS infections manifest ≥48 hours after hospital admission. Although there are no recent studies, data suggest that between 46% and 70% of *S. agalactiae* bacteremias are healthcare-associated *(82–84)*.

Recently published papers have made it clear that invasive Group B Streptococcal infection is increasingly frequent among nonpregnant adults. This appears to be particularly true of older patients and those with chronic underlying diseases (e.g., diabetes or conditions associated with immunosuppression) (85).

Group B streptococci may be subdivided into nine types on the basis of immunospecific carbohydrates *(86)*. Type I may be further divided into Ia and Ib. Type II is most commonly associated with early-onset disease (usually characterized by meningitis occurring shortly after birth). Type III has been isolated largely from blood cultures of infants taken more than 10 days after birth *(87,88)*. Use of this type of identification has been of help in documenting healthcare-associated transmission of these microorganisms.

Epidemiology and Transmission in the Hospital

Group B streptococci are carried within the gastrointestinal tract *(89,90)* and may colonize the urinary tract and the vagina. Rates of colonization vary depending on the number of cultures, the sites sampled, and whether an enrichment medium is used. Studies suggest that 20% to 25% of women carry GBS genitally during pregnancy *(91,92)*. Among infants, Ferrieri et al. *(93)* showed that the external ear was the most commonly colonized site, with nose, umbilicus, and rectum also often yielding GBS.

It has been repeatedly demonstrated that a significant proportion of infants who are colonized with group B streptococci acquire their microorganisms by healthcare-associated transmission and not from their mothers *(94)*. Easmon et al. *(95)* reported that 36% of infants who acquired GBS did so through healthcare-associated routes. (The other 64% of infants who were colonized in this study acquired infection from their mothers.) These authors and others have noted that healthcare-associated acquisition of this microorganism is associated with colonization at fewer sites and by smaller numbers of microorganisms *(96)*. Presumably, infants contaminated by maternal routes may, thus, be at greater risk for development of infection. Easmon et al. *(95)* showed that at 6 weeks after discharge from the hospital, colonization was present in only 10% of babies who were colonized with GBS during their hospitalization but whose mothers were not. In contrast, infants who were positive for GBS and whose mothers were also culture-positive with the same microorganism during hospitalization were five times as likely to be carriers at 6 weeks (52% vs. 10%).

Easmon et al. *(95)* compared the frequency of transmission in an obstetric unit with that in a neonatal intensive care unit (NICU). In the obstetric unit, 38 of 107 (36%) colonized babies acquired the microorganism from a nonmaternal source versus only 2 of 23 (9%) in the NICU *(95)*. This suggests that more careful attention to infection control measures in the NICU may be associated with a reduction in the frequency of healthcare-associated transmission of GBS *(97)*.

Group B streptococcal carriage among healthcare workers is relatively common *(98)*. In one study, the carriage rate ranged from 6% to 50% in serial prevalence surveys of NICU staff *(95)*. Eighty-eight percent of the carriers had the microorganism recovered from perianal swabs; pharyngeal carriage (or simultaneous carriage at both sites) accounted for the remainder. Despite rather frequent colonization of healthcare workers, documented transmission of identifiable strains of GBS to patients is rare. Easmon et al. *(95)* reported that a pediatrician apparently transmitted a group III phage type 11 strain to four babies on whom he did well-child examinations.

The bulk of cases of group B streptococcal infection acquired in the hospital appear to have occurred because of transient hand contamination of healthcare workers *(99)*. GBS have also been reported to contaminate devices and cause infection in this manner. Davis et al. *(100)* found group B streptococci in pressure transducer domes. The authors were able to correlate colonization with use of intrauterine transducers and documented a reduction in colonization following sterilization of domes after each maternal use.

Puerperal and Neonatal Infections

The frequency of healthcare-associated infections in neonates caused by group B streptococci is unclear. Although reported as a common cause of bacteremia and pneumonia in the past *(101)*, recent studies have not made the same observations. Two European studies of healthcare-associated infections in NICUs (one in Denmark and another in the Netherlands) did not identify any Group B streptococcal infections (102,*103*).

Only a small proportion of newborns colonized with GBS will develop clinical infection. Two syndromes in neonates have been associated with GBS infection. One is an infection of sudden onset developing within the first few days of life (early onset) and characterized by meningitis or pneumonia, often with bacteremia. The mortality rate is high, and serious sequelae in survivors of central nervous system disease are common. All three of the major serogroups are recovered with approximately equal frequency. Important risk factors associated with this syndrome include premature labor and prolonged rupture of membranes *(104)*.

The other type of neonatal infection occurs characteristically 3 to 4 weeks after birth (late onset) and is associated with a lower mortality rate. Meningitis is the most common manifestation, and sequelae are often frequent and serious. Approximately 90% of cases of late-onset disease are caused by type III microorganisms.

Although GBS neonatal infection is relatively common, recognizable outbreaks are not often described. In part, this must be because of the difficulties in distinguishing maternally acquired from healthcare-associated disease. Macfarquhar et al. (105) described an epidemic of late-onset infection occurring in five infants in an NICU. No nursery personnel carried the same types as was recovered from the patients.

In adults, GBS infections may be encountered in women following delivery. Surgical site infections in women who have had a Cesarean section and endometritis are most common. Evidence suggests that these infections are particularly common in immunocompromised women *(106)*.

Group B streptococci may also be encountered as causes of healthcare-associated urinary tract infection, pneumonia, or meningitis. GBS have been associated with intravenous line infection and have been described as the cause of a small outbreak of infections associated with arthroscopy *(107)*. The exact route of infection in this outbreak was unclear. GBS infection has been reported following cardiac catheterization and, in the one case reported, was felt to be associated with multiple puncture sites made to gain vascular access *(108)*. Burn wound infection has also occurred *(109)* as has hemodialysis catheter–related infection *(110)*.

One recent study has documented a series of Group B streptococcal prosthetic hip infections. Thirty infections were reported; 27 were thought to have been hematogenous. Treatment failure was noted to be frequent because of the ages and underlying diseases of the infected patients (*111*,112).

The most serious GBS infections are acquired maternally. For this reason, extensive efforts have been made during the past 25 years to reduce or eliminate acquisition of GBS at the time of delivery. The most popular strategy employs screening cultures and subsequent administration of antibiotics such as ampicillin during labor (113). Antibiotic administration is especially indicated in women who are at high risk for serious GBS infection or for delivering a child who is likely to be infected *(98)*. Data from the CDC suggest that a significant decline in early-onset GBS disease has occurred in recent years *(114)*.

Healthcare-associated acquisition of GBS infection is primarily a result of transmission on the hands of healthcare workers, enabling microorganisms to be spread between infected mothers or infants and other mothers or neonates. Thus, hand washing is perhaps the most important mechanism for preventing transmission of this microorganism within the hospital (see also Chapter 52).

OTHER HEALTHCARE-ASSOCIATED (NONENTEROCOCCAL) STREPTOCOCCAL INFECTIONS

Pneumococci

S. pneumoniae is a well-recognized cause of healthcare-associated infection. The first probable outbreak was described in 1903 *(115)*. A recent analysis examined the etiology of pneumonia as reflected in a large US database with information from some 59 hospitals for the period between January 1, 2002 and December 31, 2003 (116). The paper reported that 16.6% of community-acquired pneumonia was caused by *S. pneumonia*; 5.8%, 3.1%, and 5.5% of pneumococcal pneumonia cases were classified as ventilator-associated, hospital-acquired, and healthcare-associated, respectively, in origin.

A study compared 37 patients with healthcare-associated pneumococcal bacteremia (first positive blood culture performed >72 hours after admission in a patient who did not have a clinical syndrome compatible with infection on admission) with controls. Respiratory and hematologic malignancy, anemia, chronic obstructive pulmonary disease (COPD), and coronary artery disease were significantly associated with healthcare-associated pneumococcal bacteremia. There was also a strong association with death within 7 days of the date of the initial blood culture; the mortality rate was 40.5% compared with 1.2% for controls *(117)*.

Recent papers about healthcare-associated *S. pneumoniae* have emphasized the place of this microorganism as a cause of infection in compromised patients. An 8-year review of pneumococcal bacteremia from two large Spanish teaching hospitals found that 10.6% of cases were healthcare-associated. Most patients had significant underlying illness to include malignancy, COPD, heart

failure, renal failure, cirrhosis, and HIV infection *(118)*. Pneumonia was the primary infection in 70% of these patients. Nearly half of these bacteremic patients died. In a cancer center, 16/135 episodes of pneumococcal bacteremia were healthcare-associated (119). Pneumococcal pneumonia and bacteremia have also been recently noted to occur on occasion in burn patients *(120)*. A recent study of healthcare-associated bacterial pneumonia in HIV infected patients in Milan reported *S. pneumoniae* accounted for 21% of cases and was exceeded in frequency by only *Pseudomonas aeruginosa* and *S. aureus* (121).

Changes in the prevalence of *S. pneumoniae* serotypes and antibiotic resistance patterns are continuing to evolve both in the community and in the healthcare settings (122,123). Drug-resistant pneumococci were recovered from patients with healthcare-associated pneumonia more often than with community-acquired pneumonia in a study from Barcelona *(124)*. In a study that examined patients with levofloxacin-resistant *S. pneumoniae*, two-thirds were healthcare-associated. Age, nursing home residence, COPD, number of hospitalizations, and exposure to fluoroquinolones correlated with infection or colonization with the resistant pneumococcal strains *(125)*.

Fluoroquinolone-resistant isolates of *S. pneumoniae* have been documented as causes of at least two difficult-to-eradicate outbreaks of infection in long-term care facilities *(126,127)*. These microorganisms are significantly more often recovered from residents of long-term care units than from community-living elderly. In a nursing home outbreak of multidrug-resistant pneumococci, 17/74 (23%) of asymptomatic residents and 2/69 (3%) employees had nasopharyngeal carriage of these microorganisms *(128)*. Recent use of antibiotics was associated with both nasopharyngeal colonization and the development of clinical disease. In another study, more than 5 days of therapy with an oral β-lactam antibiotic in low dose has been found to be significantly associated with nasal carriage of resistant pneumococci *(129)*. Prolonged outbreaks have also been described in acute care hospitals. In the largest of these studies, 36 patients had the same strain of antibiotic-resistant *S. pneumoniae* cultured in an outbreak that persisted for 2 years. The patients were elderly and 89% had COPD. The outbreak ended after patients were treated with ceftriaxone and rifampin *(130)*.

Nursing home outbreaks caused by both antibiotic-susceptible and multidrug-resistant strains of *S. pneumoniae* are well documented *(128,131)*. Immunization programs and use of prophylactic antibiotics have usually effectively terminated these episodes. This reinforces the need for widespread routine immunization with pneumococcal vaccine among the institutionalized elderly.

Primary methods of prevention of healthcare-associated pneumococcal infection should include immunization of susceptible individuals *(132)*. Careful hand washing is also needed. Transmission of pneumococci by contaminated respiratory therapy equipment has been documented, and appropriate disinfection is needed *(133)*. A healthcare-associated central venous line infection in an infant also has been described *(134)*. In both acute care hospitals and long-term care facilities, recent use of antibiotics has been associated with development of clinical disease.

Miscellaneous Microorganisms

Group C and G Streptococci Streptococci belonging to Lancefield group C and group G may be associated with pharyngitis, pneumonia, and cellulitis. The microorganisms are often β-hemolytic and may be confused with Lancefield group A streptococci *(135,136)*. Both Group C and Group G streptococci are usually speciated as *Streptococcus dysgalactiae* subspecies equisimilis. Some streptococci that are in these Lancefield groups may be strains of *Streptococcus anginosus* (137).

Group C streptococci have been recognized as causes of puerperal infection and of surgical site infection *(138)*. In an outbreak of two postoperative surgical site infections, a surgeon was found to carry the microorganism in his nose and rectum. Administration of topical bacitracin and orally administered penicillin and vancomycin ended the carrier state. This outbreak shares many characteristics with outbreaks of group A streptococcal infection. Teare et al. *(139)* described an outbreak of 33 cases of puerperal infection in three hospitals in Britain caused by group C streptococci. Environmental contamination was documented. The outbreak strain carried M protein antigen.

Efstratiou *(140)* reported outbreaks of infections noted in a laboratory-based study of 749 strains of group C streptococci (*Streptococcus equisimilis*) and 2,348 strains of group G streptococci that were referred to the public health laboratory at Colindale, United Kingdom, over a 6-year period. Ten outbreaks were reported (Table 32-3). These included pharyngitis, cutaneous infection, and puerperal sepsis. Except for pharyngitis, all of these clusters were in hospitals or nursing homes (most pharyngitis outbreaks occurred in schools).

Group G streptococci were much more frequent causes of outbreaks. Forty-one institutions in Great Britain reported outbreaks in the 6-year period. Group G streptococci were associated with outbreaks in three burn units, where they were found to occasionally colonize the nose and pharynx of staff members and were isolated from the environment. Most outbreaks of group G streptococci reported in this study involved skin and soft tissue. Twelve puerperal outbreaks were reported; in two hospitals, the implicated serotype was isolated from bath water, toilet seats, and showers in the maternity ward. In each of the reports of puerperal fever caused by group G streptococci, none of the babies born to infected mothers had invasive disease. Haynes et al. *(141)* reported an outbreak of puerperal fever among 15 mothers that was associated with contamination of automated douches. Although group G streptococci may be recovered from the pharynx of up to 25% of normal individuals *(135)*, group C streptococci also may be recovered from a few normal individuals (3%) *(142)*. Group G streptococci appear to be increasingly frequently associated with cellulitis and other skin and soft tissue infection (143,*144*).

Streptococcus Viridans *Streptococcus milleri* and other viridans streptococci have become important causes of infection in immunocompromised patients in recent years. These microorganisms have been associated with bacteremia, endocarditis, cellulitis, abscesses (subcutaneous, intra-abdominal, and intracranial), and other infections *(145)*. Seven of eighteen bacteremias with *S. milleri* in

TABLE 32-3

Presumptive Healthcare-Associated Outbreaks of Group C and Group G Streptococci in A 6-Year Period[a]

Location	*Source*	*Number of Isolates*	*T-type*
Group C			
Pharyngitis			
Hospital A	Throat (staff)		
	Foodborne	146	204
Skin sepsis			
Hospital B—ward	Skin	4	PT1058
Hospital C—geriatric ward	Pressure sores	3	305
Hospital D—burn unit patients	Skin	13	21
—burn unit staff	Throat	3	
Puerperal sepsis			
Hospital E—maternity unit patients	Vagina	29	204
—maternity unit staff	Throat	8	204
Group G			
Skin sepsis			
22 outbreaks	Skin, wounds, ulcers	119	Varied
Puerperal infection			
12 outbreaks	Perineum, throat, vagina	104	Varied

[a]Outbreaks are presumptive, and no detailed epidemiologic data are provided.
(From Efstratiou A. Outbreaks of human infection caused by pyogenic streptococci of Lancefield groups C and G. *J Med Microbiol* 1989;29:207–219, with permission.)

one recent study were healthcare-associated *(146)*. Other studies do not report the proportion of cases that were healthcare-associated. Two recent papers stress a relationship to stem cell transplantation and to the administration of cytosine arabinoside (147,*148*). It is noteworthy that isolates of *S. viridans* recovered from healthcare-associated bloodstream infection are often antibiotic resistant even when the patient does not have a hematological malignancy *(149)*.

S. viridans has also been reported to cause pseudobacteremia. Church and Bryant *(150)* reported an outbreak in which a phlebotomist did not wear gloves and had eczema involving her hands. Skin scrapings from her hands and fingernails grew this microorganism and contaminated blood cultures.

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CHAPTER 33

Enterococcus Species

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Compared with other Gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pyogenes*, enterococci have been viewed as relatively avirulent, endogenous microorganisms with little potential for human infection. Despite their apparent lack of virulence, enterococci have emerged as important healthcare-associated pathogens (1,2,*3*). The enterococci possess several characteristics that allow them to survive and cause serious infections. They are intrinsically resistant to many commonly used antimicrobial agents, and they have considerable ability to acquire antimicrobial resistance through exchange of genetic elements with other Gram-positive cocci. They are hardy microorganisms and can survive in the environment and on the hands of healthcare personnel. These factors have allowed the enterococci to flourish and spread from patient to patient in healthcare settings (1,2,*3*).

ETIOLOGIES

Microbiologic Features and Taxonomy of Enterococci

Enterococci are catalase-negative, Gram-positive, facultative anaerobic cocci that classically belonged to the Lancefield group D streptococci. In the mid-1980s, they were officially classified, based on DNA–DNA and DNA–RNA homology, into their own genus (2,*4*,5). Their characteristic biochemical features include the ability to grow in the presence of 6.5% NaCl and at extremes of temperature (range of 10–45°C) and pH (up to 9.6). They share the ability to hydrolyze esculin in the presence of 40% bile salts with the remaining members of the group D streptococci. The ability of enterococci to hydrolyze L-pyrrolidonyl β-naphthylamide has been used as part of a rapid screening method for enterococci in the laboratory (2,5). Although other Gram-positive microorganisms (e.g., *Lactococcus, Aerococcus*, *Gemella*, *Leuconostoc*, *Lactobacillus*) may show one or more of the previously listed characteristics, these microorganisms are rarely isolated from clinical infections. Therefore, these classic physiologic tests are still useful for initial identification of enterococci in clinical laboratories (2,5).

There are five recognized groups of enterococci, with a total of 33 species *(4)*. Most species can be identified with conventional techniques using a combination of biochemical and morphologic characteristics, such as motility and pigmentation (2,5). The most clinically important species of enterococci are listed with their distinguishing biochemical features in Table 33-1. *Enterococcus faecalis* remains the major human pathogen, accounting for approximately 60% of clinical isolates of enterococci. *Enterococcus faecium* is the second most commonly isolated species, now accounting for about 30% of enterococcal clinical isolates (2,5). With the emergence of vancomycin resistance, the relative proportion of *E. faecium* in clinical isolates has been increasing. In 2006 to 2007, *E. faecium* represented 46% of enterococcal isolates from healthcare-associated infections (6). *Enterococcus gallinarum*, a motile strain of enterococcus that also exhibits intrinsic vancomycin resistance, has been associated with outbreaks of healthcare-associated infection *(7,8)*.

Typing Methods

Early epidemiologic studies of healthcare-associated enterococcal infections were limited by a lack of typing methods. Biochemical tests and antibiograms were insufficient because enterococci rarely exhibit enough variation to allow for adequate strain differentiation. Total plasmid DNA analysis, with or without restriction enzyme digestion, was used in many studies to type enterococci *(9–11)*. However, these techniques have been uniformly replaced by newer methods for bacterial typing.

Pulsed-field gel electrophoresis (PFGE) or contour-clamped homogeneous electric field electrophoresis of restriction enzyme-digested genomic DNA has been the dominant method used for typing enterococci *(12–15)*. Enterococci have a relatively low guanine plus cytosine content of DNA, which, when digested with *sma*1 (a restriction enzyme seeking G-plus C-rich sequences), yields diverse, easily interpreted patterns. These techniques produce high-resolution, reproducible bands, which allow confident interpretation *(12,14,15)*.

Newer methods of typing for enterococci have recently been applied. Ribotyping is a reproducible means of differentiating enterococcal strains, and automated systems have been developed for rapid typing. However, the reliability of the automated systems in comparison to other typing systems for enterococci has not been determined *(15)*. Amplified fragment length polymorphism has been used

TABLE 33-1

Phenotypic Characteristics of Clinically Significant *Enterococcus* Species

	Mannose	*Sorbose*	*Arginine*	*Arabinose*	*Motility*	*Yellow Pigment*
E. faecalis	+	−	+	−	−	−
E. faecium	+	−	+	+	−	−
E. avium	+	+	−	+	−	−
E. durans	−	−	+	−	−	−
E. gallinarum	+	−	+	+	+	−
E. casseliflavus	+	−	+	+	+	+
E. mundtii	+	−	+	+	−	+
E. pseudoavium	+	+	−	−	−	−
E. raffinosus	+	+	−	−	−	−
E. malodoratus	+	+	−	−	−	−

(From Teixeira LM, Carvalho MG, Merquior VL, et al. Recent approaches on the taxonomy of the enterococci and some related microorganisms. *Adv Exp Med Biol* 1997;418:379–400; Facklam RR, Sahm DF, Teixeira LM, Enteroccus. In: Murray PR, ed. *Manual of clinical microbiology*. Washington, DC: American Society for Microbiology, 1999: 297–305, with permission.)

as a newer method of typing enterococci. This method is fast, reproducible, and appears to discriminate enterococcal strains well enough for the recognition of hospital outbreaks *(16)*. Recently, a multilocus sequence typing scheme has been developed and compared with PFGE. This method appears promising for use in global epidemiologic analysis of *E. faecalis* and *E. faecium*, in addition to use in local outbreak investigations *(14)*.

ANTIMICROBIAL RESISTANCE IN ENTEROCOCCI

Enterococcal infections are a therapeutic challenge because of the intrinsic resistance of enterococci to many antimicrobials. In addition to their intrinsic resistance, enterococci have a remarkable ability to acquire antimicrobial resistance genes (2,*17*). Enterococci with high-level resistance (HLR) to multiple antimicrobials have become endemic in many institutions *(18–20)*. As humans enter an era of decreased antimicrobial effectiveness, it becomes imperative to develop appropriate infection control procedures to decrease the transmission of these microorganisms in healthcare settings.

Intrinsic Resistance

Most enterococci are inherently resistant to many antimicrobials, as shown in Table 33-2. The gene coding for intrinsic resistance resides on the chromosome and confers resistance to cephalosporins and penicillinase-resistant penicillins, clindamycin, low levels of aminoglycosides, and trimethoprim-sulfamethoxazole (TMP-SMX) (1,2,*3*,21). Most clinical isolates of enterococci are inherently tolerant to all β-lactams and glycopeptides and are typically not killed by concentrations of antimicrobials many times higher than the minimum inhibitory concentration (MIC). The relative resistance to β-lactam antimicrobials is due to low affinity of the penicillin-binding proteins of enterococci for these antimicrobials. The MICs of *E. faecalis* to penicillin average 2 to 8 μg/mL, which is approximately

TABLE 33-2

Characteristics of Antimicrobial Resistance in Enterococci

Antimicrobial	*Characteristic*
Intrinsic resistance	
Penicillins	Relative resistance, tolerance
Cephalosporins	Diminished affinity for PBPs 4, 5, 6
Clindamycin	Low-level resistance
Aminoglycosides	Low-level resistance
Trimethoprim/ sulfamethoxazole	*In vivo* resistance
Quinupristin/dalfopristin (*E. faecalis*)	Possible efflux
Acquired resistance	
Macrolides	Transposon, plasmid-mediated
Tetracyclines	Transposon, plasmid-mediated
Lincosamides	High-level, plasmid or transposon
Chloramphenicol	Transferable acetyltransferase activity
Aminoglycosides	High-level, plasmid or transposon
Penicillin (without β-lactamase)	Altered PBPs
Penicillin (with β-lactamase)	Transposon, plasmid-mediated
Vancomycin	Plasmid- or chromosome-mediated
Quinolones	Plasmid-mediated
Quinupristin/dalfopristin (*E. faecium*)	Drug inactivation, ribosomal mutation, efflux
Linezolid	Ribosomal mutation
Daptomycin	Mechanisms not yet fully understood
Tigecycline	Mechanisms not yet fully understood

PBP, penicillin-binding protein.

10 to 100 times greater than those for most streptococci (21). *E. faecium* strains are even more resistant, with MICs of 16 to 32 μg/mL and higher (21).

In addition, all enterococci exhibit resistance to low concentrations of aminoglycosides (MIC = 8–64 μg/mL for gentamicin). This resistance trait appears to be due to a decreased uptake of the drug. Even in the presence of low-level aminoglycoside resistance, aminoglycosides may be used in combination with a cell-wall active agent (i.e., a penicillin or vancomycin) to achieve synergistic killing (21,*22*). The combination of an aminoglycoside with a penicillin or vancomycin is required for reliable bactericidal therapy for the treatment of serious enterococcal infections (21,*22*).

Enterococci are intrinsically resistant to TMP-SMX because they are able to use exogenous folates to bypass the inhibitory effects of TMP-SMX. *In vitro* susceptibility testing is unreliable in enterococci because media used in these tests do not contain thymidine or folates (2). Animal studies confirm that TMP-SMX is ineffective *in vivo* despite apparent *in vitro* susceptibility *(23,24)*.

Acquired Resistance

High-Level Aminoglycoside Resistance HLR to streptomycin and gentamicin was first identified in the 1970s *(25)*. Over the next decade, the prevalence of these resistant strains increased dramatically in diverse geographic areas *(25,26)*. HLR (MICs >2,000 μg/mL) confers resistance to the synergistic killing normally observed with combinations of cell-wall active agents and an aminoglycoside *(25)*.

HLR to aminoglycosides in enterococci occurs primarily through acquisition of genes encoding aminoglycoside-modifying enzymes; these resistance genes are usually found on a transferable plasmid (21). Streptomycin is inactivated by an enzyme that adenylates its 6-hydroxyl position *(25)*. A second mechanism of streptomycin resistance confers HLR (MICs up to 128,000 μg/mL) through ribosomal resistance *(25)*.

HLR to gentamicin in most clinical isolates is mediated by a bifunctional aminoglycoside-modifying enzyme with 6′-acetyltransferase and 2″-phosphotransferase activity. The presence of this enzyme confers HLR to gentamicin, tobramycin, kanamycin, amikacin, sisomicin, and netilmicin *(25)*. The gene encoding for HLR to gentamicin has a DNA sequence homologous to the gene-conferring gentamicin resistance in *S. aureus (26,27)*, and has been localized to transposons found on conjugative plasmids and chromosomes, which has allowed spread to multiple unrelated strains of enterococci *(11,28,29)*. Additional gentamicin resistance genes encoding other 2″-phosphorylating enzymes have been identified in clinical isolates *(26,30)*. Arbekacin may have synergistic activity against enterococci with HLR to aminoglycosides *(31)*.

HLR to gentamicin does not always correlate with HLR to streptomycin; therefore, screening for HLR to both streptomycin and gentamicin is important *(26)*. There are several screening methods currently available, but the disk method and the single-concentration agar plate method are most reliable for detecting high-level aminoglycoside resistance in enterococci and are recommended by the Clinical Laboratory Standards Institute (CLSI) (formerly the National Committee for Clinical Laboratory Standards) *(32)*. Disks containing 120 μg of gentamicin generate a zone of 15 mm or less in strains with HLR to gentamicin. For streptomycin, disks containing 300 μg give rise to zones of 12 mm or less in HLR strains *(7)*. Automated susceptibility testing is now also being used to screen for high-level aminoglycoside resistance in enterococci *(33)*.

β-Lactam Resistance Penicillin resistance in enterococci occurs through two distinct mechanisms (21,*34–36*). The most common mechanism of penicillin resistance occurs primarily in *E. faecium* and correlates with increased amounts of a low affinity penicillin-binding protein (21,*34,35*). A large, multicenter study of enterococcal bloodstream isolates reported that only 12.5% of *E. faecium* isolates were susceptible to penicillin *(37)*. In the United States, ampicillin resistance is highly associated with vancomycin resistance in *E. faecium (37–39)*, but in Sweden an outbreak of ampicillin- and quinolone-resistant *E. faecium* was identified *(40)*. *In vitro* penicillin or ampicillin susceptibility generally predicts susceptibility to imipenem *(41)*. However, imipenem-resistant, ampicillin-sensitive *E. faecium* have been identified *(42)*.

Since 1981, numerous centers have reported β-lactamase-producing strains of enterococci *(10,36,43)*. The β-lactamase gene has been localized to transferable plasmids or to the chromosome in some isolates *(36)*. The β-lactamase gene in enterococci is homologous with the *S. aureus* β-lactamase gene and has features suggesting that it resides on a transposon similar to *S. aureus* transposon Tn4201 *(44)*. Routine susceptibility tests may not reliably detect β-lactamase-producing strains *(43)*. Several β-lactamase tests, including nitrocefin disks, have been used to successfully identify β-lactamase production *(36)*.

Vancomycin Resistance Vancomycin-resistant enterococci (VRE), first detected in Europe in 1988, have increased in prevalence dramatically in the United States (1,*45*,46,47) and worldwide *(48,49)*. There are several phenotypes and genotypes for vancomycin resistance in enterococci, and some of these phenotypes have been studied in detail (Table 33-3). *vanA* and *vanB* are the most predominant phenotypes in clinical isolates of VRE (1,*45*,47). All phenotypes code for alternate biosynthetic pathways that alter the D-ala-D-ala cell wall precursors that normally bind vancomycin. *vanA*, *vanB*, and *vanD* genes code for D-ala-D-lac ligases *(50,51)*, whereas *vanC* and *vanE* genes code for D-ala-D-ser ligases *(52)*.

vanA strains exhibit high-level, inducible resistance (MICs >64 μg/mL) to both vancomycin and teicoplanin *(53)*. The *vanA* trait is carried by a gene cluster located in a transposon, Tn*1546 (54)*. The transposon is usually found on a plasmid, which is transferable to other Gram-positive cocci. This accounts for the presence of *vanA* genes in widely heterogeneous strains of enterococci *(37,55)*. Although *vanA* is usually found in *E. faecium* and *E. faecalis*, it has been identified in *E. gallinarum* and other enterococcal species *(45)*. In addition, there have now been nine reported cases of infection with *vanA*-mediated vancomycin-resistant *S. aureus* in the United States *(56,57)*.

vanB strains have variable resistance to vancomycin (MICs 16 to >1,000 μg/mL) but in general remain susceptible to teicoplanin. The genes that code for *vanB* trait are

TABLE 33-3

Characteristics of Phenotypes of Glycopeptide-Resistant Enterococci

	Phenotype					
Characteristic	***vanA***	***vanB***	***vanC***	***vanD***	***vanE***	***vanG***
Min. inhibitory concentration (μg/mL)						
Vancomycin	64–>1,000	4–>1,000	2–32	16–64	16	12–16
Teicoplanin	16–512	0.5–>32	0.5–1	2–4	0.5	0.5
Ligase activity	D-ala-D-lac	D-ala-D-lac	D-ala-D-ser	D-ala-D-lac	D-ala-D-ser	ND
Genetic	Acquired	Acquired	Intrinsic, chromosomal	Acquired	Acquired	ND
Major *Enterococcus* species	*E. faecium* *E. faecalis* *E. durans* *E. mundtii* *E. avium*	*E. faecalis* *E. faecium*	*E. casseliflavus* *E. gallinarum*	*E. faecium*	*E. faecalis*	*E. faecalis*

ND, not done.

very similar to *vanA* genes, are usually found within large mobile elements located on the chromosome, and can be transferred to other enterococci. The *vanC* phenotype is typically found intrinsically on the chromosome of motile species of enterococci, *E. gallinarum* (*vanC-1*) and *E. casseliflavus* (*vanC-2* and *vanC-3*) *(58–60)*. These strains are moderately resistant to vancomycin (MICs, 8–16 μg/mL) but remain susceptible to teicoplanin. The resistance in these isolates is not inducible or transferable *(58,59)*.

The *vanD* phenotype has constitutive intermediate resistance to vancomycin and low-level resistance to teicoplanin *(51,61)*. *vanE* resistance is nontransferable and confers a low-level resistance phenotype *(62,63)*. The *vanG* phenotype has moderate-level resistance to vancomycin (MIC = 16 μg/mL), has no resistance to teicoplanin, and is negative by polymerase chain reaction (PCR) for *vanA*, *vanB*, *vanC*, or *vanE (64)*. Vancomycin-resistant strains of enterococci that are dependent on vancomycin for growth have been identified from clinical isolates *(65–67)*.

Many laboratories have difficulty detecting vancomycin resistance when the MICs are less than 64 μg/mL *(68)*; however, HLR can be detected more readily *(69)*. The agar screen test using 6 μg/mL of vancomycin in brain–heart infusion agar is a simple, sensitive, confirmatory test and is recommended by CLSI *(7,68)*. Automated susceptibility testing of isolates is also commonly performed *(70)*. Heteroresistance to vancomycin, confirmed by presence of the *vanA* gene by PCR, has been identified recently in a clinical isolate *(71)*. PCR assays have been developed for identification of VRE isolates and are now commonly used *(72)*.

Resistance to Newer Antimicrobials *E. faecalis* is inherently resistant to the combination antimicrobial quinupristin/dalfopristin, with MICs of 4 to 32 μg/mL *(73,74)*. This is thought to be a species characteristic and may be related to an efflux mechanism *(74)*. *E. faecium* does not have inherent resistance, and most strains of *E. faecium* remain susceptible to quinupristin/dalfopristin (75). Mechanisms of resistance to quinupristin/dalfopristin in *E. faecium* include inactivation by enzymes, structural or conformational alterations in ribosomal target binding sites, and efflux of the antimicrobial out of cells (75,*76*).

Linezolid, an oxazolidinone, has activity against most enterococci, including VRE *(77)*. However, linezolid resistance was reported in isolates from 9 of 501 patients treated with linezolid during the manufacturer's compassionate use program and was related to ribosomal mutations *(78)*. Although large prevalence studies reveal near universal susceptibility of enterococci to linezolid *(79)*, healthcare-associated outbreaks of linezolid-resistant strains of VRE have occurred *(18,20)*.

Daptomycin, a new cyclic lipopeptide antimicrobial, also has activity against most enterococci, including VRE *(80)*. Enterococcal isolates have been almost universally susceptible to daptomycin in large surveillance studies *(81,82)*. However, sporadic cases of resistance have been reported in patients with and without prior exposure to daptomycin *(83–86)*. Resistance mechanisms have not been fully elucidated. Proposed mechanisms include decreased ability to adequately disrupt cell membrane potential, physical changes in the bacterial cell wall, protein binding leading to low serum concentrations, and chromosomal mutations *(83,85,86)*.

Tigecycline is a new broad-spectrum glycylcycline antimicrobial that is active against most enterococci, including VRE *(87)*. Tigecycline is closely related to the tetracycline class of antimicrobials but overcomes common resistance mechanisms associated with this class, including efflux pumps and ribosomal protection *(87)*. Thus far, surveillance studies have demonstrated nearly universal susceptibility of enterococci to tigecycline *(88)*. There is one reported case of resistance, in which tigecycline-resistant *E. faecalis* was isolated from the urine of a patient after prolonged therapy with tigecycline *(89)*. The mechanism of resistance was not fully elucidated in this case but was not related to tetracycline-resistance mechanisms.

EPIDEMIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS

Descriptive Epidemiology

The prevalence of enterococci in healthcare-associated infections has increased over the past three decades. In current reports from the National Healthcare Safety Network (NHSN) at the Centers for Disease Control and Prevention (CDC), enterococci rank as the third most common cause of all healthcare-associated infections hospital wide (6). In data from January 2006 through October 2007, enterococci accounted for 16% and 15% of healthcare-associated bloodstream infections (BSIs) and UTIs, respectively, and for 12% of all healthcare-associated infections (6).

At the same time their prevalence has increased, the enterococci have also developed increased antimicrobial resistance. One institution reported its first clinical isolate of high-level gentamicin-resistant enterococci in 1981, but, by 1989, 20% of clinical isolates were high-level gentamicin-resistant and, by 1992, 23% of nonurinary isolates were highly resistant to gentamicin (90). Other institutions noted a similar increase in prevalence of high-level gentamicin-resistant isolates; some centers reported that 50% to 55% of clinical isolates exhibited HLR *(9,91)*. In a recent survey of more than 8,000 enterococcal isolates, 14% to 32% of enterococcal strains were gentamicin resistant, and 30% to 46% were streptomycin resistant, with variations reflected by geographic area *(92)*.

Even more dramatic has been the continued increase in the prevalence of VRE in the United States (6,*45*,46). Between January 2006 and October 2007, the NHSN reported that 36% of enterococcal isolates from healthcare-associated infections were vancomycin resistant (6). *E. faecium* were more frequently vancomycin resistant (79%) compared with *E. faecalis* (7.5%) (6). Rates of VRE vary between geographic areas and institutions *(92)*. Other areas of the world report lower prevalence of VRE than the United States (*45*,46,*92*). Latin America reports 0% to 4% VRE, whereas Europe reports 1% to 3% VRE (*45*,46,*92*). The prevalence of VRE in Canada may have increased in recent years, with VRE accounting for 6.7% of enterococcal isolates in a recent study *(93)*.

Reservoirs

Enterococci are normal inhabitants of the human gastrointestinal tract. *E. faecalis* is found in concentrations of 10^5 to 10^7 colony-forming units (CFUs)/g of feces in 80% of hospitalized patients. *E. faecium* is recovered in smaller amounts in 30% of adult patients (2,*3*,90). Other parts of the gastrointestinal tract such as the oropharynx and hepatobiliary tract may also harbor enterococci (90,*94*). The gastrointestinal tract of hospitalized patients is the major reservoir for resistant enterococci *(10,95–100)*. Rectal colonization was found in 100% of patients with VRE BSI and may persist for years after identification *(100–103)*. Prolonged colonization has been associated with prolonged hospitalization, ICU care, and antimicrobial use *(96,102)*. In addition, higher density colonization by VRE has been associated with use of antianaerobic antimicrobial regimens *(95)*.

Enterococci may also colonize the gastrointestinal tract of healthcare personnel, as illustrated by an outbreak of a β-lactamase-producing enterococcus on an infant/toddler ward, where the resistant strain was isolated from 8 of 33 personnel *(10)*. Healthcare personnel colonization with VRE is uncommon, but a recent study showed that 12 of 228 healthcare personnel carried VRE *(104)*. In addition, identical strains of VRE were identified in household members of two colonized healthcare personnel *(104)*. Antimicrobial therapy may place healthcare personnel at risk for colonization with VRE *(105)*. The significance of colonization of healthcare personnel with VRE in the transmission of VRE has not been defined.

Other major sites of colonization that are reservoirs for enterococci in hospitalized patients include skin, wounds, and chronic pressure ulcers *(101,106)*. In patients with VRE BSI, 86% were found to have VRE colonizing their skin in the inguinal or the antecubital fossa areas *(97)*. Enterococci, when present in wounds, are usually found in mixed culture (2,90). Asymptomatic women may also carry enterococci in high numbers in their vagina, and more than 60% of men in the hospital may carry enterococci in their perineal or meatal areas (2,90,107).

Enterococci are also hardy microorganisms, which allow them to survive well on environmental surfaces *(13,104)*. Resistant enterococci have been cultured from environmental surroundings of infected or colonized patients in many studies *(9,10,100,108–113)*. Heavy contamination of the surrounding environment is more likely to occur when the patient has diarrhea or is incontinent *(100,112,114,115)*. Medical equipment may also become contaminated with resistant enterococci and serve as a reservoir for these microorganisms. In one notable outbreak of infection resulting from VRE, the epidemic strain was cultured from electronic thermometers within the ICU *(116)*. VRE has since been found to contaminate electronic ear thermometers, blood pressure cuffs, patient gowns and linens, fabric seat cushions, beds, bed rails, bedside tables, and commodes *(13,100,109,112,117,118)*. Recent studies showed that ICU patients are more likely to acquire VRE if prior room occupants were VRE-positive, demonstrating the role of environmental contamination in VRE transmission *(113,119)*.

Residents of long-term care facilities may serve as a reservoir for introduction of resistant enterococci into the hospital *(13,106,120)*. Rectal VRE colonization of patients in a single long-term care facility increased from 9% in December 1994 to 22% in January 1996 *(13)*. In another hospital where VRE has become endemic, it was found that 45% of patients admitted to the hospital from long-term care facilities were colonized with VRE *(106)*. VRE colonization at admission was associated with the presence of a pressure ulcer and prior use of antimicrobials *(106)*.

In Europe, VRE colonization of nonhospitalized people was identified in the early 1990s. Evidence suggested that foodborne VRE may lead to human colonization in the community setting *(121,122)*. Avoparcin, a glycopeptide used as a food supplement in animals, was identified as an important factor in the emergence of VRE in the community setting *(121,122)*. Use of avoparcin has now been banned in many countries, but VRE colonization of animals has persisted at lower rates, likely due to horizontal transfer of resistance determinants, environmental contamination, and use of other antimicrobials in animal feed *(123)*. One study demonstrated that persons who ingested meat products contaminated with antimicrobial-resistant

enterococci developed transient intestinal colonization with VRE *(124)*. In the United States, avoparcin has not been approved for use as a food additive; however, resistant enterococci have been found in the community *(125,126)*. In 200 patients admitted to a community hospital, 10 patients were colonized with enterococci with HLR to aminoglycosides, and two patients were colonized with ampicillin-resistant enterococci *(125)*. VRE colonization of outpatients without hospital exposures is rare in the United States *(125–127)*, but person-to-person transmission of VRE has been reported in the household setting *(128,129)*. Virginiamycin, a streptogramin similar to quinupristin/dalfopristin, has been used in animal feed since 1974 in the United States. A large proportion of chicken sold in the United States was contaminated with quinupristin/dalfopristin-resistant enterococci *(130)*. At this point, persons living in the community are not a major reservoir for VRE or other resistant enterococci, but the potential for increased dissemination in the community is concerning.

Modes of Transmission

Early studies suggested that enterococci isolated from sites of infection were from the host's own gastrointestinal tract (107). Since the emergence of antimicrobial resistance and more sophisticated molecular typing tools, numerous studies have shown that person-to-person spread of enterococci is a significant mode of transmission in healthcare settings *(9,10,39,43,91,112,131)*. Zervos et al. *(91)* used total plasmid content and a high-level gentamicin-resistance marker, which was uncommon at that time, to show exogenous acquisition of enterococci. Since the emergence of VRE, the understanding of the spread of enterococci within healthcare settings has become more complete. The most important method of spread of VRE and other resistant enterococci is through transient carriage on the hands of healthcare personnel *(10,13,107,112,132)*. Regional dissemination of VRE has resulted from interfacility transfer of colonized patients *(133,134)*.

Recent studies suggest that the environment may have a role in the transmission of resistant enterococci (*100,108–111,113–117*,135). Medical equipment used on multiple patients should be considered a possible route of patient-to-patient transmission. Resistant enterococci heavily contaminate environmental surfaces in both acute care and extended care facilities *(10,13,91,100)*. It has been shown that hands and gloves of healthcare personnel become contaminated with VRE after contact with patients' environments, suggesting that environmental contamination may be an intermediate step in person-to-person transmission of VRE via healthcare personnel *(136)*.

Risk Factors for Enterococcal Infections

Early studies examining risk factors for the development of enterococcal UTIs identified urinary tract instrumentation or catheterization; other genitourinary pathology; and the previous use of antimicrobials, especially cephalosporins, as significant risk factors (107,*137*). Most patients who became colonized with resistant enterococci had a history of serious underlying illnesses, being bedridden, or having had prior surgery (*9*,90,*91*).

Risk factors for acquisition of VRE include serious underlying disease or debilitation *(138,139)*, organ transplantation *(140–145)*, chronic kidney disease *(138,139,146)*, malignancy *(147,148)*, prolonged hospital stay *(147,149–151)*, intrahospital transfers *(149)*, diarrhea *(118)*, and enteral feedings *(152,153)*. Residence in an ICU setting has been a major risk factor for acquisition of VRE *(147,151)*. However, VRE has increased steadily in frequency in non-ICU settings (154). Recent studies highlight the importance of colonization pressure (defined as the proportion of other patients colonized) or proximity to VRE-colonized patients (including prior room occupants) as significant risk factors for acquisition of VRE *(103,119,152,153,155,156)*. Changes in gastrointestinal function, resulting from either oral medication or gastrointestinal bleeding, may affect the risk of colonization with VRE. A recent retrospective case–control study on the effect of oral medication on acquisition of VRE identified presence of central lines and use of vancomycin or antacids as independent risk factors for VRE colonization *(157)*. Interestingly, gastrointestinal bleeding or use of hydrocodone with acetaminophen protected against colonization (Table 33-4).

TABLE 33-4

Major Risk Factors for Colonization with VRE

Risk Factor	*References*
Underlying disease or debilitation	*(138,139)*
Organ transplantation	*(140–145)*
Chronic kidney disease	*(138,139,146)*
Malignancy	*(147,148)*
Prolonged hospital stay	*(147,149–151)*
Intrahospital transfers	*(149)*
Diarrhea	*(118)*
Enteral feedings	*(152,153)*
Colonization pressure	*(103,152,153,155,156)*
Antimicrobial use	
Multiple antimicrobials	*(151)*
Antianaerobic antimicrobials	*(98,153,157,161,162)*
Vancomycin	*(138,149,158)*
Cephalosporins	*(96,148,149,151,152,163)*

Previous antimicrobial therapy is the most consistent risk factor for colonization with resistant enterococci *(95,139,147–150,152,158,159)*. The acquisition of gentamicin-resistant enterococci has been associated with previous treatment with cephalosporins or aminoglycosides *(9,91)*. Imipenem was found to significantly predispose to acquisition of ampicillin-resistant enterococci *(160)*. VRE colonization has been associated with use of multiple antimicrobials *(151)*, antianaerobic antimicrobials *(98,153,157,161,162)*, vancomycin *(138,149,158)*, and cephalosporins *(96,148,149,151,152,163)*.

PATHOGENESIS OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROCOCCI

Generally, enterococci are human commensals and have minimal pathogenic potential in the normal host. However, in the immunocompromised patient or when invasive

procedures are performed, enterococci are common opportunistic pathogens. The increase in prevalence of enterococci in healthcare-associated infections is more related to the accumulation of antimicrobial resistance than to inherent pathogenicity in enterococci (6,*17*,*164*).

Hemolysin has been identified as a potential virulence factor in enterococci (2,*165*). Patients with BSI caused by hemolytic, gentamicin-resistant *E. faecalis* were shown to have a fivefold increased risk of death compared with patients with nonhemolytic, gentamicin-susceptible strains *(165)*. It is unclear from this study whether the increased mortality was due to the presence of hemolysin or an aminoglycoside-resistant phenotype.

Other potential virulence factors include production of enterococcal surface protein (Esp), aggregation substances (Agg), or gelatinase (2,*17*,*164*,*166*,*167*). One study noted that hemolysin and Agg were found more frequently in blood isolates and isolates from liver transplant recipients, whereas Esp was found more frequently in fecal isolates. The authors speculated that hemolysin and Agg may be associated with infection, whereas Esp is associated with colonization and spread *(167)*. Recently, however, among 398 enterococcal BSI isolates, 64% of isolates produced gelatinase, 32% carried the *esp* gene, and 11% produced hemolysin. There was no association of these putative virulence markers with 14-day mortality *(166)*. More studies will be necessary to further define true virulence factors in enterococci.

CLINICAL MANIFESTATIONS OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROCOCCI

Urinary Tract Infection

In young healthy women, enterococci cause <5% of UTIs. However, in persons who have had urinary catheterization or instrumentation, have urinary tract pathology, or have received antimicrobials, the proportion of UTIs associated with enterococci increases dramatically (6,*137*,*168*,*169*). Morrison and Wenzel *(137)* found an increase in the rate of UTIs caused by enterococci from 12.3 to 32.2 cases per 10,000 patient discharges. According to the most recent data from the NHSN, enterococci are the third most common cause of catheter-associated UTIs, accounting for 15% of such infections (6).

Risk factors for enterococcal UTI are urinary tract instrumentation, catheterization, and genitourinary tract pathology (107,*137*,*169*). The previous use of antimicrobials, especially cephalosporins, has also been associated with enterococcal UTI (*137*,*169*). One study showed a parallel rise in healthcare-associated enterococcal UTI and in cephalosporin use in a single hospital *(137)*. Prior antimicrobial use was found to be more frequent in patients with enterococcal UTI than in controls in a rehabilitation facility with a high rate of enterococcal UTI *(169)*. Little has been published about specific risk factors for VRE UTI.

Early studies suggested that enterococci associated with UTIs were predominantly from the patients' own gastrointestinal tract. Patients found to be colonized with enterococci later developed enterococcal UTI with microorganisms identical to their previously cultured enterococci (107). More recent studies suggest that direct crossinfection is not the predominant source of enterococci in UTIs *(169)*. However, fecal microorganisms of hospitalized patients may be altered through the acquisition or selection of hospital-specific strains *(97,168)*.

The clinical manifestations of UTI caused by enterococci are indistinguishable from those of UTIs caused by other microorganisms. The spectrum of disease ranges from asymptomatic bacteriuria to bacteremic pyelonephritis. Mortality resulting from enterococcal UTI in the absence of BSI is low (see Chapter 20) (107,*137*,*168*,*169*). In a study of 97 evaluable patients with VRE bacteriuria, 37 patients were colonized with VRE, 21 had asymptomatic bacteriuria, and 13 patients had symptomatic UTI. The status of 27 patients was not ascertainable *(168)*. Patients with symptomatic UTI were more likely to have malignancy *(168)*.

Bloodstream Infection

The incidence of BSI resulting from enterococci has increased over the past three decades (6,170). Maki and Agger (170) cited a threefold increase in healthcare-associated enterococcal BSI in their hospital between 1970 and 1983. In their study, healthcare-associated BSIs accounted for 77% to 78% of enterococcal BSIs (170). Recent data indicate that enterococci are the second most common cause of healthcare-associated BSIs, accounting for 16% of central line-associated BSIs (6).

Enterococcal BSI is associated with prolonged hospitalization, malignancy, neutropenia, urethral catheterization, intravascular lines, recent surgery, biliary tree complications, and major burns (see Chapter 25) (*142*,170,*171*,*172*). Prior antimicrobial therapy is also associated with enterococcal BSI. In particular, use of a cephalosporin, imipenem, aztreonam, or ciprofloxacin has been shown to predispose to BSI (170,*172*,*173*). In children, the most common predisposing factors for enterococcal BSI are central lines, gastrointestinal lesions, and pulmonary infiltrates *(174)*.

As the prevalence of VRE has increased, BSIs due to VRE have increased (6,*175*,*176*). VRE account for 36% of enterococci isolated from central line-associated BSIs (6). BSI resulting from VRE has been associated with severity of illness *(177,178)*, underlying disease (especially hematologic malignancy with receipt of chemotherapy) *(175,178,179)*, human immunodeficiency virus (HIV) infection *(180)*, liver transplantation *(180)*, prolonged hospitalization *(171,181)*, corticosteroid use *(177)*, drug abuse *(180)*, acute and chronic kidney disease *(175,182)*, central line *(171)*, indwelling bladder catheter *(182)*, hyperalimentation *(171)*, and previous gastrointestinal colonization with VRE *(183)*. Prior exposure to antimicrobials, especially vancomycin, has been a consistent risk factor for VRE BSI *(177,178,182,183–187)*. Antimicrobials with antianerobic activity (e.g., clindamycin, metronidazole, and carbapenems) and *Clostridium difficile* infection have also been associated with increased risk of VRE BSI *(171,184,188,189)*.

Risk factors for VRE BSI in high-risk patient populations have been assessed. In patients undergoing liver transplantation, VRE BSI was associated with coinfections with other pathogens and biliary complications requiring repeat laparotomy *(141,142)*. VRE BSI in patients with malignancy has been associated with vancomycin use *(182,189,190)*, neutropenia *(190)*, *C. difficile* infection *(188)*, diabetes mellitus *(182)*, or gastrointestinal procedures *(182)*.

Recurrence of VRE BSI in patients with cancer has been associated with prolonged gastrointestinal colonization *(103,191)*.

In secondary enterococcal BSI without endocarditis, the urinary tract is the most common source of BSI, accounting for 19% to 43% of cases (170,*172*). Other major sources of enterococcal bacteremia include hepatobiliary tract and intra-abdominal infections (90,170,*172*). Soft tissue infections are another major source of BSI, with 15% to 30% of BSIs arising from these sites (170,*172*). It is not surprising, given the nature of common sources of BSI, that enterococcal BSI is frequently polymicrobial. Enterococci are associated with other bacteria in 25% to 46% of BSI cases (90,170,*172*).

The clinical manifestations of enterococcal BSI are influenced by whether enterococci are isolated alone or as part of a polymicrobial BSI. When caused solely by enterococci, BSI is typically an indolent disease, frequently characterized by fever only. Signs of local infection may be minimal. BSI is rarely associated with disseminated intravascular coagulation or shock. VRE are more likely than vancomycin-susceptible enterococci to occur as the sole isolated blood pathogen *(171,181)*. Polymicrobial BSI and VRE BSI are much more likely to be associated with the development of shock (50%), thrombocytopenia, or disseminated intravascular coagulation (30%) (170). Multiple studies have indicated higher rates of sepsis and shock, refractory infection and serious morbidity, and increased length of stay and hospital costs in patients with VRE BSI *(175,180,181,183,192–194)*.

Overall mortality of enterococcal BSI has been estimated to be 30% to 76% (170,*172*,*177*,*180*,*181*,*183*,*192–195*), with an attributable mortality of 7% to 37% *(181,195)*. Mortality resulting from polymicrobial BSI was two times higher than mortality associated with BSI resulting from enterococci alone *(184)*.

Whether vancomycin resistance increases mortality resulting from enterococcal BSI is still unclear. Some studies show no increased mortality with VRE BSI when compared with BSI caused by vancomycin-susceptible enterococci *(178,194,196)*. However, a growing number of studies, including a recent meta-analysis, have found that vancomycin resistance is an independent risk factor for death in patients with enterococcal BSI (*177*,*180*,*181*,*183*,*193*,*195*,197). Mortality resulting from VRE BSI is associated with severe underlying disease, hematologic malignancy, presence of shock, and liver failure *(177,181,192)*. Treatment with effective antimicrobial agents within 48 hours independently predicts survival from VRE BSI *(177)*.

Endocarditis

Enterococci are the third most common cause of endocarditis, accounting for 5% to 20% of cases of native valve endocarditis *(198,199)*. Patients with enterococcal endocarditis are predominantly men, with an average age of 56 to 59 years. In women, enterococcal endocarditis occurs during the childbearing years. A source of enterococci is usually not found; however, in many cases the genitourinary tract is implicated. Mandell et al. *(198)* found that 50% of men with enterococcal endocarditis had a previous history of enterococcal UTI or genitourinary tract instrumentation and that 43% of women had a history of childbirth or a genitourinary tract procedure in the preceding 3 months. Patients with underlying valvular heart disease are at greatest risk for developing enterococcal endocarditis *(198,199)*; however, 42% of patients in the Mandell et al. *(198)* series had no underlying heart disease.

Although endocarditis resulting from enterococci occurs more commonly in the community setting, healthcare-associated endocarditis also occurs (170,*200*). In a recent series, 26% of cases of enterococcal endocarditis were healthcare-associated, and patients with healthcare-associated infection had significantly higher mortality *(200)*. There are now multiple cases of endocarditis due to VRE reported in the literature, all of which have been healthcare-associated (201). The vast majority of patients with VRE endocarditis had significant underlying comorbidities, including chronic kidney disease with receipt of hemodialysis and transplantation. Many of these patients were treated successfully using newer antimicrobial agents.

Intra-abdominal and Pelvic Infections

The clinical manifestations of enterococcal intra-abdominal infections are similar to infections caused by other microorganisms. Enterococci are usually found in mixed culture when isolated from intra-abdominal infections *(202)*. Nichols and Muzik *(202)* found that enterococci were rarely isolated in postoperative infections after penetrating abdominal trauma unless there was gastrointestinal perforation and the patient received broad-spectrum cephalosporins. Others have found an increased prevalence of enterococci in intra-abdominal infections from a hepatobiliary source (90,*143*). In reviews of enterococcal BSI, intra-abdominal sites are often the source of BSI (170,*172*). When enterococcal BSI arises from an intra-abdominal site, the mortality is high with rates more than 40% (170,*172*).

Patients undergoing orthotopic liver transplantation (OLT) are at high risk of developing intra-abdominal infections resulting from enterococci, in particular VRE *(140–145)*. Enterococcal BSI, including VRE BSI, is more likely to occur following OLT if hepatobiliary surgical complications and infection occur *(141,142,144)*. In one series, 14 of 34 patients with VRE infection following OLT had an intra-abdominal site of infection *(141)*. In another study, 23 of 27 infections with VRE had an intra-abdominal site. Risk factors for VRE infection in this patient population include biliary complications requiring re-exploration, prolonged ICU stay, and administration of vancomycin preoperatively *(144)*. A recent study demonstrated that patients who acquired VRE colonization after transplantation had higher mortality than noncolonized recipients *(203)*.

Skin and Soft Tissue Infections

Enterococci are rarely isolated in pure culture from skin and soft tissue infections. However, they are identified frequently in mixed surgical site infections, diabetic foot ulcers, pressure ulcers, and burns (2). Enterococci accounted for 9.3% of isolates from a recent large international surveillance study of skin and soft tissue infections *(204)*. In several studies of enterococcal BSI, skin and soft tissue infections were identified as the source of bacteremia in 15% to 30% of cases (90,170,*172*). Infected burn wounds have been found to be a significant source of enterococcal BSI; BSI secondary to burn wounds is associated with a high mortality rate (170,*172*).

Neonatal and Pediatric Infections

Enterococci account for approximately 5% of bacteriologically confirmed cases of neonatal BSI *(205)*. Risk factors for enterococcal sepsis in neonates include low birth weight, prolonged nonumbilical central line, bowel resection or other abdominal surgery, prolonged hospitalization, and treatment with cephalosporins *(206,207)*. The development of enterococcal meningitis in neonates and older children has been associated with anatomic central nervous system defects or prior neurologic procedures, especially ventriculoperitoneal shunts (see Chapter 27) *(208,209)*.

Although VRE colonization and infection are less common in children than in adults, outbreaks of VRE have been described in neonatal and pediatric patients *(207, 210–212)*. Risk factors for VRE colonization and infection have included neutropenia, vancomycin use, and broad-spectrum antimicrobial use *(210–212)*. Overall, prospective prevalence studies have shown wide variability in colonization rates in pediatric populations, ranging from 0% to 50% *(213–216)*.

Other Miscellaneous Infections

Outside the neonatal setting, enterococci are a rare cause of meningitis. Risk factors for enterococcal meningitis include prior neurologic procedures, especially ventriculoperitoneal shunts *(209,217)*. Other risk factors include enterococcal UTI, endocarditis, and the immunocompromised state *(209)*. Other unusual infections associated with enterococci include endogenous endophthalmitis, arthritis (including prosthetic joint infection), or osteomyelitis *(218,219)*. Enterococci are rarely implicated as the cause of lower respiratory tract infections, although there have been reports of enterococcal pneumonia occurring in patients with advanced age, multiple comorbidities, and underlying immunosuppression *(220)*. Many of these patients developed empyema requiring surgical drainage.

Impact of Vancomycin Resistance on Patient Outcome

Recent matched case–control studies confirm that infections with VRE decrease survival, increase length of stay, and significantly increase costs of hospitalization *(161, 221–223)*. In one institution, hospital costs for a patient with VRE were $52,449 compared with $31,915 for controls *(161)*. Similarly, VRE infection was associated with an attributable ICU cost of $33,251 and increased length of hospital stay of 22 days *(224)*. In addition, patients identified as carrying VRE waited significantly longer for placement into long-term care facilities when compared with matched controls, requiring an average of 2.5 requests for placement *(225)*.

PREVENTION AND CONTROL OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROCOCCI

As antimicrobial resistance in enterococci increases in prevalence and therapeutic options become more limited, the prevention of emergence and spread of resistant enterococci is imperative. Although most outbreaks of VRE have been controlled with strict application of isolation precautions, a multidisciplinary approach is recommended for continued prevention and control of multidrug-resistant enterococci.

Decreasing Risk of Colonization

Numerous studies have emphasized the role of previous antimicrobials as a risk factor for colonization and infection resulting from enterococcal species *(226–230)*. Therefore, a key element for decreasing the risk of colonization with resistant enterococci is to limit the injudicious use of antimicrobials that select for their growth (*162*,*226*,*230*,231). Some hospitals have effectively used restriction of vancomycin to help control outbreaks of VRE *(226,230)*. Vancomycin use has been closely linked to central line-associated BSI rate and prevalence of methicillin-resistant *S. aureus (232)*. Feedback of specific prescriber use of vancomycin with benchmarking data has resulted in decreased vancomycin use and decreased VRE prevalence *(228)*.

In addition, formulary restriction of cephalosporins may be important in decreasing the risk of colonization with enterococci, including VRE *(230)*. However, one institution had an increase in VRE colonization while restricting vancomycin and cephalosporins and noted that clindamycin restriction may be an important component of an antimicrobial stewardship program for controlling VRE *(162)*. Although recommendations for antimicrobial stewardship have been outlined, many hospitals do not have stewardship programs that fully meet the recommendations (233,*234*).

Along with selective use of antimicrobials, another necessary measure to decrease infection resulting from enterococci is to reduce the use of invasive devices whenever possible. Urinary catheterization predisposes to enterococcal UTIs (107,*137*). In addition, central line use has been recognized as a risk factor for the development of enterococcal bacteremia (170). Finally, attempts should be made to eliminate the modifiable risk factors for colonization and infection with resistant enterococci as mentioned previously (Table 33-4).

Interruption of Transmission

Early identification of patients infected and colonized with antimicrobial-resistant enterococci is an important step in interrupting transmission of these microorganisms (*157*,231,*235*,*236*). Active screening for VRE colonization, when used with other infection control measures, has been found to be effective in decreasing prevalence of VRE colonization and infection *(236,237)*. In addition, active surveillance and control has been shown to be cost-effective for hospitals *(235,238–240)*. For active surveillance for gastrointestinal VRE colonization, perirectal swabs have been effective in most studies *(235,241–243)*; however, false-negative results may occur in patients with low-density colonization *(244)*. Some have used passive surveillance through routine laboratory culturing or culturing stool samples sent for *C. difficile* studies to identify and control VRE colonization *(111,245,246)*. However, passive reporting may underestimate the prevalence of VRE *(247)*. Therefore, the Society for Healthcare Epidemiology of America (SHEA) now recommends obtaining active surveillance cultures for high-risk patients at the time of admission and at periodic time intervals (e.g., weekly) thereafter (231).

High-risk patients typically include ICU patients and may include patients with a history of previous hospitalization or other known risk factors for VRE colonization *(248)*. It is essential that hospital microbiology laboratories use accurate screening methods for VRE and have a system for quickly reporting these microorganisms so that appropriate precautions may be instituted (5,231).

Isolation precautions with private rooms, gowns, and gloves have been used and recommended for the prevention of transmission and control of VRE (231,249). However, in a hospital with a high rate of endemic VRE, the addition of gown use did not decrease acquisition of VRE when compared with glove use alone *(250)*. Several studies support the Healthcare Infection Control Practices Advisory Committee (HICPAC) guidelines for control of VRE and indicate that gowns have an added benefit to the use of gloves in the ICU setting (249,*251*,*252*). Isolation precautions have been successful, for the most part, in ending epidemics as long as all reservoirs have been identified and eradicated. Cohorting of colonized patients, in addition to isolation precautions, have been used in outbreak situations to help control transmission of VRE *(253)*.

Hand hygiene is a key element in controlling spread of resistant enterococci (231,249,254). Gloves reduce hand carriage of VRE but do not completely prevent contamination of hands *(255)*. In one study, 5 of 17 healthcare personnel were found to have VRE on the hands after glove removal, emphasizing the importance of hand hygiene after removal of gloves *(255)*. Use of alcohol hand rub is now generally recommended for hand hygiene (254). In an *in vitro* study of the efficacy of various hand disinfectants against enterococci, propanol-based compounds were found to be highly effective *(256)*. At one institution, the incidence of VRE colonization or infection decreased after introduction of alcohol hand rub for hand hygiene *(257)*.

Elimination of Reservoirs

Patients harboring resistant enterococci in their gastrointestinal tract are the major reservoirs for transmission within hospitals, but healthcare workers may also carry enterococci. Eradication of enterococci from human carriers has been problematic *(101,258,259)*. During an outbreak of β-lactamase-producing gentamicin-resistant enterococci, a 14-day course of oral vancomycin and rifampin, based on the isolate's antimicrobial susceptibilities, was used to eradicate carriage in a nurse *(10)*. Eradication of VRE from the intestinal tract has been attempted with several oral antimicrobial regimens with little success *(97,258–260)*. Ramoplanin, a nonabsorbable glycolipopeptide with bactericidal activity against VRE, was successful in temporarily suppressing VRE in the gastrointestinal tract of colonized patients. However, the suppressive effects were lost by 3 weeks after discontinuing treatment *(259)*. In this study, repopulation of the intestinal tract with VRE within 7 days of discontinuing ramoplanin represented relapse with a genotypically similar isolate of VRE *(98)*.

While eradication of VRE from the gastrointestinal tract may not be possible, skin represents another important reservoir for VRE that may be more easily addressed. A recent study demonstrated that daily bathing of ICU patients with the antiseptic chlorhexidine lowered the rate of VRE acquisition and BSI *(260)*.

In many studies, the environment surrounding infected patients had become heavily contaminated with enterococci (*10*,*91*,*100*,135,*261*). Noncritical medical equipment, such as thermometers, stethoscopes, and blood pressure cuffs, should be dedicated to a single VRE colonized patient (231). If equipment must be used on multiple patients, it should be disinfected after each use (231). Other authors have incorporated a thorough cleaning of the environment into control measures during an epidemic *(262)*. More recently, it has been shown that enforcement of routine environmental cleaning reduces environmental contamination with VRE and patient acquisition of VRE *(263,264)*. Enterococci, including VRE, appear to be susceptible to disinfectants routinely used in hospitals *(265)*. Screening for environmental contamination may be performed, when applicable, through use of Rodac imprints or use of swabs with enrichment broth *(111,242)*.

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CHAPTER 34

Enterobacteriaceae

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The family Enterobacteriaceae comprises a wide array of gram-negative bacilli whose reservoirs include soil, water, plants, and the gastrointestinal tracts of humans and animals. As a group, Enterobacteriaceae are the most frequent bacterial isolates recovered from inpatient and outpatient clinical specimens *(1)*. In 2006 to 2007, Enterobacteriaceae accounted for 21% of pathogens isolated from all infection sites in the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Surveillance System, the successor to the CDC's National Healthcare-associated Infections Surveillance (NNIS) System (2).

OVERVIEW

Microbiologically, all members of the Enterobacteriaceae are facultative anaerobes that, with few exceptions, ferment glucose, reduce nitrate to nitrite, and are oxidase negative *(3)*. Several approaches to classifying the Enterobacteriaceae have been used over the years, including phenotypic subgroupings *(4)*, DNA-relatedness studies *(5)*, and a combination of the two methods *(6)*. A summary of a current classification is presented in Table 34-1 *(7)*.

For identification of aerobic gram-negative bacilli, many hospital microbiology laboratories now use automated rapid identification systems rather than conventional biochemical testing *(3)*. Of particular importance to infection control is the ability to determine in the microbiology laboratory whether healthcare-associated infections are due to the spread of a single species. This requires the ability to type strains by classic or newer molecular methods (Table 34-2) *(8)*. Pulsed-field gel electrophoresis (PFGE) has been the most widely used method of genotyping, and for small sets of isolates empiric guidelines have been formulated to interpret chromosomal DNA restriction patterns produced by this method *(9)* (see Chapter 102). These guidelines have been validated for some species *(10)*. Currently though, PCR-based (multiple-locus variable number tandem repeat Analysis [MLVA]) and sequence-based methods (multiple-locus sequence typing [MLST] and whole genome sequencing) have become the standard.

As the use of invasive devices, broad-spectrum antibiotics, and immunosuppressive agents has increased in hospitals, the Enterobacteriaceae, particularly *Escherichia coli*, have become somewhat less prevalent, and gram-positive microorganisms, especially staphylococci and enterococci, more prevalent as causes of healthcare-associated infection. In 1999 and in 2006 to 2007 CDC data, the major device-associated infections, that is, central-line–associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), and ventilator-associated pneumonia (VAP), were each caused most often by the same four pathogens, respectively (2,*11*); the one exception was that for VAP, in the 2006 to 2007 data, *Acinetobacter baumannii* tied *Enterobacter* spp. as the third most frequent pathogen (2).

To illustrate the changing overall role of Enterobacteriaceae in the pathogenesis of healthcare-associated infections, Table 34-3 presents NNIS data from 1980 to 1982 and 1990 to 1996 and NHSN data from 2006 to 2007. Comparisons between NNIS and NHSN need to be made with caution due to differences between the two systems (e.g., NHSN includes units outside of intensive care, has no minimum hospital size requirement for participation, and has a greatly expanded hospital base due to mandated use in many states for public reporting purposes). The percentage of pathogens recovered from healthcare-associated infections that were Enterobacteriaceae declined from 42% in 1980 to 1982 to 29% in 1990 to 1996, and continued to trend down to 21% for 2006 to 2007, primarily because of less frequent recovery of *E. coli*. This trend is apparent and continues in all major infection sites. For example, Enterobacteriaceae accounted for 18% of the 14,424 isolates causing bloodstream infections (BSIs) in the 1990 to 1996 NNIS data, but accounted for only 10% of the 21,943 isolates causing BSIs in the 1992 to 1999 data *(11)* and for 12.4% of 11,428 isolates from CLABSIs in 2006 to 2007 (2). Selected data from other recent multicenter healthcare-associated surveillance systems are shown in Table 34-4.

Although the overall percentage of healthcare-associated infections due to the Enterobacteriaceae has declined, Enterobacteriaceae remain important healthcare-associated pathogens. They have been implicated in almost a third (34%) of all healthcare-associated urinary tract infections (UTIs), in nearly a fifth (18%) of all SSIs, in up to 12% of all BSIs, and in 23% of all VAP. Overall, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., and *K. oxytoca* were the most common healthcare-associated pathogens from the family Enterobacteriaceae and together accounted for about one-fifth of all healthcare-associated isolates in 2006 to 2007 (2).

TABLE 34-1

Aerobic Gram-Negative Bacilli: Enterobacteriaceae (Pertinent Characteristics: Ferment Sugars; Oxidase Negative; Most Reduce Nitrate to Nitrite)

Current Name	*Synonym*	*Current Name*	*Synonym*
Budvicia aquatica		*Leclercia adecarboxylata*	*Escherichia adecarboxylata*
Buttiauxella noackiae	CDC enteric group 59		CDC enteric group 41
Cedecea davisae	CDC enteric group 15	*Leminorella grimontii*	CDC enteric group 57
Cedecea lapagei		*Leminorella richardii*	
Cedecea neteri	*Cedecea* sp. 4	*Moellerella wisconsensis*	CDC enteric group 46
Cedecea sp. 3		*Morganella morganii* ssp. *morganii*	*Proteus morganii*
Cedecea sp. 5			
Citrobacter amalonaticus	*Levinea amalonatica*	*Morganella morganii* ssp. *sibonii*	*Proteus morganii*
Citrobacter braakii	*Citrobacter freundii*		
Citrobacter diversus		*Pantoea agglomerans*	*Enterobacter agglomerans*
Citrobacter farmeri	*Citrobacter amalonaticus* biogroup 1	*Pantoea dispersa*	*Xenohabdus luminescens*
		Photorhabdus luminescens	
Citrobacter freundii	*Colobactrum freundii*	*Pragia fontium*	
Citrobacter gillenii	*Citrobacter* genomospecies 10	*Proteus mirabilis*	
	Citrobacter freundii	*Proteus penneri*	*Proteus vulgaris* biogroup 1
Citrobacter koseri	*Citrobacter diversus*	*Proteus vulgaris*	*Proteus vulgaris* biogroup 1
	Levinea malonatica	*Providencia alcalifaciens*	*Proteus inconstans*
Citrobacter murliniae	*Citrobacter* genomospecies 11	*Providencia rettgeri*	*Proteus rettgeri*
	Citrobacter freundii	*Providencia rustigianii*	*Providencia alcalifaciens* biogroup 3
Citrobacter rodentium	*Citrobacter* genomospecies 9	*Providencia stuartii*	*Proteus inconstans*
	Citrobacter freundii	*Rahnella aquatilis*	
Citrobacter sedlakii	*Citrobacter* genomospecies 8	*Salmonella bongori*	*Salmonella* subgroup 5
	Citrobacter freundii	*Salmonella choleraesus* ssp. *arizonae*	*Salmonella* subgroup3a
Citrobacter werkmanii	*Citrobacter* genomospecies 7		
	Citrobacter freundii	*Salmonella choleraesuis* ssp. *choleraesius*	*Salmonella* subgroup 1
Citrobacter youngae	*Citrobacter* genomospecies 5		
	Citrobacter freundii	*Salmonella choleraesuis* ssp. *diarizonae*	*Salmonella* subgroup 3b
Edwardsiella hoshinae			
Edwardsiella tarda		*Salmonella choleraesuis* ssp. *houtenae*	*Salmonella* subgroup 4
Enterobacter aerogenes	*Aerobacter aerogenes*		
Enterobacter agglomerans group		*Salmonella choleraesuis* ssp. *indica*	*Salmonella* subgroup 6
Enterobacter amnigenus		*Salmonella choleraesuis* ssp. *salamae*	*Salmonella* subgroup 2
Enterobacter asburiae	CDC enteric group 17		
Enterobacter cancerogenus	*Enterobacter taylorae*	*Serratia ficaria*	
	Erwinia cancerogena	*Serratia fonticola*	
	CDC enteric group 19	*Serratia grimesii*	*Serratia liquefaciens*
Enterobacter cloacae		*Serratia liquefaciens*	*Enterobacter liquefaciens*
Enterobacer gergoviae		*Serratia marcescens*	
Enterobacter hormaechei	CDC enteric group 75	*Serratia odoriferae*	
Enterobacter intermedius	*Enterobacter intermedium*	*Serrattia plymuthica*	
Enterobacter kobei		*Serratia proteamaculans* ssp. *proteamaculans*	*Serratia liquefaciens*
Enterobacter sakazakii			
Erwinia persicinus		*Serratia proteamaculans* ssp. *quinovora*	*Serratia liquefaciens*
Escherichia blattae			
Escherichia coli		*Serratia rubidaea*	
Escherichia fergusonii	CDC entric group 10	*Shigella boydii*	*Shigella* biogroup C
Escherichia hermannii	CDC enteric group 11	*Shigella dysenteriae*	*Shigella* biogroup A
Escherichia vulnerius	CDC enteric group 1	*Shigella flexneri*	*Shigella* biogroup B
Ewingella americana	CDC enteric group 40	*Shigella sonnei*	*Shigella* biogroup D
Hafnia alvei	*Enterobacter hafniae*	*Tatumella ptyseos*	CDC group EF-9

(*Continued*)

TABLE 34-1

Aerobic Gram-Negative Bacilli: Enterobacteriaceae (Pertinent Characteristics: Ferment Sugars; Oxidase Negative; Most Reduce Nitrate to Nitrite) (*Continued*)

Klebsiella ornithinolytica	*Klebsiella* oxytoca *ornithine* Positive	*Trabulsiella guamensis*	CDC enteric group 90
Klebsiella oxytoca		*Yersinia aldovae*	
Klebsiella planticola	*Klebsiella travisanii*	*Yersinia bercovieri*	*Yersinia enterocolitica* biogroup 3b
Klebsiella pneumoniae ssp. *ozaenae*	*Klebsiella ozaenae*	*Yersinia enterocolitica*	*Pasteurella enterocolitica*
Klebsiella pneumoniae ssp. *pneumoniae*	*Klebsiella pneumoniae*	*Yersinia frederiksenii*	
Klebsiella pneumoniae ssp. *rhinoscleromatis*	*Klebsiella rhinoscleromatis*	*Yersinia intermedia*	
Klebsiella terrigena		*Yersinia kristensenii*	
Kluyvera ascorbata	CDC enteric group 8	*Yersinia mollaretii*	*Yersinia enterocolitica* biogroup 3a
Kluyvera cryocrescens		*Yersinia pestis*	*Pasteurella pestis*
Kluyvera georgiana	CDC enteric group 36/37	*Yersinia pseudotuberculosis*	*Pasteurella pseudotuberculosis*
	Kluyvera species group 3	*Yersinia rohdei*	
		Yokenella regensburgei	*Koserella trabulsii* CDC enteric group 45

Note: Diagnostic laboratories may report *Salmonella* serovars by name, for example, *Salmonella typhi* or *Salmonella* serovar *typhi*.
CDC, Centers for Disease Control and Prevention.
Enterobacteriaceae discussed in the text are highlighted.
(Adapted from Bruckner DA, Colonna P, Bearson BL. Nomenclature for aerobic and facultative bacteria. *Clin Infect Dis* 1999;29:713–723.)

Though Enterobacteriaceae comprise a slightly smaller portion of healthcare-associated infections than in the past, the alarming increase in antimicrobial resistance, particularly to carbapenem antibiotics and the presence of resistance cassettes on transmissible genetic elements, compels healthcare professionals to understand the pathogenesis, infection control, and preventive measures to limit their spread.

PATHOGEN-SPECIFIC FACTORS IN THE PATHOGENESIS OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROBACTERIACEAE

Multiple factors are involved in the pathogenesis of infection caused by Enterobacteriaceae. As discussed below, a variety of pathogen-specific factors, device-related factors, and host factors act together to determine the likelihood of infection. The virulence of the microorganism (i.e., the ability to invade and cause disease) relates to both pathogen factors and to the immune status of the patient.

Adhesion

Bacterial adhesion is a highly specific phenomenon that leads to attachment of bacteria to mucosal surfaces and, thus, to colonization and potentially to bacterial overgrowth and tissue invasion. Adhesins may also function as invasins, promote biofilm formation, and transmit signals to epithelial cells leading to inflammation *(19,20)*. Among Enterobacteriaceae, adhesion is mediated by both fimbrial and nonfimbrial adhesins (Table 34-5) that are encoded on plasmids and on the bacterial genome, forming "pathogenicity islands" *(21)*. The locus for enterocyte effacement on the chromosome encodes the virulence types necessary for attachment and effacement of *E. coli* to enterocytes *(22)*. The *E. coli* fimbrial adhesins are among the most studied and the best characterized of the bacterial adhesins.

P fimbriae anchor bacteria to uroepithelial cells *(29)* and are found in strains that cause pyelonephritis in adults and children *(30–32)*. The symbol P was chosen because P-fimbriated *E. coli* were a frequent cause of pyelonephritis and because glycolipids were receptors for P fimbriae and antigens in the P blood group system *(33)*. Compared to non–P-fimbriated strains of *E. coli*, isolates with P fimbriae can adhere to specific receptors on human colonic epithelial cells (leading to colonization), spread more easily to the urinary tract, have a better ability to persist in kidneys and bladders, and enhance the inflammatory response *(33)*.

A relation between adherence and virulence has been demonstrated. Among *E. coli* strains from patients with different forms of UTIs, *in vitro* adherence to uroepithelial cells was found in 80% of the patients with pyelonephritis, 40% to 50% of the patients with acute cystitis, and 20% of the patients with asymptomatic bacteriuria *(33)*. Studies of bacteremia secondary to urosepsis have shown that *E. coli* strains that cause urosepsis in healthy patients almost always have P fimbriae, whereas *E. coli* urosepsis in immunocompromised patients is less often due to such P-fimbriated strains *(30–32)*. In a study of fimbrial types found in respiratory isolates from intensive care

TABLE 34-2

Characteristics of Bacterial Typing Systems

Typing System	*Strains Typeable*	*Reproducibility*	*Proportion of Discriminatory Power*
Phenotypic methods			
Biotyping	All	Fair	Poor
Antimicrobial susceptibility testing	All	Fair	Poor
Serotyping	Most	Good	Fair
Bacteriophage typing	Most	Fair	Poor
Immunoblotting	All	Excellent	Good
Multilocus enzyme electrophoresis	All	Excellent	Good
Genotypic methods			
Plasmid profile analysis	Most	Fair	Fair
Restriction endonuclease analysis	All	Good	Fair
Ribotyping	All	Excellent	Fair
PFGE	All	Good	Excellent
Polymerase chain reaction restriction	All	Excellent	Good digests
Arbitrarily primed polymerase	All	Good	Good chain reaction
MLVA	All	Excellent	Excellent
MLST	All	Excellent	Excellent

Note: These judgments represent the views of Maslow et al. *(10)*; many systems remain incompletely evaluated, and characteristics may vary when the systems are applied to different species.
(Modified from Maslow JN, Mulligan ME, Arbeit RD. Molecular epidemiology: application of contemporary techniques to the typing of microorganisms. *Clin Infect Dis* 1993;17:153–164.)

unit (ICU) patients with presumed healthcare-associated pneumonia, P fimbriae were found in approximately half of the *E. coli* respiratory isolates *(34)*. This rate is higher than the rate of P fimbriation commonly found in fecal isolates (14–16%) and, thus, raises the question of how the presence of this adhesin may be advantageous to strains causing pulmonary infection *(34)*. Another study looked at the role of the *papG* class II gene, a P-fimbrial structural allele causing uroepithelial attachment of *E. coli*, and the pathogenesis of *E. coli* bacteremia in upper UTIs and ascending cholangitis. The authors found a significant difference between the presence of the virulence factor, *papG* class II, in bacteremic patients with upper UTI compared to bacteremic patients with ascending cholangitis and to controls *(35)*.

Cranberry juice consumption may offer protection against P-fimbriated strains of *E. coli* by the action of cranberry proanthocyanidin (condensed tannin), which inhibits P-fimbriated *E. coli* from adhering to uroepithelial cells *(36)*. A randomized controlled study with 50 women per arm compared drinking 50 mL of cranberry juice concentrate daily for 6 months to drinking 100 mL of lactobacillus GG 5 days a week for 1 year, compared to controls. The authors found an absolute risk reduction for recurrent UTI of 20% in the group that drank cranberry juice *(37)*.

S fimbriae are present on many *E. coli* strains that cause infant meningitis. The presence of binding sites for S fimbriae on blood vessels in the central nervous system (CNS) and on epithelial cells of the choroid plexus and of the ventricle of the infant rat brain provides a model for the pathogenesis of neonatal *E. coli* meningitis *(38)*. The binding affinity of S fimbriae for vascular endothelium and epithelium of the choroid plexus and the ventricles decreases after the neonatal period in rats, paralleling the decrease in susceptibility to *E. coli* meningitis *(39)*. S fimbriae also allow *E. coli* to bind to intact endothelial cells *(38,40)* and thus may be an important virulence factor for septicemia. When isolates of *E. coli* that caused a variety of invasive bacterial infections were compared to fecal isolates in healthy children, P fimbriae and S fimbriae were predominant in *E. coli* isolates causing invasive disease *(41)*.

Type I pili have been associated with uropathogenic *E. coli* (UPEC). Type I pili facilitate entry of UPEC into bladder epithelial cells, with subsequent exfoliation *(42)*. The ability of UPEC to invade and persist in bladder epithelial cells has been suggested as an explanation of recurrent UTIs.

Type IV pili have been identified in enteropathogenic *E. coli*, which frequently cause childhood diarrhea in developing countries. Type IV pili are known as bundle-forming pili (BFP) and are critical to the full virulence of these bacteria *(43)*. Mutants without these pili could not attach to epithelial cells *in vitro* and were relatively benign when fed to human volunteers. These pili facilitate bacterial bundling into rope-like filaments that attach to epithelial cells; subsequently, the clumped bacteria disperse to cause infection *(43)*.

In addition to Type 1 pili and P fimbriae, the Dr adhesion family of UPEC has been associated with pyelonephritis in pregnant women *(44)*. The Dr adhesin family includes a fimbrial adhesin and nonfimbrial adhesins and is termed Dr for the blood group antigen, a common receptor for this family of adhesins *(45)*. Dr adhesins are associated with bacterial persistence in the urinary tract and facilitate invasion of the bladder and kidney tissue and binding

TABLE 34-3

Distribution of Selected Enterobacteriaceae and Other Pathogens Isolated from all Major Infection Sites, CDC

	Percentage (n)			*Rank*		
Pathogen	***1980–1982***	***1990–1996***	***2006–2007***	***1980–1982***	***1990–1996***	***2006–2007***
Selected Enterobacteriaceae						
Citrobacter spp.	1	1	NA	12	11	NA
Enterobacter spp.	5	6	5	6	6	8
E. coli	20	12	10	1	2	5
K. pneumoniae	6	5	6	5	8	7
Klebsiella spp.	2	1	1	10	12	10
P. mirabilis	5	3	NA	7	9	NA
Proteus spp.	1	0	NA	13	13	NA
S. marcescens	2	1	NA	11	10	NA
Serratia spp.	0	0	NA	14	14	NA
Total	**42**	**29**	**21**	NA	NA	NA
Other pathogens						
P. aeruginosa	10	9	8	4	5	6
A. baumannii	NA	NA	3	NA	NA	9
S. aureus	11	13	14	2	1	2
Coagulase-negative staphylococci	5	11	15	8	3	1
Enterococci	10	10	12	3	4	3
Candida albicans	3	5	11	9	7	4
Other	19	23	16	NA	NA	NA
Total	**100 (132,686)**	**100 (101,821)**	**100 (33,848)**			

(Data from CDC and refs. 2, *12*, and *13*.)

to decay accelerating factor, a host protective protein that prevents autologous complement mediated damage (*46*,47). Currently, it is unknown if this group of adhesins is expressed during UPEC-associated CAUTIs.

Autotransporter (AT) proteins are another group of adhesins associated with UTI virulence *(48)*. Antigen 43 (Ag 43), a bacterial surface AT protein, has been identified in UPEC and enteropathogenic *E. coli (48)*, though not specifically in CAUTI. Antigen 43 confers characteristic surface properties such as autoaggregation and promotes bacterial biofilm formation, and the Ag 43a variant recently has been shown to promote long-term persistence in the urinary bladder in mouse models of UTI *(49)*. These autotranporters may be future targets for novel vaccines against gram-negative pathogens *(50)*.

The role of adhesins in the pathogenesis of infection caused by other Enterobacteriaceae is not well characterized. Type 1, 3, and 6 fimbriae have been found in *Klebsiella*, but their function as virulence factors remains largely unknown *(51,52)*. The majority of respiratory isolates of *K. pneumoniae* and *K. oxytoca* from ICU patients with presumed healthcare-associated pneumonia have been shown to express type 3 fimbriae and a mannose-resistant, *Klebsiella*-like (MR-K) hemagglutinin *(34)*. Multidrug-resistant *K. pneumoniae* strains from a variety of healthcare-associated infections have been found to colonize the human intestinal tract through a plasmid-encoded 29,000-dalton surface protein *(51)* that facilitates adherence to gastrointestinal epithelium. Type 3 fimbriae also are commonly found in *Klebsiella* isolates associated with human UTIs *(51)*. An MR-K fimbria has been isolated in *Providencia stuartii* and appears to be related to adherence to genitourinary catheters *(53)*. Cell adhesins that allow attachment to exfoliated uroepithelium *(54–56)* have been found in *Proteus* spp. as well. Nonfimbrial adhesive factors also are being characterized in the Enterobacteriaceae *(57,58)*. An R-plasmid encoded nonfimbrial adhesive factor has been isolated from strains of *K. pneumoniae* responsible for a variety of healthcare-associated infections *(57)*.

Capsules

The bacterial capsule, which is well characterized for *Klebsiella* spp., *E. coli*, and *Salmonella typhi*, can partly protect the microorganisms against the bactericidal effect of serum and against phagocytosis *(57,59,60)*. However, most of the Enterobacteriaceae do not possess a substantial bacterial capsule and do not have serum resistance. In a prospective observational study from six United States university teaching hospitals evaluating the incidence and the risk factors for the development of endocarditis in bacteremic patients with prosthetic cardiac valves, a significant proportion of cases of new endocarditis were due to gram-negative aerobic bacilli, often when a portal of entry was found *(61)*. This study suggests that the previous hypothesis that endocarditis was unlikely in the presence of gram-negative bacteremia, presumably because gram-negative bacilli are

TABLE 34-4

Examples of Multicenter Surveillance Studies of Healthcare-Associated Enterobacteriaceae

							No.	*%*
Year	*Ref*	*Study Eponym*	*No. of Centers*	*Countries*	*Types of Units*	*Source of Isolates*	*Total Bacteria Isolates*	*Isolates = enterobacteriaceae*	
1993–2004	(14)	Merck	70[a]	USA	ICU	Blood, urine, wound, respiratory; all gram-negative bacilli	74,394	45,242	61
1997–1999	(15)	SENTRY	25	Europe	ICU + non-ICU	Blood, urine, skin, and soft tissue, respiratory	17,934	5,212	29
1997–2004	(99)	MYSTIC	41	Europe	ICU + non-ICU	NR; all Enterobacteriaceae	17,203	17,203	100
1999–2004	(99)	MYSTIC	10–15	USA	ICU + non-ICU	NR; all Enterobacteriaceae	6,726	6,726	100
2000–2002	(16)	TSN	87	Canada	ICU	NR	54,445	17,967	33
2000–2002	(16)	TSN	48	Italy	ICU	NR	34,609	10,452	30
2000–2002	(16)	TSN	169	Germany	ICU	NR	48,385	17,419	36
2000–2002	(16)	TSN	63	France	ICU	NR	62,459	20,049	32
2000–2002	(16)	TSN	283	USA	ICU	NR	26,624	7,987	30
2001	(17)	SENTRY	25	N. America	ICU	Blood, urine, respiratory	1,321	432	33
2005–2006	(18)	CAN-ICU	19	Canada	ICU	Blood, urine, wound, respiratory	4,180	1,225	29
2006–2007	(2)	NHSN	463	USA	ICU + non-ICU	Blood, urine, respiratory, wound	33,848	7,203	21

[a]Average number of centers participating each year.

serum susceptible or if a portal of entry is identified, may not be correct.

A capsule, when present, can also directly suppress the host immune response *(62)*. In invasive *E. coli* disease in children, K1 and K5 capsules are found most commonly *(41)*. It has been suggested that these capsules are more virulent, because they are structurally similar to human antigens, and therefore may be spared by or elude specific host defense mechanisms. The size of the capsule and the rate of capsule polysaccharide production appear to influence bacterial virulence *(62)*.

Iron Chelators

The ability of some gram-negative bacteria to acquire iron for growth becomes an important factor in many gram-negative infections. Almost all the iron in the human body is bound to various proteins such as hemoglobin, myoglobin, and transferrin, thereby limiting the availability of free iron for utilization by bacteria. Some Enterobacteriaceae contain low molecular weight, high-affinity iron chelators called siderophores. The chelator permits the bacteria to scavenge iron from the host for growth purposes.

Aerobactin is an iron-chelating bacterial siderophore associated with increased virulence in *E. coli (63)* and *Klebsiella (64,52)*. In Enterobacteriaceae, the catechol enterobactin is the most commonly occurring iron-chelating siderophore but does not appear to be associated with increased bacterial virulence *(64,65)* possibly because enterobactin is more antigenic than aerobactin and causes a strong antibody response in the host that diminishes enterobactin's ability to take up iron *(65)*.

Yersinia enterocolitica 1B, *Y. pseudotuberculosis*, and *Y. pestis* have been found to contain chromosomal gene sets designated high-pathogenicity islands (HPIs) that are involved in the synthesis, transport, and regulation of the siderophore yersiniabactin. This HPI has also been found in other genera including *E. coli*, *Klebsiella*, *Citrobacter*, and *Enterobacter (66–68)*. *Y. enterocolitica* has increased virulence in patients receiving desferrioxamine therapy, presumably because *Yersinia* can use desferrioxamine to meet some of its growth requirements more effectively in these patients *(69,70)*.

Another method by which bacteria may acquire iron is hemolysis. Hemolysins are cytotoxic proteins encoded by chromosomal or plasmid genes. The chromosomal

Percent of Total Isolates						
Escherichia	***Klebsiella***	***Enterobacter***	***Serratia***	***Proteus***	***Morganella***	***Citrobacter***
19	17	14	6	4	NR	2
19	6	3	NR	2	NR	NR
35	27	19	7	8	NR	5
35	24	13	8	12	NR	8
13	6	4	3	NR	NR	NR
8	4	3	2	2	NR	NR
12	8	5	NR	3	NR	NR
16	3	3	NR	3	NR	NR
9	6	4	3	NR	NR	NR
10	9	7	3	2	NR	2
13	7	5	2	1	NR	1
10	7	5	NR	NR	NR	NR

localization seems to be predominant for *E. coli* causing extraintestinal infections, whereas hemolysins are usually carried on plasmid genes in *E. coli* strains from veterinary sources. Hemolysins are cytotoxic for erythrocytes, and *in vitro* for polymorphonuclear leukocytes, monocytes, and isolated renal tubular cells. These proteins contribute to virulence in intraperitoneal infection models, but their role in ascending UTIs is uncertain. Hemolysin production is frequent in pyelonephritic clones of *E. coli*, but does not enhance bacterial persistence in kidneys and bladders *(33,41)*.

Other Pathogen Factors and Tropisms

Other virulence factors, such as bacterial motility *(71)*; the ability to grow in alkaline pH; the ability to colonize skin (especially hands) of healthcare workers; the ability to produce urease, which catalyzes hydrolysis of urea in the urine and increases urinary pH *(72)*; and the ability to produce biofilms *(73)*, contribute to the ability of various members of the Enterobacteriaceae to produce disease, especially in healthcare settings. Enterobacteriaceae liberate numerous toxins, endotoxin being one of the most lethal, which contribute to bacterial virulence (Table 34-5). The role of endotoxins in healthcare-associated infection is no different from their role in community-acquired infection. Finally, some virulence factors have been associated with worsened patient outcome, although precise mechanisms of tissue injury are unknown. For example, a minor outer membrane protein (molecular weight of 32,000) is found more often in strains of *Citrobacter koseri* causing neonatal meningitis and abscess than in strains of *C. koseri* from other body sites *(74)*. Evidence from an infant rat model suggests that strains of *C. koseri* with this outer membrane protein can produce more extensive histopathologic changes within the brain *(75)*.

Infections by several species of Enterobacteriaceae have been associated with specific devices, materials, and/or procedures because of increased device affinity or specific tropisms. For example, *Proteus mirabilis* is an urease-producing bacterium that has been associated with bacteriuria and obstructed urinary catheters in patients with long-term indwelling bladder catheters *(76)*. Urease catalyzes the hydrolysis of urea in the urine, thus alkalinizing it; this permits the formation of struvite and carbonate-apatite stones or sludge or concretions within the catheter lumen, leading to catheter obstruction. Other members of the

TABLE 34-5

Examples of Pathogen-Specific Virulence Factors in Enterobacteriaceae

Virulence Factor	*Pathogen (Reference)*	*Infection*
Bacterial adhesins		
Fimbrial adhesins		
Dr adhesins	*E. coli (44)*	Pyelonephritis
P fimbriae	*E. coli (23,29)*	UTI/pyelonephritis
Type I fimbriae	*E. coli (23,29)*, *K. pneumoniae (51)*	Cystitis
S fimbriae	*E. coli (23,29)*	Neonatal sepsis/meningitis
Colonization factor	*E. coli (23,29)*	Diarrhea Ag (CFAI, CFAII)
K88, K89	*E. coli (8,23)*	Diarrhea
Type 3 fimbriae	*K. pneumoniae (51)*	Cystitis/UTI
Type 6 fimbriae	*K. pneumoniae (51)*	Unknown
MR-K hemagglutinin	*P. stuartii (53)*	LT catheter UTI
Cell adhesin	*P. mirabilis (24,54–56)*	UTI (unknown)
Type IV pili	*E. coli (43)*	Diarrhea
Nonfimbrial adhesins		
Dr adhesins	*E. coli (44)*	Pyelonephritis
R-plasmid–encoded	*K. pneumoniae (57,58)*	UTI, CSF shunt infection adhesive factor
Antigen 43	*E.coli (49)*	UTI
Bacterial toxins		
Hemolysin (α,β)	*E. coli (25)*	UTI/pyelonephritis
Enterotoxin	*E. coli (25)*	Diarrhea
Verotoxin	*E. coli (25)*	HUS, HC, diarrhea
Endotoxin	*E. coli (25)*	Sepsis
Bacterial capsules		
K antigens	*E. coli (26,27,75)*	Extraintestinal/invasive disease
	K. pneumoniae (59,62,90)	Unknown
Bacterial siderophores		
Aerobactin	*E. coli (63)*	Pyelonephritis, cystitis
	K. pneumoniae (28,64)	Pyelonephritis
Urease production	*Proteus (76)*	LT catheter UTI
Outer membrane proteins	*C. diversus (28,74)*	Brain abscess
	Yersinia spp. *(90)*	Increased virulence

CFA I, II, colonization factor antigen I, II; HC, hemorrhagic colitis; HUS, hemolytic-uremic syndrome; LT, long-term; MR-K, mannose-resistant *Klebsiella*-like hemagglutinin; UTI, urinary tract infection.

Enterobacteriaceae family, including *Morganella morganii*, *K. pneumoniae*, *P. vulgaris*, and *P. stuartii*, also produce urease. Although no association between bacteriuria and catheter obstruction has been demonstrated for these microorganisms *(76)*, some, such as *P. stuartii*, are very commonly associated with long-term bladder catheterization. An MR-K hemagglutinin has been identified in *P. stuartii* that increases adherence to catheter material *(53)*.

The cell-surface characteristics of *K. pneumoniae* may also play a role in increased adherence to ventriculoperitoneal shunts. For example, when a multiresistant strain of *K. pneumoniae* was compared to its spontaneous *in vitro* antibiotic-susceptible derivative, the derivative was more adherent to the surface of ventriculoperitoneal catheters *(58)*. Genetic studies suggested that the absence of a plasmid-mediated outer membrane protein led to increased adherence to the ventriculoperitoneal shunt surface.

Enterobacter sakazakii has been associated with several neonatal outbreaks and sporadic cases of sepsis, meningitis, and diarrhea *(77–81)*. No environmental source for *E. sakazakii* has been identified *(81)*. Most outbreaks have been associated with either intrinsic or extrinsic contamination of powdered milk substitute. *E. sakazakii* has been isolated from powdered infant formula produced in 13 different countries by multiple manufacturers *(79,82)*, suggesting that this microorganism has the propensity to contaminate such products. *In vitro* studies show that *E. sakazakii* survives better than *E. cloacae* in infant formula *(77)*.

Y. enterocolitica has a well-documented association with blood transfusion–related sepsis *(83,84)*. Apparently, blood donors with asymptomatic gastrointestinal infection with *Y. enterocolitica* and transient bacteremia at the time of blood donation are the most common source of such cases *(85)*. The environment of cold stored red blood cells favors the

growth of *Y. enterocolitica* more than the growth of other, more likely contaminants (e.g., skin flora from donors) since *Y. enterocolitica* survives better than most bacteria at refrigeration temperatures. In addition, progressive hemolysis of stored blood may provide an ongoing supply of iron for *Yersinia's* growth. Virulent strains of *Yersinia* can also grow in calcium-free media such as that produced by citrate chelation of red blood cells for storage. Serotype 0:3 has accounted for the majority of cases of transfusion-related *Yersinia* sepsis. This serotype shows a persistent resistance to the bactericidal effect of serum at cold temperatures and has a growth–response curve that is directly related to the iron content of the culture medium *(86)*.

Enterobacter spp. and *Citrobacter* spp. thrive in aqueous environments and may cause healthcare-associated bacteremia by their ability to grow in infusion fluids *(87)*. *Enterobacter* spp. can fix nitrogen, allowing for replication in nitrogen-deficient fluids, and have been shown to have more rapid replication than *E. coli*, *Klebsiella*, *Pseudomonas*, or *Proteus (88)* in dextrose-containing solutions.

Examples of Genetics of Some Virulence Factors

R-plasmids, commonly found in Enterobacteriaceae, are also associated with bacterial virulence. They carry genes encoding virulence factors, such as adhesive factors *(57)*, enterotoxins, and hemolysins *(89)*. Plasmids code for outer membrane proteins for various Enterobacteriaceae. In *Y. enterocolitica*, a 70-kb plasmid codes proteins of the outer membrane that are associated with resistance to complement-mediated opsonization, to neutrophil phagocytosis, and to bactericidal activity of human serum *(90)*. Similar plasmids have been isolated in *Y. pseudotuberculosis* and *Y. pestis*. Two soluble plasmid-mediated antigens, V and W, have been isolated from virulent strains of *Y. pestis*, *Y. pseudotuberculosis*, and *Y. enterocolitica (90)*. Because plasmids are also important determinants of antimicrobial resistance, they may allow pathogens to link drug resistance and virulence determinants, which may be transferred together to other species.

Temporal Evolution of Antibiotic Resistance

The increasing prevalence of antibiotic-resistant Enterobacteriaceae has contributed to the difficulty in treating healthcare-associated infections (2,*91*,92). Antibiotic resistance often is related to excessive or widespread use of a particular antibiotic *(93)*. For example, aminoglycoside and cephalosporin resistance in *Klebsiella* has been correlated with exposure to and intensity of use of these drugs *(94,95)*. Mechanisms of antibiotic resistance in the Enterobacteriaceae include enzyme production that can inactivate or modify the drug (e.g., β-lactamase production), diminished permeability of antibiotics, and altered antibiotic target sites. Bacteria may acquire these mechanisms of resistance spontaneously via chromosomal mutation or via transfer of plasmids or transposable genetic elements from other bacteria *(96)*. Genes that determine resistance to different classes of antibiotics may occur on a single plasmid so that use of one antimicrobial can lead to resistance to other classes of antibiotics.

Common mechanisms of β-lactam antibiotic resistance include chromosomal mutation, which is frequent and offers a bacterial survival advantage during antibiotic therapy. This is the mechanism of resistance found in Enterobacteriaceae, such as *Enterobacter*, *Serratia*, indole-positive *Proteus*, and *Citrobacter*, which carry chromosomal genes that encode a type 1 β-lactamase *(96,97)*. These bacteria can undergo single-step mutations to constitutive high-level β-lactamase production. Thus, initially susceptible strains of *Enterobacter* and other Enterobacteriaceae may develop spontaneous resistant mutants to broad-spectrum cephalosporins during 20% to 50% of courses of therapy *(98)*. These AmpC enzymes may be present on plasmids and therefore, transmissible to other species such as *E. coli* and *Klebsiella* (99,*100*). The AmpC β-lactamase hydrolyzes cephamycins and oxyimino-β-lactamases (or third-generation cephalosporins) (101). AmpC enzymes are not inhibited by β-lactamase inhibitors such as clauvulanic acid, a characteristic that distinguishes them from extended-spectrum β-lactamases (ESBLs) (102).

Enterobacteriaceae have responded to the widespread use of β-lactam antibiotics with inactivation of these drugs by a variety of β-lactamases (such as TEM-1, TEM-2, and SHV-1 β-lactamases), which are typically plasmid-encoded *(96)*. These resistances were overcome by the pharmaceutical industry development of second- and third-generation cephalosporins and combinations of β-lactam antibiotics with β-lactamase inhibitors. However, in 1982, the first Enterobacteriaceae with resistance to broad-spectrum cephalosporins, such as cefuroxime, cefotaxime, and ceftazidime, were isolated in Europe *(103,104)*. These ESBLs arose by point mutations, which arose in the face of widespread use of antibiotics. ESBLs differ in only one or a few amino acids from the original TEM-1, TEM-2, and SHV-1 β-lactamases and are also plasmid-mediated *(96)*. Hundreds of ESBLs have been identified (101,*105–108*). Although the first ESBLs were reported from Europe, they have spread to most continents during the last two decades (*109*,110). Some of these ESBLs are highlighted in Table 34-6. *Klebsiella* spp. and *E. coli* have been the primary carriers of ESBLs in North America and Europe (111,112). ESBL profiles differ dramatically between the United States and Canada and between North America and Europe (111,112). Large surveillance studies have shown various rates of ESBL production depending on geographic location, on whether surveillance relied only on phenotypic data or used confirmatory microbiologic testing, and on which patient care areas were assessed (i.e., ICU vs. other wards) (Table 34-7).

While the healthcare-associated pathogen distribution remains similar *(11,116)*, increasing antibiotic resistance among Enterobacteriaceae infections is a major cause of concern in healthcare facilities. CDC reported that from 1998 to 2002 to 2003, there was a 47% increase in the rate of resistance to third-generation cephalosporins among *K. pneumoniae* recovered from healthcare-associated infections in ICU patients *(91)*. In addition, comparing 1986–2003 to 2006–2007, among pathogens causing device-associated healthcare-associated infections (HAIs) (2), resistance to extended-spectrum cephalosporins increased among healthcare-associated *E. coli* (6% vs. 6–11%) and *K. pneumoniae* (21% vs. 21–27%) isolates, and resistance to carbapenems increased among *Pseudomonas aeruginosa* (21% vs. 25%). Among all HAIs, while resistant gram-positive species represent the four most common antimicrobial-resistant pathogens, *P. aeruginosa* isolates resistant to

TABLE 34-6

Selected β-Lactamases of Enterobacteriaceae

β-Lactamase	*Enzyme Abbreviation*	*Name Origin*	*Year Described*	*Countries Where Prevalent*	*Species Carry Enzyme*	*Antibiotics Affected*	*Antibiotics Which Retain Activity*	*Unique Epidemiology*
Broad spectrum	TEM-1, TEM-2	TEM for 1st patient	1940 *(113)*	US	Most *K. pneumoniae,* Some *E. coli* *H. influenzae*, *N. gonorrhoeae*	Penicillin G, aminopenicillins, carboxypenicillin, ureidopenicillin, narrow-spectrum ceph	β-Lactam/β-lactamase inhibitor 4th generation cephalosporins Can show inoculum effect	
	SHV-1	SHV for variable response to sulfhydrl inhibitors		Canada, US			β-Lactam/β-lactamase inhibitor 4th generation cephalosporins Can show inoculum effect	
	OXA	Hydrolyze oxacillin				As above cloxacillin, methicillin, oxacillin	β-lactam/β-lactamase inhibitor	
Expanded-spectrum	TEM and SHV family		1983		*K. pneumoniae*, *E. coli*		Cephamycins, carbapenems	
	CTX-M	Hydrolyze cefotaxime and ceftzidime	1991 *(114)*	South America: Argentina Asia: Japan, China, Korea, Taiwan, India, Vietnam Eastern Europe: Poland Western Europe: Spain, Italy, Greece, UK Canada	*E. coli*, *K. pneumoniae*	Cefotaxime, ceftazidime, aztreonam, cefepime Trimethoprim/sulfamethoxazole tetracycline, gentamicin ciprofloxacin (125)	Variable activity: piperacillin/tazobactam	Community associated UTI
	PER			Italy, Turkey, South America	*Salmonella enterica* serovar	Penicillin, cephalosporins	Susceptible to clavulanic acid	

				Korea	*typhimurium (115)*, *E. coli*, *K. pneumoniae*, *P. mirabilis* *Pseudomonas*, *Acinetobacter* spp.			
	VEB	Vietnamese child first case	1999	France, Kuwait, China Korea	*E. coli*, *K. pneumoniae*, *E. cloacae*, *E. sakazakii*, *Pseudomonas* spp.	Ceftazidime, cefotaxime Aztreonam		
	OXA family	Oxacillin-hydrolyzing abilities		Turkey, France	*Pseudomonas*	Cefepime	Can be resistant to all β-lactams	
Carbapenemases	KPC		1996	US, New York City	*Klebsiella*, *E. coli*, *P. mirabilis*,	3rd and 4th generation cephalosporins, Carbapenems	Tigecycline, polymixins (colistin)	
				Israel	*S. cubana*, *E. cloacae*			
				Greece	*K. oxytoca*			
	IMP			Japan	*S. marcescens*, *Pseudomonas*		Aztreonam	
	NDM-1	New Dehli metallobeta-lactamase	2008	India, Pakistan	*E. coli, K. pneumoniae, E. cloacae*	Fluoroquinolones, aminoglycosides, beta-lactams including carbapenems	Tigecycline and colistin (137)	Travel related to medical tourism (seeking care abroad for a surgical procedure due to lower cost or faster availability)
	VIM	Verona integron-encoded metallo-beta-lactamase	2001	Greece	Mostly *K. pneumoniae* but also *E. coli, P. mirabilis*	Fluoroquinolones, aminoglycosides, beta-lactams including carbapenems	Tigecycline and colistin	Travel to Greece *(140)*
Amp C-plasmid mediated	CMY			US	*Salmonella*	Ceftriaxone, other oxyimino-β-lactams Cephmycins	Carbapenems but diminished porin expression can make carbapenems ineffective	

TABLE 34-7

Escherichia Coli and Klebsiella Pneumoniae Trends in Antimicrobial Resistance[a]

						E. coli								
						Bacteremia			*UTI*			*Pneumonia*		
Year	*Ref*	*Study Eponym*	*No. of Centers*	*Countries*	*Types of Units*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*
Fluoroquinolone														
1998–1999	372	ICARE	23	USA	ICU									
1998–1999	372	ICARE	23	USA	non-ICU									
2000–2002	16	TSN	87	Canada	ICU									
2000–2002	16	TSN	48	Italy	ICU									
2000–2002	16	TSN	169	Germany	ICU									
2000–2002	16	TSN	283	USA	ICU									
2002–2004	14	Merck	70[d]	USA	ICU	546		16	1,147		16	684		19
2002–2007	92	INICC	93	18:Latin America, Asia, Africa, Europe	ICU									
2005–2006	18	CAN-ICU	19	Canada	ICU	73		23	283		20	122		21
2006–2007	2	NHSN	463	USA	ICU + non-ICU	310	289 (93)	31	2,009	1,920 (96)	25	271	255 (94)	23
Third generation cephalosporins[g]														
1996–1999	372	ICARE	23	USA	ICU									
1996–1999	372	ICARE	23	USA	non-ICU									
2000–2002	16	TSN	87	Canada	ICU									
2000–2002	16	TSN	48	Italy	ICU									
2000–2002	16	TSN	169	Germany	ICU									
2000–2002	16	TSN	63	France	ICU									
2000–2002	16	TSN	283	USA	ICU									
2002–2004	14	Merck	70[d]	USA	ICU	546		3	1,147		3	684		5
2002–2007	92	INICC	93	18:Latin America, Asia, Africa, Europe	ICU									
2005–2006	18	CAN-ICU	19	Canada	ICU	73		6	283		4	122		3
2006–2007	2	NHSN	463	USA	ICU + non-ICU	310	258 (83)	8	2,009	1,577 (79)	6	271	173 (64)	11
Cefepime														
2000–2002	16	TSN	87	Canada	ICU									
2000–2002	16	TSN	48	Italy	ICU									
2000–2002	16	TSN	169	Germany	ICU									
2000–2002	16	TSN	63	France	ICU									
2000–2002	16	TSN	283	USA	ICU									
2002–2004	14	Merck	70[d]	USA	ICU	546		2	1,147		2	684		4

		K. pneumoniae										
		Bacteremia			*UTI*			*Pneumonia*				
No. of Isolates	*Pooled Mean Resistance Rate*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*Pooled Mean Resistance Rate*
20	2[b]										Not tested	
22	3[c]										Not tested	
776	14										485	4
496	13										287	21
3,137	11										1,228	4
14,920	12										9,626	6
2,874	17[e] 43	407		18	442		16	1,121		17	2,256	17[f] NR
536	21	26		4	51		0	122		3	224	4
											Not tested	
20	2[h]										18	8[i]
20	0.53[j]										20	5[k]
3,829	2										1,736	1
1,423	4										816	15
534	<1										166	<1
834	1										112	5
15,897	2										10,337	5
2,874	5[l] 54	407		14	442		10	1,121		12	2,256	12 68
536	4	26		0	51		0	122		0	224	<1
		563	483 (86)	27	722	579 (80)	21	446	329 (74)	24		
207	2										98	0
1,426	1										552	6
2,830	1										1,068	4
4,358	<1										840	3
10,356	2										7,276	3
2,874	3	407		9	442		7	1,121		8	2,256	8

(*Continued*)

TABLE 34-7

***Escherichia Coli and Klebsiella Pneumoniae* Trends in Antimicrobial Resistance (*Continued*)**

						E. coli								
						Bacteremia			*UTI*			*Pneumonia*		
Year	*Ref*	*Study Eponym*	*No. of Centers*	*Countries*	*Types of Units*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*
Carbapenem														
2000–2002	16	TSN	87	Canada	ICU									
2000–2002	16	TSN	48	Italy	ICU									
2000–2002	16	TSN	169	Germany	ICU									
2000–2002	16	TSN	63	France	ICU									
2000–2002	16	TSN	283	USA	ICU									
2002–2004	92	Merck	70[d]	USA	ICU	546		0	1,147		<1	684		0
2005–2006	18	CAN-ICU	19	Canada	ICU	73		0	283		0	122		0
2006–2007	2	NHSN		USA	ICU + non-ICU	310	226 (73)	<1	2,009	871 (43)	4	271	163 (60)	2

[a]Rounded to nearest integer.
[b]Increase from 0.9 in 1996–1997.
[c]Increase from 1.4 in 1996–1997.
[d]Average number of centers participating each year.
[e]Increase from 0.9 in 1993.
[f]Increase from 7.9 in 1993.
[g]Ref (*372*) % resistant to ceftazidime, ceftriaxone or cefotaxime; ref (92) % resistant to ceftriaxone or cefotaxime and remainder of studies, % resistant to ceftriaxone.
[h]Increase from 0.57 in 1996–1997.
[i]Increase from 2.4 in 1996–1997.
[j]Decrease from 0.69 in 1996–1997.
[k]Increase from 3.6 in 1996–1997.
[l]Increase from 1 in 1993.

fluoroquinolones, carbapenems, and β-lactam/β-lactamase inhibitor combinations represent the fourth, fifth, and sixth most common resistant pathogens, respectively. *K. pneumoniae* resistant to third-generation cephalosporins, *E. coli* resistant to fluoroquinolones, and *A. baumannii* resistant to carbapenems also are prominent causes of CLABSI, CAUTI, and VAP (Table 34-7).

In a surveillance study of 35,790 isolates (more than 50% of which were respiratory) from United States, ICUs in 43 states and the District of Columbia demonstrated decreasing susceptibility of gram-negative bacilli (including *Enterobacter* spp. and *Klebsiella*) to ciprofloxacin from 86% in 1994 to 76% in 2000 *(117)*. This decline coincided with increased national use of fluoroquinolones measured by sales of pharmaceuticals to retail stores and healthcare facilities. Resistance to ciprofloxacin was associated with crossresistance to other classes of broad-spectrum antimicrobial agents, including aminoglycosides, carbapenems, and third-generation cephalosporins *(117)*. CDC data from 2006 to 2007 show that among Enterobacteriaceae, resistance to fluoroquinolones, as well as to extended-spectrum cephalosporins and carbapenems, was higher than noted in surveillance studies from the late 1990s; fluoroquinolone-resistance rates for *E. coli* from CLABSIs, CAUTIs, and VAP were 30.8%, 24.8%, and 22.7%, respectively (Table 34-7).

Epidemiology of Selected β-Lactamases

Spread of multidrug-resistant *E. coli* clonal group A (CGA), was described initially in London, England, in 1986 *(118)* and has now been reported in cohorts of women with UTIs in California, Minnesota, and Michigan. This CGA *E. coli* accounted for almost 50% of community-acquired UTIs that were resistant to trimethoprim-sulfamethoxazole *(119)*. This clone also has been associated with the development of pyelonephritis *(120)* and anecdotally in a renal transplant patient from Buffalo, New York, with pneumonia and bacteremia who had taken trimethoprim-sulfamethoxazole prophylactic therapy *(121)*. In a study of 103 women with symptoms of cystitis and a positive urine culture, 15% had trimethoprim-sulfamethoxazole–resistant *E. coli*. In this small study, independently associated risk factors for having a pathogen resistant to trimethoprim-sulfamethoxazole

		K. pneumoniae										
		Bacteremia			*UTI*			*Pneumonia*				
No. of Isolates	*Pooled Mean Resistance Rate*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*No. of (%) Tested for Resistance*	*% R*	*No. of Isolates*	*Pooled Mean Resistance Rate*
3,386	0										1,766	0
2,254	0										1,066	0
5,172	0										2,351	0
8,994	0										1,567	0
15,353	0										10,263	0
2,874	<1	407		2	442		<1	1,121		<1	2,256	<1
536	0	26		0	51		0	122		0	224	0
		563	452 (80)	11	722	388 (54)	10	446	302 (68)	4		

included travel (within 3 months to Asia, S. America, Canada, or Europe) and Asian race. Prior exposure to the antibiotic and having a child in daycare were not associated with resistance *(122)*.

The burden of antibiotic-resistant pathogens has led to increased awareness of colonization with ESBLs in nonoutbreak and in community settings. In Spain, the rate of ESBL-producing isolates in fecal samples from hospitalized patients and outpatients increased significantly from 0.3% and 0.7% respectively, in 1991, to 11.8% and 5.5%, respectively, in 2003; and 3.7% of healthy volunteers, with no history of antibiotic use or hospitalization within 3 months, were colonized. In 1991, ESBL-producing isolates included *E. coli*, *Klebsiella*, and *Citrobacter*, whereas in 2003, all ESBL producers were *E. coli*. CTX-M and SHV enzymes were detected in outpatients, while TEM enzymes were limited to inpatients; the genetic diversity among isolates suggested horizontal transfer of genetic structures such as plasmids, transposons, or integrons, rather than clonal dissemination *(123,124)*.

CTX-M β-lactamases have become the predominant ESBL family in Europe, Africa, Asia, South America, and North America and are now beginning to be reported in the United States (125–127). CTX-M isolates emerged from the rarely pathogenic commensal genus, *Kluyvera*, and are typically associated with greater activity against cefotaxime than ceftazidime, though some are capable of hydrolyzing ceftazidime *(128)*. The phenotype for CTX-M isolates often demonstrates resistance to multiple antibiotics, including aminoglycosides, tetracyclines, sulfonamides, and fluoroquinolones, due to other genes present on the $bla_{\text{CTX-M}}$ plasmid (110,*129*).

CTX-M have been identified largely in community settings, primarily among patients with *E. coli* UTIs (125,130). *E. coli*–producing CTX-M enzymes have been identified in domestic animals, food products, sewage, and stool samples from healthy volunteers *(131,132)*. In the United Kingdom, many patients with community-onset CTX-M UTIs were elderly individuals who have multiple underlying illnesses and history of exposure to a hospital setting within the prior 3 years (126). In a study of 311 nonhospitalized patients with community-acquired UTI by ESBL-producing bacteria, multivariate analysis revealed independent risk factors associated with UTI included prior hospitalization

or antibiotic treatment within 3 months, age over 60 years, diabetes, male gender, *K. pneumoniae* infection, and prior use of second- or third-generation cephalosporins, quinolones, or penicillin *(133)*.

Fecal samples from 294 residents from 16 nursing homes in Ireland demonstrated multidrug-resistant *E. coli* in 40% of specimens (a rate that was 40 times that in the community). Half of these carriers had no history of hospitalization in the prior 1.5 years and only 13.5% had known history of ESBL colonization or infection. Half of the isolates carried the CTX-M-15 enzyme. Multivariate analysis showed independent host risk factors including days of fluoroquinolone use and UTI *(134)*.

Resistance to carbapenems has become more prevalent in Enterobacteriaceae, especially *K. pneumoniae* and *E. coli*. Dissemination of these resistant pathogens, which are common etiologies of healthcare-associated and community infections, is of particular concern because there are few antibiotic choices for treatment and none are orally available. Carbapenem-resistant Enterobacteriaceae (CRE) may be due to three carbapenemases including metallo-β-lactamases, *K. pneumoniae* carbapenemases, and oxacillinases *(135,136)*. The New Delhi metallo-β-lactamase (NDM-1) has been identified in *K. pneumoniae* and *E. coli* and has become widespread in India and Pakistan (137). NDM-1 has been identified in European, North American travelers who have sought medical care in India, due to lower cost and shorter waiting times for surgical procedures, termed "medical tourism" *(138,139)*. NDM-1 isolates have spread clonally, the common mode of spread, and have also spread by dissemination of a plasmid encoding the NDM-1 sequence into multiple species of Enterobacteriaceae. "Plasmid outbreaks" may allow for more rapid transfer of resistance when plasmid recipient bacteria are well adapted to their environment with efficient person-to-person spread. Plasmid rearrangement may lead to accumulation of resistance mechanisms. The NDM-1 gene confers resistance to fluoroquinolones, aminoglycosides, and β-lactams, including carbapenems, but remains sensitive to tigecycline and colistin *(136)*.

In addition, the Verona integron–encoded metallo-β-lactamase (VIM) carbapenemase has been identified in a returning US traveler who had a diarrheal illness on a Mediterranean cruise ship and was hospitalized in Greece, where VIM resistance mechanism has been previously identified (140).

K. pneumoniae carbapenemases (KPCs), KPC-1 to KPC-7, confer resistance or decreased susceptibility to almost all β-lactams (141), leaving few therapeutic options to treat infected patients, and are the most common mechanism of carbapenem resistance among Enterobacteriaceae in the United States *(142)*. Enterobacteriaceae that produce KPCs were first reported in 1996 from *K. pneumoniae* isolated in North Carolina *(143)*. KPC isolates were next recognized in New York City where molecular analysis revealed that 78 of 95 *K. pneumoniae* isolates from 10 acute-care hospitals belonged to one ribotype, suggesting crosstransmission *(144)*. By 2004, 24%, and by 2006, 38% of *K. pneumoniae* isolates from Brooklyn or other New York hospitals were KPC positive (145,*146*). KPCs may have spread from the United States to Israel, where KPC-2 and KPC-3 clones have caused outbreaks in Tel Aviv hospitals *(147)* and Athens *(148)*. The U.S.- and Israeli-derived isolates are genetically linked, suggesting spread by travelers and patients *(149)*.

KPC enzymes have spread to other Enterobacteriaceae including *E. coli*, *S. cubana*, *E. cloacae*, *P. mirabilis*, and *K. oxytoca* in up to 20 US states (141). KPCs have been identified in S. America, China, and less commonly in Europe, related to regional epidemics. Spread of KPCs occurs via large plasmids and transposons (141). *In vivo* transfer of bla_{KPC} carrying plasmids between two Enterobacteriaceae species has been documented *(150)*. KPC detection is challenging due to heterogeneous expression of β-lactam resistance and poor detection by automated systems due to variable levels of carbapenem resistance and low inocula. Screening tests to detect KPC-producing *Enterobacter* spp. by resistance to ertapenem have been reliable, but a confirmatory test is necessary because ertapenem resistance may arise from ESBL or AmpC production with outer membrane defects. Confirmatory testing may include modified Hodge test (though this will also detect other carbapenemases) or the disc diffusion method with ertapenem substrate and 3-aminophenyl boronic acid as an inhibitor that allows differentiation of KPC-type β-lactamase from other enzymes (141).

CDC data from 2006 to 2007 show 4% to 11% of *K. pneumoniae* healthcare-associated isolates were resistant to carbapenems, with the highest percentage of resistance seen in isolates from CLABSIs. New York hospitals have contributed disproportionately to the percentage of resistance isolates, based on a statewide resistance rate of approximately 21%; however, even when New York state hospitals are excluded from the CDC data, the resistance rate to carbapenems among *K. pneumoniae* was approximately 5%, representing increasing carbapenem resistance in many geographic regions (2).

Chapters 85 and 86 discuss antibiotic resistance in more detail.

EPIDEMIOLOGY OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROBACTERIACEAE

Reservoirs/Sources

The primary reservoirs for the Enterobacteriaceae are water, soil, and the human gastrointestinal tract *(3)*. Oropharyngeal and gastrointestinal colonization of hospital patients is common. Intestinal carriage of Enterobacteriaceae is associated with increased risk of infection. For example, the gastrointestinal tract is an important reservoir in outbreaks of healthcare-associated *K. pneumoniae* UTIs. A prospective study examining the role of intestinal colonization with multiply resistant *K. pneumoniae* demonstrated that 14 of 31 patients who became intestinal carriers of *K. pneumoniae* developed clinical infections with the same serotype, whereas only 11 of 101 patients who were not intestinal carriers developed clinical disease *(151)*.

In outbreaks of multidrug-resistant *P. mirabilis*, gastrointestinal carriage of the epidemic strain by susceptible patients has been shown to be an important reservoir for outbreak development and propagation *(152)*. In one study, approximately 75% of patients with healthcare-associated *Proteus* infections were intestinal carriers of the microorganism *(153)*. In contrast, the major reservoir of *P. rettgeri* has been

the urinary tract *(154)*, and in one study of 2,693 fecal isolates tested, no *P. stuartii* microorganisms were isolated *(155)*.

Many of the members of the family Enterobacteriaceae have a propensity for certain environments and reservoirs. *Serratia* thrives in moist environments. It frequently contaminates solutions and hospital equipment *(156,157)*. Its human reservoirs are the urinary and the respiratory tracts, primarily in patients subjected to devices such as indwelling bladder catheters *(156)* or endotracheal tubes *(158)*. The gastrointestinal tract may be the primary reservoir in infants and children but is an uncommon reservoir of *Serratia* in adults.

Enterobacter spp. thrive in moist environments and have been found contaminating the environment *(159)*, distilled water and humidifiers *(160)*, and infusion fluids *(161,162)*. Enterobacter also may be found in low numbers in the intestinal flora of 40% to 80% of healthy outpatients *(163)*. Multiple studies have shown increased rates of rectal colonization by Enterobacter after patient use of cephalosporin antibiotics *(163–165)*. *E. cloacae* is found more frequently than *E. aerogenes* and more often leads to clinical disease *(163)*.

C. freundii is the most prevalent *Citrobacter* microorganism found in stool and is an occasional cause of gastrointestinal disease (gallbladder, peritonitis) *(166,167)*.

Long-term acute-care facilities (LTACHs) and nursing homes serve as reservoirs and amplifiers of multidrug-resistant pathogens. LTACHs were initially created to care for, and thus ease the burden of Medicare spending for, difficult-to-wean patients from acute-care ICUs (168). LTACH patients usually have multiple significant comorbidites; often have multiple invasive devices, such as a central venous catheter or urinary catheters; and may require total parenteral nutrition—all of which place LTACH patients at high risk for healthcare-associated infections.

Host and Related Factors Controlling Colonization

Host factors are important in controlling the extent of colonization with Enterobacteriaceae, as discussed below. Host factors are also important in determining the susceptibility of the host to developing disease. Bacterial virulence factors tend to be associated with disease in patients with normal immunity, whereas bacteria without these virulence factors often can only cause disease in patients with diminished immunity (e.g., the very young and the very old), in patients with abnormal anatomy (e.g., hydronephrosis), or in patients whose mucosal barriers are breached by invasive devices. Site-specific infections and host factors are discussed briefly here and in the site-specific chapters.

A number of studies have shown that the patient's endogenous oropharyngeal flora is a common source of Enterobacteriaceae that cause infection in the hospitalized patient *(169–171)*. Oropharyngeal colonization with these bacteria is uncommon in healthy subjects, but increases with severity of underlying diseases or the presence of other risk factors for infection *(172)*. Many patients are colonized with potentially pathogenic Enterobacteriaceae before admission to the hospital *(173–175)*. These bacteria may increase in colony counts under selective pressures of antibiotic use in the ICU *(173,176)* or with increased duration of hospitalization *(177,178)*.

Oropharyngeal colonization with gram-negative bacteria is an important risk factor for the development of healthcare-associated pneumonia. In the early 1970s, 23% of patients with oropharyngeal colonization developed healthcare-associated pneumonia as compared to only 3% of the patients without colonization *(179)*. Similar findings were reported 25 years later; in multivariate risk factor analysis, oropharyngeal colonization with Enterobacteriaceae was the most important risk factor for the development of VAP *(177)*, and the risk of gram-negative pneumonia was estimated to be approximately eight times greater in patients with gram-negative bacillary oropharyngeal colonization *(172)*.

In contrast to oropharyngeal colonization, intestinal colonization with Enterobacteriaceae is universal in healthy subjects and hospitalized patients. However, intestinal colonization with resistant *E. coli* strains has been shown to increase with length of hospital stay. Approximately 30% to 40% of patients admitted to the hospital become colonized with hospital flora, including antibiotic-resistant Enterobacteriaceae, within 48 hours of admission. This rate of colonization increases in critically ill patients *(172)*. Although there is an association between an increased duration of antibiotic exposure and the likelihood to acquire colonization (and infection) with antibiotic-resistant Enterobacteriaceae, effects of modulation of antibiotic exposure on these resistance levels are not straightforward, and most studies suffered from methodological insufficiencies *(180)*. In a randomized crossover study in two ICUs in the Netherlands, a 40% reduction in β-lactam use (at the cost of a 243% increase in fluoroquinolone use) failed to reduce acquisition rates with cephalosporin-resistant Enterobacteriaceae but was associated with higher acquisition of cephalosporin-resistant Enterobacteriaceae with coresistance to the fluoroquinolones *(181)*.

Gastric pH The stomach is usually not colonized with gram-negative bacteria. However, in critically ill patients, gastric colonization frequently occurs and its incidence increases with time *(182,183)*. Gastric colonization with gram-negative bacteria has been assumed to be an important risk factor for the development of VAP. According to the hypothesis of the gastropulmonary route of infection, bacteria colonizing the stomach will subsequently colonize the oropharynx and be aspirated into the lower respiratory tract *(184,185)*. However, the relevance of the gastropulmonary hypothesis has been debated, since several studies failed to show an important role of gastric colonization in the pathogenesis of VAP *(186–188)*. Therefore, intragastric acidity influences gastric colonization, but whether this influences respiratory tract colonization and infection remains uncertain.

Fibronectin In normal hosts, fibronectin, a glycoprotein, is present on oral epithelial cells and facilitates adherence of gram-positive bacteria. It has been observed that loss of fibronectin uncovers cellular-binding sites and leads to increased rates of oropharyngeal colonization by gram-negative bacilli. One hypothesis to explain the loss of fibronectin is that salivary protease secretion, which degrades fibronectin, is increased in critically ill patients *(189,190)*.

Hormonal Modulation of Colonization Very little is known about the relationship between hormones and colonization. It has been observed that recurrent UTIs

occur in many postmenopausal women. Investigators have hypothesized that lack of estrogen leads to diminished colonization of the vagina by lactobacilli. Normally, lactobacilli adhere to uroepithelial cells and have been shown to exclude the adherence of *E. coli*, *K. pneumoniae*, and *P. aeruginosa (191)*. The absence of lactobacilli appears to result in increased vaginal pH (>4) and increased rates of colonization by Enterobacteriaceae, especially *E. coli*. In one study, intravaginal estriol administration resulted in increased colonization by lactobacilli, decreased vaginal pH, decreased Enterobacteriaceae colonization, and significantly reduced incidence of recurrent UTI in postmenopausal women *(192)*.

Biliary Tract and Urinary Tract Obstruction Colonization and stasis facilitate the development of acute cholangitis and UTI. Wang et al. *(35)* examined the role of *E. coli* virulence factors and host factors in patients with *E. coli* bacteremia who met clinical and radiographic criteria for acute cholangitis or upper UTI. The authors found that obstruction was an important host factor leading to bacteremia (100% of those with acute cholangitis and bacteremia were obstructed; 31% of those with upper UTI were obstructed). The most common causes of biliary obstruction included choledocholithiasis, cholangiocarcinoma, ampullary carcinoma, and pancreatic head tumor, and the causes of urinary tract obstruction included nephrolithiasis, ureteral tumor, neurogenic bladder, benign prostatic hypertrophy, and uterine tumor.

Neutrophil Elastase Neutrophil elastase (NE) is the first neutrophil factor that targets bacterial virulence proteins. In neutrophils with inactivated NE, *Shigella* escapes from phagosomes, increasing bacterial survival. NE cleaves virulence factors in *Shigella*, *Salmonella*, and *Yersinia (193)*.

Modes of Transmission and Outbreaks of Enterobacteriaceae

Enterobacteriaceae are primarily spread in the hospital from person to person via the hands of healthcare personnel or from environmental reservoirs to patients (Fig. 34-1). These modes of transmission have been documented in multiple outbreaks of healthcare-associated UTIs due to *Klebsiella*, *P. rettgeri*, and *Serratia*, as well as in multiple neonatal intensive care unit (NICU) outbreaks due to the Enterobacteriaceae. The majority of studies commonly cited in discussions of the epidemiology of healthcare-associated infections caused by the Enterobacteriaceae are analyses of common source (Table 34-8) or person-to-person outbreaks. Thus, most of the data characterizing the epidemiology of Enterobacteriaceae are derived from retrospective studies of epidemic strains.

Many healthcare-associated outbreaks caused by Enterobacteriaceae that produce ESBLs have been reported *(215–218)*. Most outbreaks occurred in special care wards such as ICUs and oncology wards; *K. pneumoniae* was involved in almost all outbreaks; and extensive use of third-generation cephalosporins, mostly as monotherapy, frequently was a risk factor *(217–220)*. Some outbreaks were caused by the spread of a single ESBL gene among multiple genotypes of Enterobacteriaceae *(217,220,221)*, although horizontal spread of bacteria with ESBLs has been described as well *(222,223)*. As with methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), environmental contamination may contribute to the epidemiology of Enterobacteriaceae containing ESBLs *(223,224)*. Situations of endemicity of colonization with ESBL-producing Enterobacteriaceae have been reported *(225–228)*. For example, in Chicago, ceftazidime resistance due to TEM-10 has been endemic among multiple strains of *K. pneumoniae* and *E. coli*; the prevalence of these strains was especially high in nursing home patients *(225)*. In addition, ESBL-producing Enterobacteriaceae were already endemic in a French ICU in 1990; the risk for patients to acquire these bacteria was 4.2% in the first week of stay in the ICU and increased to 24% by the fourth week, and most cases of colonization were caused by the same strain type *(226)*.

A regional outbreak of KPC-producing *K. pneumoniae* that affected multiple facilities, including tertiary care and community hospitals and nursing homes, appeared to have spread from a single LTACH *(229)*. Infections due to KPC microoganisms tend to occur in immunocompromised patients and those with invasive devices *(230,231)*. Risk factors associated with acquisition of KPC pathogens include prolonged hospitalization, stay in ICU, immunosuppression, and exposure to multiple antibiotics *(230,232)*. Prior antibiotic regimens did not necessarily

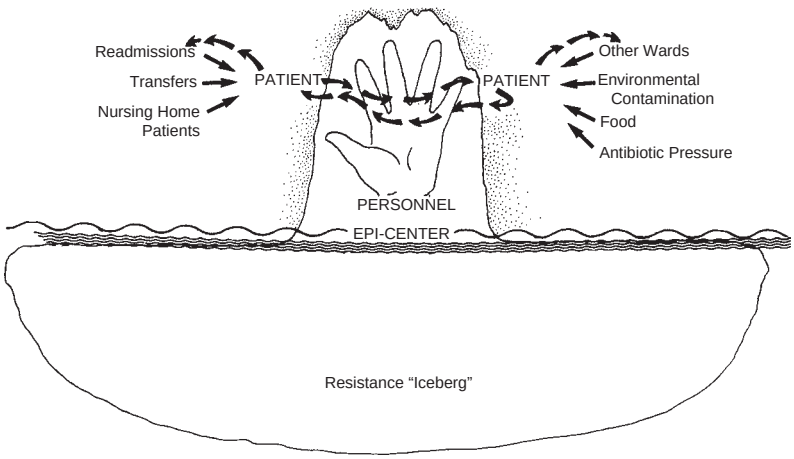

FIGURE 34-1 Infection control "iceberg," depicting the epidemiology of infections in hospitals, emphasizing the often unrecognizable colonization of patients with antibiotic-resistant Enterobacteriaceae and other potential pathogens (e.g., other gram-negative bacilli, MRSA, VRE). (Reproduced from Weinstein RA, Kabins SA. Strategies for prevention and control of multiple drug resistant healthcare-associated infection. *Am J Med* 1981;70:449–454, with permission from Elsevier.)

TABLE 34-8

Examples of Common-Source Outbreaks due to Enterobacteriaceae

Species (Ref.)	*Sites*	*Number of Cases (Attack Rate per 100 Discharges)*	*Source*	*Risk Factors*	*Antibiotic Resistance*
P. rettgeri, P. stuartii (194)	Urine	48	Urinary leg bag	Chronic indwelling urinary catheter	Gentamicin
P. stuartii (195)	Urine, blood	4	Urinals, patients with condom catheters	NA	Sensitive to amikacin, carbenicillin, cefoxitin only
S. liquifaciens (196)	Blood	12	Pooled epoetin alpha	Hemodialysis	NA
S. marcescens (197)	No clinical infection	30 (colonized)	Breast pump	Infants receiving pumped human milk	NA
S. marcescens (198)	Eye	3	Eye dropper	Keratoplasty	NA
S. marcescens (199)	Urine	32	Urometers and urine-measuring containers	Exposure to ICU indwelling urinary catheter antibiotics exposure to urine measuring devices	Sensitive to nalidixic aicd and/or amikacin only
S. marcescens (200)	Blood	6	Mean arterial pressure monitor	ICU hospitalization with arterial line	NA
S. marcescens (201)	Blood, wound	6	Quaternary ammonium disinfectant	Use of cardiopulmonary bypass with extra corporeal circulation	NA
S. marcescens (202)	Blood	7	Pressure transducer	Use of intraarterial balloon pump and pulmonary artery pressure measurement	NA
S. marcescens (203)	Blood	21	Dialyzer	Hemodialysis	Ampicillin, tetracycline
S. marcescens (204)	Knee/shoulder joints	10	Aqueous benzalkonium chloride	Joint infection in same physician	NA
S. marcescens (251)	Lung, wound, blood, urine	14	Reusable 12-lead electrocardiogram bulb	Open heart surgery severity of underlying disease	NA
S. marcescens (250)	Wound	4	Extrinsically contaminated saline solution	Volume of saline injected into mammary implant	Ampicillin, cefazolin
S. marcescens (205)	Urine	10	Urinary tract of asymptomatic catheterized patients	Increased length of hospital stay, >3 UTIs in previous 6 mo	Ampicitlin, cephalothin, cefoxitin, gentamicin, tobramycin, ticarcillin, nitrofurantoin
S. marcescens (162)	Lung, blood, CSF, urine	6	Graduated cylinder to measure urine output	NA	Gentamicin, tobramycin
E. sakazakii (77)	Blood, stool, urine	4	Powdered infant formula	Receiving implicated formula	NA
C. freundii (206)	Blood	3	Intrinsically contaminated 5% dextrose in lactated Ringer solution	Receiving intravenous fluid	NA
E. agglomerans, E. cloacae (207)	Blood	378	Elastomer disk within screw cap of intravenous fluid bottle	Receiving intravenous fluid manufactured by one company	*E. cloacae*—ampicillin, cephalothin *E. agglomerans*—nitrofurantoin
E. cloacae (160)	Blood	4	Distilled water containers (respiratory) humidifiers	NA	Gentamicin, tobramycin, kanamycin, piperacillin, chloramphenicol

(*Continued*)

TABLE 34-8

Examples of Common-Source Outbreaks due to Enterobacteriaceae (*Continued*)

Species (Ref.)	*Sites*	*Number of Cases (Attack Rate per 100 Discharges)*	*Source*	*Risk Factors*	*Antibiotic Resistance*
E. cloacae (208)	Blood	15	Hydrotherapy water (bum unit)	Extent of bum, severity of underlying diseases	Streptomycin, chloramphenicol carbenicillin, ampicillin,cephalothin
Salmonella typhimurium (259)	Stool	18	Eggs	Consumed fresh egg nog	NA
S. typhimurium (262)	Stool	7	Fiberoptic endoscope	Upper endoscopy	NA
S. enteritidis (209)	Blood, Stool	4	Refrigerator and sink in hemodialysis unit	Hemodialysis	NA
S. enteritidis (210) (serotype drypool)	Stool	11	Luncheon food	NA	NA
S. enteritidis (260) (serotype drypool)	Stool	404	Eggs	Eating hospital-prepared mayonnaise	NA
Salmonella eimsbuettel (261)	Stool	25	Rectal thermometer	Newborn infants receiving rectal thermometers, mothers, staff	NA
Salmonella worthington (263)	CSF, stool, blood	18	Rubber tubing of oropharyngeal suctioning apparatus	Oropharyngeal suctioning in NICU	
S. marcescens (211)	Blood	18	Contaminated intravenous $MgSO_4$	Receiving IV $MgSO_4$ purchased from compounding pharmacy that created anticipatory batches of medication without prescription	NA
S. marcescens (212)	Blood	162	Prefilled heparin and/or saline syringes	Use of prefilled heparin and/or saline syringes from manufacturing company failing to use adequate controls to ensure sterility of prefilled syringes	NA
S. marcescens (213)	Tracheal aspirates	5	Contaminated unmedicated liquid soap	Exposure to central or percutaneous venous catheters; longer exposure to endotracheal intubation housing in room with contaminated soap dispenser	Resistant to amoxicillin, amoxicillin/clavulanate, cefalotin cefamandole, colistin
K. pneumoniae (214)	Blood, urine, respiratory perfusion needle (colonization)	10	Contaminated rinse solution (tap water) for neonatal aspiration tubing	Mucus aspiration performed at birth or on arrival in the emergency department	Resistant to quinolones, cefotaxime, ceftazidime, gentamicin, and TMP/SMX; SHV-2 and CTX-M15 ESBL identified

CSF, cerebrospinal fluid; ICU, intensive care unit; NA, not available.

include a carbapenem, but all patients were exposed to either another β-lactam or a fluoroquinolone *(230)*.

Over the past decade, CTX-M enzymes have caused numerous healthcare outbreaks in Europe. CTX-M-15 has been the dominant enzyme in Hungarian, Spanish, and Scandinavian outbreaks. Most outbreak isolates were from UTIs or BSIs *(216,233,234)*.

TYPES OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY ENTEROBACTERIACEAE

Urinary Tract

UTIs are the most common healthcare-associated infection in the United States. Approximately 35% of the pathogens associated with healthcare-associated UTIs are members of the family Enterobacteriaceae. *E. coli* is the leading pathogen, implicated in 21% of all CAUTIs (NHSN data 2006–2007) (2). *K. pneumoniae* is the fifth leading cause of healthcare-associated UTIs and is recovered from 8% of cases. *Enterobacter* spp. are ranked sixth and are recovered from 4% of cases (Table 34-9).

In 2005, CDC began collecting data on device-associated infections. Healthcare-associated UTI is now reported as CAUTI. Criteria for defining CAUTI may be found at http://www.cdc.gov/nhsn/library.html. For 2006 to 2008, NHSN acute-care hospitals reported pooled mean CAUTI rates from 0 to 14.4 infections per 1,000 urinary catheter days (235); so, Enterobacteriaceae cause approximately 5 infections per 1,000 catheter days.

Risk factors for healthcare-associated UTIs usually are host- and device-related rather than pathogen-related, with the presence of a urinary catheter being most important. The catheter predisposes to UTIs in several ways. It offers a possibility for bacteria to enter the bladder along external or internal surfaces of the catheter and for development of a biofilm that can protect bacteria from antibiotics and host defenses; adhesion to mucosal surfaces will be facilitated; the catheter may blunt adequate antibacterial polymorphonuclear leukocyte function; and catheter drainage is frequently imperfect,

TABLE 34-9

Most Frequently Reported Enterobacteriaceae and Selected Other Pathogens Associated with Healthcare-Associated UTI, CDC

	Percentage (n)				*Rank*			
	Hospital Wide		*ICUs*		*Hospital Wide*		*ICUs*	
Pathogen	***1980–1982***	***1990–1996***	***2006–2007[a]***	***1992–1999***	***1980–1982***	***1990–1996***	***2006–2007[a]***	***1992–1999***
Enterobacteriaceae								
Citrobacter spp.	2	2	NA	NA	11	8	NA	NA
Enterobacter spp.	4	5	4	5	6	6	6	6
E. coli	32	24	21	18	1	1	1	1
K. pneumoniae	7	8	8	6	4	4	5	5
Klebsiella spp.	2	1	1	NA	9	10	10	NA
P. mirabilis	7	5	NA	NA	5	6	NA	NA
Proteus spp.	1	0	NA	NA	13	12	NA	NA
S. marcescens	1	1	NA	NA	12	10	NA	NA
Serratia spp.	0	0	NA	NA	14	12	NA	NA
Total	**56**	**46**	**34**	**29**				
Other pathogens								
P. aeruginosa	12	11	10	11	3	3	4	4
A. baumannii	NA	NA	1	NA	NA	NA	9	NA
S. aureus	2	2	2	2	10	8	8	8
Coagulase-negative staphylococci	3	4	3	3	7	7	7	7
Enterococci	14	16	15	14	2	2	3	3
C. albicans	3	8	15	16	8	4	2	2
Other *Candida* spp. or NOS	NA	NA	6	NA	NA	NA	NA	NA
Other	10	13	14	26				
Total	**100**	**100**	**100**	**100**				
(*n*)	(56,316)	(35,079)	(9,377)	(30,701)				

[a]CDC NHSN 2006 to 2007 data reports device-associated hospital-associated infections from 912 ICUs (88% of 1,040 reporting units) and 128 non-ICUs (12% of 1,040 reporting units). Of 8,579 CAUTIs, 6,778 (79%) were from ICUs and 1,801 (21%) were from non-ICUs.
NA, not available.
(Data from refs. 2, *11, 12* and *13*; data from 1980 to 1982 and 1990 to 1996 represent the hospital-wide component, and data from 1992 to 1999 the ICU component of the National Healthcare-associated Infections Surveillance (NNIS) system.)

leading to residual urine volumes in the bladder *(236)*. In multivariate analysis, nine independent risk factors for catheter-associated bacteriuria were found: duration of urinary catheterization, absence of use of a urinometer, microbial colonization of the drainage bag, diabetes mellitus, absence of antibiotic use, female gender, indications for other than surgery or output measurement, abnormal serum creatinine, and errors in catheter care *(237)*. Other risk factors reported include any urinary tract or catheter obstruction to flow (e.g., prostatic hypertrophy or stones) and periurethral colonization *(236,238)*. In the presence of urinary catheters with or without obstruction, relatively nonvirulent microorganisms can cause infection *(30–32)*. For instance, P fimbriae, the most important virulence factor in non–CAUTIs, were found in only 10% of *E. coli* strains recovered during febrile episodes of CAUTIs *(236)*. The incidence of new-onset bacteriuria is approximately 5% to 10% per day during the first week of catheterization. The prevalence of bacteriuria increases during the first month of catheterization until virtually all patients have bacteriuria *(239)*.

Routes of entry of bacteria into the bladder vary for catheterized men and women. Approximately 70% of bacteriuria cases in women occur as a result of periurethral entry of Enterobacteriaceae that have colonized the perineum *(240,241)*. In men, because the urethral passage is longer, the primary route of bacterial entry presumably is through the catheter lumen *(238,241)*. Although periurethral colonization in men does occur, transient hand carriage of pathogens by personnel leading to crossinfection may have a greater role in healthcare-associated UTIs in men *(238)*. Broad-spectrum antibiotics alter flora, increasing colonization with resistant Enterobacteriaceae and thus increasing the likelihood of UTI with these strains. In two studies, *E. coli* and *Proteus* accounted for a progressively smaller, and *Serratia* and *Pseudomonas* a progressively greater, proportion of healthcare-associated UTIs as length of hospitalization and catheterization increased *(242,243)*.

Antimicrobial resistance has continued to pose an increasing challenge over the past decade. NHSN data from 2006 to 2007 demonstrate that approximately one-quarter of CAUTI are caused by fluoroquinolone-resistant *E. coli*. For CAUTI due to *K. pneumoniae*, approximately 20% were resistant to third-generation cephalosporins and 10% were resistant to carbapenems (2) (see also Chapter 20).

Pulmonary

The second most common site of healthcare-associated infection is the lungs *(244)*. The pathogenesis of healthcare-associated pneumonia most often involves the patient's aspiration of oropharyngeal contents, or inoculation of contaminated material directly into an endotracheal tube *(245)*. Duration of ventilation and oropharyngeal colonization with Enterobacteriaceae are important risk factors for pneumonia *(177)*. Oropharyngeal colonization with Enterobacteriaceae can also occur via exogenous contamination from respiratory therapy equipment and from patient-to-patient spread of bacteria on the unlearned hands of personnel (see also Chapter 22).

Respiratory tract infections outnumber symptomatic UTIs in the ICU. The May 2007 Extended Prevalence of Infection in Intensive Care (EPIC II) 1-day worldwide point prevalence study included 14,414 patients in 1,265 ICUs from 75 countries; 7,087 patients were considered to be infected. Respiratory infection accounted for 64% of infections and represented the most common site of infection in each of seven participating regions around the world. Sixty-two percent of the infections were due to gram-negative pathogens, of which *Pseudomonas* spp. (20%) and *E. coli* (16%) were the most common isolates *(246)*.

Approximately 23% of VAP episodes were due to Enterobacteriaceae in the 2006 to 2007 NHSN summary of antimicrobial-resistant healthcare-associated pathogens (2). *Enterobacter* spp., along with *A. baumannii*, were the third (each 8.4%) leading cause of VAP after *S. aureus* and *P. aeruginosa* (24.4% and 16.3%, respectively) (Table 34-10).

For individual pathogens, highest percentages are found for *S. aureus* and *P. aeruginosa,* but as a group Enterobacteriaceae still represent an important proportion of pathogens, especially when VAP is diagnosed after 4 days of mechanical ventilation (late-onset pneumonia). At that time, most patients have respiratory tract colonization with these pathogens. In contrast, early-onset pneumonia (i.e., diagnosed within 4 days of ventilation) is more frequently caused by streptococci and *Haemophilus influenzae*. These community-acquired bacteria colonize the upper respiratory tract at the time of intubation. However, in a comparison of patients with early-onset pneumonia, defined as occurring within 96 hours of ICU admission (n = 235 patients [56%]) to late-onset pneumonia (n = 185 patients [44%]) in a medical ICU and a surgical ICU from a teaching hospital, *Enterobacter* spp. represented 10% of isolates from both groups, *K. pneumoniae* represented 5.5% and 6.5%, respectively, *E. coli* was found in 2.6% and 1.6%, respectively, and *Citrobacter* represented approximately 1% of each *(247)*. These data and more recent studies have challenged the notion that early-onset VAP reflects community-acquired pathogens.

Surgical Site Infections

Approximately 17% of incisional SSIs involve Enterobacteriaceae (NHSN 2006–2007) (2). *E. coli* accounts for 10% and *Enterobacter* spp. account for 4% of pathogens recovered from incisional surgical site infections (Table 34-11). The pathogens isolated from surgical site infections vary primarily with the type of surgery performed. In surgical procedures involving clean-contaminated, contaminated, and dirty fields, the pathogens isolated reflect the normal endogenous flora of the resected organ *(248,249)*. Antibiotic prophylaxis may permit selective overgrowth of antimicrobial-resistant Enterobacteriaceae.

Enterobacteriaceae have been associated with extrinsic contamination of devices and solutions used perioperatively, leading to surgical site infections. For example, *Serratia marcescens* has contaminated saline solutions, leading to surgical site infection after breast reconstruction with silicone mammary prostheses *(250)*, and has contaminated reusable electrocardiogram bulbs, leading to postoperative sternal and leg incision infections in cardiac surgery patients *(251)* (see also Chapter 21).

In NHSN data, 23% of *E. coli* from SSIs were resistant to fluoroquinolones; in these data, *E. coli* was the fifth most common pathogen after the gram-positive pathogens MRSA, VRE, and ARE, and *A. baumannii* (2).

TABLE 34-10

Most Frequently Reported Enterobacteriaceae and Selected Other Pathogens Associated with Ventilator-Associated Healthcare-associated Pneumonia in ICU, CDC

	Percentage (n)		*Rank*	
Pathogen	***1992–1999***	***2006–2007[a]***	***1992–1999***	***2006–2007[a]***
Enterobacteriaceae				
Citrobacter spp.	NA	NA	NA	NA
Enterobacter spp.	11	8	3	3
E. coli	4	5	6	6
K. pneumoniae	7	7	4	5
Klebsiella spp.	NA	2	NA	8
P. mirabilis	NA	NA	NA	NA
Proteus spp.	NA	NA	NA	NA
S. marcescens	NA	NA	NA	NA
Serratia spp.	NA	NA	NA	NA
Total	**22**	**22**		
Other pathogens				
P. aeruginosa	17	16	2	2
A. baumannii	NA	8	NA	3
S. aureus	18	24	1	1
Coagulase-negative staphylococci	NA	1	NA	9
Enterococci	2	1	7	10
C. albicans	5	2	5	7
Other	32	23		
Totals	**100 (39,810)**	**100[b] (5,960)**		

[a]CDC NHSN 2006 to 2007 data reports device-associated hospital-associated infections from 912 ICUs (88% of 1,040 reporting units) and 128 non-ICUs (12% of 1,040 reporting units). Of 4,524 VAPs, 4,354 (96%) were from ICUs and 170 (4%) were from non-ICUs.
[b]Sum not 100 because of rounding to nearest integer.
NA, not available.
(Data from refs. 2, and *11*; data from 1992 to 1999 represent the ICU component, of NNIS.)

Diarrhea

Although *Salmonella*, *Shigella*, *Yersinia*, *E. coli*, *Citrobacter*, and *Enterobacter* all have been implicated as healthcare-associated diarrheal pathogens, the Enterobacteriaceae are uncommon causes of healthcare-associated diarrhea. Healthcare-associated infectious diarrhea due to Enterobacteriaceae usually represents exogenously acquired disease. The mode of transmission is either the fecal-oral route by crossinfection or common source infection secondary to contaminated food or medicine. Patients may have indirect contact with an infectious patient either by sharing a room or a bathroom or via the hands of hospital personnel *(162,252,253)*.

Salmonella infections are the most common of the healthcare-associated diarrheal diseases due to the Enterobacteriaceae. Between 10% and 30% of the reported cases of *Salmonella* infection in the United States occur in institutions (hospitals, nursing homes, custodial facilities) *(254,255)*. Healthcare-associated infection with *Salmonella* is more common in developing countries *(256,257)*. Fifty percent of healthcare-associated cases of salmonellosis in the United States occur in newborn nurseries and pediatric wards *(255,258)*.

Sources of *Salmonella* in healthcare-associated outbreaks include other patients and contaminated foods, especially eggs, and devices. In the past, contaminated egg products, hospital eggnog *(259)*, and raw eggs used in the preparation of mayonnaise *(260)* have led to large outbreaks of healthcare-associated diarrhea. The routine availability of pasteurized egg products should eliminate this problem in US hospitals. The mayonnaise outbreak that occurred in 1989 was the largest healthcare-associated outbreak of *S. enteritidis* in US history, with 404 (42%) of 965 inpatients in a single hospital affected, resulting in nine deaths *(260)*.

Contaminated devices, rectal thermometers *(261)*, gastroscopes *(262)*, and rubber tubing of oropharyngeal suction devices *(263)* all have been associated with healthcare-associated *Salmonella* infection. Soiled linens have been reported as a source of healthcare-associated *Salmonella* infection in laundry workers in both hospital and nursing home outbreaks of *Salmonella* gastroenteritis *(264–266)*.

TABLE 34-11

Most Frequently Reported Enterobacteriaceae and Selected Other Pathogens Associated with Healthcare-Associated Surgical Site Infection, CDC

	Percentage (n)			*Rank*		
Pathogen	***1980–1982***	***1990–1996***	***2006–2007***	***1980–1982***	***1990–1996***	***2006–2007***
Enterobacteriaceae						
Citrobacter spp.	1	1	NA	11	10	NA
Enterobacter spp.	6	7	4	6	6	6
E. coli	13	8	10	2	4	4
K. pneumoniae	4	3	3	8	7	7
Klebsiella spp.	1	1	1	9	10	9
P. mirabilis	5	3	NA	7	7	NA
Proteus spp.	1	0	NA	13	13	NA
S. marcescens	1	1	NA	10	10	NA
Serratia spp.	0	0	NA	14	13	NA
Total	**32**	**24**	**18**			
Other pathogens						
P. aeruginosa	7	8	6	4	4	5
A. baumannii	NA	NA	1	NA	NA	9
S. aureus	18	20	30	1	1	1
Coagulase-negative staphylococci	6	14	14	5	2	2
Enterococci	11	12	11	3	3	3
C. albicans	1	3	2	12	7	8
Other	25	20	19			
Total	**100 (28,906)**	**100 (17,871)**	**100[a] (7,025)**			

[a]Sum not 100 because of rounding to nearest integer.
(Data from refs. 2, *12*, and *13*.)

Neonatal outbreaks generally are associated with infant-to-infant spread, presumably on the hands of hospital personnel, from an index patient who acquired the infection at delivery from the mother.

The correlation of specific serotypes and sources should be considered when *Salmonella* is isolated in the hospital. For example, *S. choleraesuis* has been associated with pork products, *S. cubana* with carmine dye, *S. dublin* with beef products, and *S. pullorum* with poultry products.

Healthcare-associated transmission of *Shigella* has been reported *(267,268)*, and termed "asylum dysentery" in the early 1900s *(269)*. An outbreak of *Shigella dysenteriae* type 1 occurred at a chronic care psychiatric facility in Durban, South Africa, involving 10 patients, 4 of whom died. The infection in the index case was thought to be community-acquired. Strict adherence to infection control measures (cohorting, hand hygiene, and restriction of food supplies brought in from outside the hospital) resulted in control of the outbreak. The high mortality rate was attributed to late recognition of the etiologic agent and failure to treat with appropriate antimicrobials *(268)*.

E. coli is a serious healthcare-associated enteric pathogen for newborn infants and young children. The commonest scenario is crossinfection and environmental contamination from an infected child with diarrhea due to an enteropathogenic *E. coli*. Asymptomatic carriers also are an important cause of epidemics. Although most healthcare-associated enteric disease is due to enteropathogenic *E. coli*, there has been one large hospital nursery outbreak due to enterotoxigenic *E. coli (270)*. Enterohemorrhagic *E. coli* has been reported in several healthcare-associated outbreaks *(271–275)*. Transmission has been attributed to person-to-person spread, environmental contamination, and contaminated lettuce *(276)*.

There have been at least four reports of healthcare-associated transmission of *Y. enterocolitica* diarrhea *(277–280)*. The mode of transmission is similar to that of the other enteric pathogens, with indirect contact spread from patient to patient via shared fomites and via the hands of personnel. A retrospective analysis of *Yersinia* infections in one hospital revealed 18 infections over 4 years; 5 infections appeared to be healthcare-associated *(280)*. In most of these cases, a patient admitted with *Y. enterocolitica* gastroenteritis appeared to be the source of crossinfection. *Y. enterocolitica* is a rarely recognized enteric healthcare-associated pathogen, perhaps because it is difficult to isolate in the laboratory, because clinicians do not have a high index of suspicion for *Yersinia* as a pathogen, and because many patients may not be symptomatic *(281)*. The outbreaks that have been reported to date have been small, and it is likely that such outbreaks may be missed easily.

Antimicrobial resistance has been a problem seen in cases of healthcare-associated diarrhea infections. *S. enterica* serotype Livingstone with the CTX-M-27 enzyme caused a diarrhea outbreak in Tunisia during 2002 in 16 heavily antibiotic-treated neonates; 3 developed bacteremia and 2 died. Isolates also were resistant to aminoglycosides and sulfamethoxazole/trimethoprim *(282)*. Fluoroquinolone-resistant *S. enterica* serotype Schwarzengrund resulted in 11 ill patients at two nursing homes and an acute-care facility in Oregon during 1996 to 1998. Prior fluoroquinolone use was associated with infection in four of five nursing home residents at one facility. Transmission likely occurred patient to patient or through contaminated surfaces *(283)*.

Bacteremia

As a group, Enterobacteriaceae account for approximately 13% of healthcare-associated BSIs (NHSN, 2006–2007) (2). *K. pneumoniae*, *E. coli*, and *Enterobacter* spp. are the most common Enterobacteriaceae causing such bacteremias (Table 34-12). For 2006 to 2008, NHSN acute-care hospitals reported pooled mean CLABSI rates from 0 to 5.5 infections per 1,000 catheter days (235); so, Enterobacteriaceae cause approximately 0.66 infections per 1,000 catheter days. In a Spanish multicenter study, *K. pneumoniae*, *E. coli*, *and E. cloacae* accounted for 5.6%, 2.5%, and 1.9%, respectively, of 590 cases of healthcare-associated bacteremia *(284)*.

Approximately half of *E. coli* bacteremias are healthcare-associated. The most common portal of entry of infection for both community-acquired and healthcare-associated *E. coli* bacteremia is the urinary tract *(285,286)*. The overall mortality rate from *E. coli* bacteremia is approximately 20% *(284,285)*. Bacteremias that originate outside the urinary tract tend to have a worse outcome.

The majority of bacteremias due to *Enterobacter* spp., primarily *E. cloacae* and *E. aerogenes*, are healthcare-associated. Several large series of cases of bacteremia due to *Enterobacter* spp. report that 67% to 84% of the bacteremias were healthcare-associated *(285,287–290)*. Approximately one-third of these cases are polymicrobial. Major portals of entry for *Enterobacter* spp. in bacteremic patients include the lung, surgical sites/skin wounds, the urinary tract, and central

TABLE 34-12

Most Frequently Reported Enterobacteriaceae and Selected Other Pathogens Associated with Healthcare-Associated BSI, CDC

	Percentage (n)				*Rank*			
	Hospital Wide		*ICUs*		*Hospital Wide*		*ICUs*	
Pathogen	***1980–1982***	***1990–1996***	***2006–2007[a]***	***1992–1999***	***1980–1982***	***1990–1996***	***2006–2007[a]***	***1992–1999***
Enterobacteriaceae								
Citrobacter spp.	1	1	NA	NA	12	9	NA	NA
Enterobacter spp.	6	4	4	5	6	7	6	4
E. coli	13	5	3	2	2	4	8	8
K. pneumoniae	8	5	5	3	4	4	5	7
Klebsiella spp.	2	1	1	NA	10	9	10	NA
P. mirabilis	2	1	NA	NA	11	9	NA	NA
Proteus spp.	0	0	NA	NA	14	13	NA	NA
S. marcescens	3	1	NA	NA	8	9	NA	NA
Serratia spp.	1	0	NA	NA	13	13	NA	NA
Total	**36**	**18**	**13**	**10**				
Other pathogens								
P. aeruginosa	6	3	3	4	7	8	7	6
A. baumannii	NA	NA	2	NA	NA	NA	9	NA
S. aureus	13	16	10	13	1	2	4	3
Coagulase-negative staphylococci	11	31	34	37	3	1	1	1
Enterococci	7	9	16	14	5	3	2	2
C. albicans	3	5	6	5	9	4	3	5
Other *Candida* spp.	NA	NA	6	NA	NA	NA	3	NA
Other	24	18	11	17				
Total	**100**	**100**	**100[b]**	**100**				
(*n* = isolates)	(7,815)	(14,424)	(11,428)	(21,943)				

[a]CDC NHSN 2006 to 2007 data reports device-associated hospital-associated infections from 912 ICUs (88% of 1,040 reporting units) and 128 non-ICUs (12% of 1,040 reporting units). Of 10,064 BSIs, 8,709 (87%) were from ICUs and 1,355 (13%) were from non-ICUs.
[b]Sum does not equal 100 due to rounding to nearest integer.
NA, not available.
(Data from refs. 2, *11, 12,* and *13*; data from 1980 to 1982 and 1990 to 1996 represent the hospital-wide component, and data from 1992 to 1999 the ICU component, of NNIS.)

venous lines, in descending order of frequency *(287–292)*. The use of devices (e.g., endotracheal tubes, Foley catheters) and the prior use of antibiotics appeared to be associated with increased risk of *Enterobacter* bacteremia. Mortality rates of 24% to 69% have been reported *(284,287–290)*.

Large series that describe *Klebsiella* bacteremia report that approximately one-half to three-quarters of these bacteremias are healthcare-associated *(293–297)*; up to 25% of these cases are polymicrobial *(293,294)*. Major portals of entry include the urinary tract and the lung, although in some series the gastrointestinal tract and the intravenous catheters were major sites of primary infection (*293,294,297*,298). Patients with pneumonia as a primary source of bacteremia tend to have a worse outcome (*293,295,297*,298). In children, *Klebsiella* bacteremia has been reported in outbreaks in the NICU *(299)*. Widespread colonization of the gastrointestinal tract and respiratory tract with *Klebsiella* has been documented in these outbreaks, as has hand carriage of these strains by hospital personnel. Overall mortality rates for healthcare-associated *Klebsiella* bacteremia vary from 21% to 55% (*284,293,296,297,300*,301).

Bacteremia due to *Citrobacter* spp. is primarily a healthcare-associated infection *(302,303)*. It occurs most frequently in elderly or very young patients, with initial sites of infection in the urinary tract, gastrointestinal tract, and wounds, in decreasing frequency of occurrence. *C. koseri* is frequently associated with genitourinary or intra-abdominal disease, and *C. freundii,* the most prevalent *Citrobacter* spp. found in stool *(166,303,304)*, is associated with gallbladder disease and peritonitis. Bacteremia with *Citrobacter* is commonly preceded by instrumentation at the site of the primary infection. Mortality rates from *Citrobacter* bacteremia are high (~50%) and are related to severity of the patient's underlying medical condition *(303)*.

One series of bacteremias due to *Serratia* reported that 82% were healthcare-associated 23% had polymicrobial bacteremia. The portal of entry was unknown in 64% of patients. Clinical syndromes included primary bacteremia (in two-thirds of patients), pneumonia, UTI, thrombophlebitis, and surgical site infection. Mortality rates attributable to *Serratia* bacteremia have been reported from 32% to 41% *(305,306)* (see also Chapter 19).

Rates of antimicrobial-resistant BSIs have been studied extensively for Enterobacteriaceae. Studies have shown an added burden of BSI caused by resistant Enterobacteriaceae and an association with increased mortality. A retrospective study at a 997-bed tertiary care center in the Netherlands quantified changes in incidence of healthcare-associated bacteremias caused by antibiotic-susceptible and antibiotic-resistant pathogens in adults admitted for >48 hours during 1996 to 2005. Of 1785 cases of healthcare-associated bacteremia, 538 (30.1%) were caused by Enterobacteriaceae. The proportion of antibiotic-resistant pathogens causing healthcare-associated bacteremia increased from 3% to 8% from the first 5 years to the second 5 years of the study. These increases were most pronounced for amoxicillin-resistant *Enterococcus faecium* (from 12% to 31.5%) and for multidrug-resistant Enterobacteriaceae (from 0.7% to 4.7%). The incidence density (daily risk of healthcare-associated bacteremia measured as the number of healthcare-associated bacteremias per number of patients who were admitted for at least 2 days before acquiring healthcare-associated bacteremia) of highly resistant microorganisms increased on average by 26.1% annually, compared to an increase of 3% per year of susceptible pathogens. Though there was no increase in the overall burden of healthcare-associated bacteremia from Enterobacteriaceae, the ratio of increased incidence densities of resistant to susceptible Enterobacteriaceae was 38. Antibiotic-resistant pathogens did not replace episodes of less resistant pathogens, but rather added to the existing burden of healthcare-associated bacteremia *(307)*. ESBL-producing Enterobacteriaceae bacteremia was the subject of a meta-analysis in which 16 studies were reviewed through April 2006 and found an association with increased mortality and delay in effective therapy in ESBL-associated bacteremia, though studies lacked controls for confounding variables *(308)*.

A single-center Spanish tertiary care facility prospectively reviewed 4,758 episodes of *E. coli* bacteremia from 1991 to 2007, 29% of which were healthcare-associated acquisition. Fluoroquinolone-resistant strains were identified in 1,300 (27%) of cases and third-generation cephalosporin-resistant strains were present in 211 (4%), of which 84% were isolated after 2001. Independent risk factors for infection with an antibiotic-resistant strain included healthcare-associated acquisition, urinary catheterization, and previous treatment with the implicated antibiotic to which the pathogen had become resistant, fluoroquinolones, or β-lactam therapy, respectively. The most common source for healthcare-associated fluoroquinolone-resistant bacteremia was a central-line catheter (51%). Common sources for healthcare-associated ESBL bacteremia were skin/soft tissue infection (13%) and catheter-related (11%). Overall, 9% of patients died; risk for death was associated with shock at presentation and inappropriate empiric antimicrobial therapy *(286)*.

Increasingly, ESBL-producing *Klebsiella* are causing bacteremia *(309,310)*. In a retrospective study of 162 *K. pneumoniae* isolates, 44 (27.2%) were ESBL producing. In a multivariate analysis, risk factors for ESBL-producing *Klebsiella* bacteremia, compared to non–ESBL-producing strains, included presence of a biliary drainage catheter, prior antibiotic therapy, and healthcare-associated acquisition of bacteremia. Mortality attributable to *Klebsiella* bacteremia did not differ significantly between the two groups (23.3% vs. 20% in ESBL producers vs. nonproducers, respectively) *(309)*. *K. pneumoniae* resistant to carbapenems has emerged as one of the most concerning antimicrobial-resistant pathogen threats over the past decade. A matched retrospective historical cohort study of carbapenemase-resistant *K. pneumoniae* bacteremias in an Israeli tertiary university teaching hospital found a crude mortality rate of 71.9% and an attributable mortality rate of 50% in 32 case-patients from 2005 to 2008. The mortality risk ratio was 3.3 (95% CI, 2.9–28.5) for case-patients. Case-patients were more likely than patients without bacteremia to require ICU care, ventilator support, and use of a central venous catheter (301).

Central Nervous System Infections

Healthcare-associated CNS infections occur primarily in neurosurgical patients, neonates, and patients undergoing procedures that penetrate the CNS *(311)*. A review of gram-negative bacillary meningitis showed that 69% of the cases occurred in postneurosurgical patients, with the majority (70%) of infections due to *E. coli (312)*. A descriptive review of

55 adult cases of *Klebsiella* meningitis over 13 years found that "spontaneous" meningitis occurred in 80% and postneurosurgical meningitis occurred in 20% of patients. Underlying conditions in the patients with spontaneous meningitis included diabetes mellitus (70%), alcoholism (30%), and chronic otitis media (17%). Other less common underlying diseases included neoplasm, stroke, nasopharyngeal carcinoma, and end-stage renal disease *(313)*.

In a study of 171 cases of pediatric healthcare-associated meningitis from 1992 to 2007, 9.5% were due to Enterobacteriaceae. The most common isolates were *E. coli* in nine (50%) patients, *K. pneumoniae* in three (16.7%), and a patient each had *E. cloacae*, *C. freundii*, *P. mirabilis*, and *S. enteriditis*. Risk factors included neonatal age, low birth weight, head trauma, and neurosurgery. Mortality in the patients with healthcare-associated meningitis due to Enterobacteriaceae was significantly greater than was mortality in the entire cohort of 171 patients: 29.9% versus 15.1%, respectively *(314)*.

In neonates, the most common etiologic agent of gram-negative bacillary meningitis remains *E. coli*. The K1 strains are the etiologic agents in most cases *(75)*. Unusual pathogens associated with outbreaks of neonatal meningitis include *C. koseri*, *S. marcescens*, and *E. sakazakii*. *C. koseri* has been reported to cause meningitis and CNS abscess in both preterm and full-term infants. One cluster of healthcare-associated neonatal *C. koseri* meningitis cases was found to be due to hand carriage of this strain by a nurse with dermatitis. Removal of the nurse from the unit resulted in decreased rates of neonatal colonization with *C. koseri* and no further clinical cases of *C. koseri* sepsis and meningitis *(315)*. During reported outbreaks of *C. koseri* infections in nurseries, rates of fecal and umbilical carriage are high (50% to nearly 100%), yet few infants acquire clinical disease *(316)*. One case of *C. koseri* brain abscess has been reported in an adult following a community-acquired *C. koseri* UTI *(317)*. A case of multiple brain abscesses in association with bacteremia has been reported with *S. paratyphi* B in an infant *(318)*.

S. marcescens meningitis occurs primarily in neonates, particularly in premature infants requiring ICU care. Most of these infants have multiple invasive catheters and have received a prior course of antibiotics *(319)*. Notable features of *Serratia* meningitis in infants include a propensity for progression to ventriculitis, a frequent lack of cerebrospinal fluid pleocytosis and of hypoglycorrhachia (present in only 50% of cases), the development of *Serratia* meningitis despite receiving therapy for *Serratia* bacteremia, concurrent soft tissue infection or UTI with *Serratia*, and a high mortality rate (>45%) *(319)* (see also Chapters 27, 49, and 52).

PREVENTION AND CONTROL OF HEALTHCARE-ASSOCIATED INFECTIONS DUE TO ENTEROBACTERIACEAE

Hand Hygiene

The importance of hand hygiene cannot be overemphasized. Hand transfer of the Enterobacteriaceae between patients by healthcare personnel has been implicated in numerous outbreaks of healthcare-associated infection *(320)*. It is felt that most endemic infections also are transmitted by the hands of healthcare workers *(321)*. In most studies, the Enterobacteriaceae are only transient hand flora; *Acinetobacter* is usually the only gram-negative bacillus found consistently in hand cultures. For example, *Klebsiella* has been shown to survive on the hands for about 2 hours *(322)*. In one study, however, approximately 60% of people demonstrated endemic hand carriage of gram-negative bacilli, primarily the Enterobacteriaceae *(323)*. In that study, healthcare workers with hand dermatitis carried gram-negative bacilli more frequently and in greater numbers than other healthcare workers *(324)*. The investigators also found that continuous hand carriage (over 3–6 weeks) was common. In an epidemic in an NICU, a nurse with hand dermatitis was found to be the reservoir for the epidemic strain of *C. koseri (315)* .

Observations of hand-washing behavior in university hospital ICUs have found compliance rates ranging from 28% to 41% *(325)*. Strategies such as increasing the number of sinks and installing automated sinks have not been shown to improve hand-washing compliance and have had little effect on infection rates *(326–330)*. Efficacy of specific hand-cleansing agents in preventing horizontal pathogen transmission has not been studied extensively. Based on efficacy of hand degerming, ease of use, and salutary effect on the condition of the hands of healthcare workers, alcohol-based hand rubs are now recommended for hand hygiene between patient contacts *(331)* (see Chapter 91).

Other Conventional Methods of Infection Control

Conventional infection control methods are summarized in Table 34-13. Barrier precautions, when used aggressively,

TABLE 34-13

Examples of Conventional Infection Control Policies[a]

Identify reservoirs
Colonized and infected patients
Environmental contamination; common sources
Halt transmission among patients
Improve hand washing and asepsis
Barrier precautions (gloves, gowns) for colonized and infected patients
Eliminate any common source; disinfect environment
Separate susceptible patients
Close unit to new admissions if necessary
Halt progression from colonization to infection—examples of site-specific measures
Discontinue nonessential devices
Extubate and remove nasogastric tube
Position patients to decrease risk of aspiration
48-h (or less frequent) ventilator circuit tubing changes
Proper removal of ventilator tubing condensate
Proper endotracheal suctioning technique
Antisepsis bathing of patients
Modify host risk
Treat underlying disease and complications
Control antibiotic use

[a]See Chapters 17 to 27 for more detailed site-specific control measures.
(Adapted from Baine WB, Gangerosa EJ, Bonnet JV, et al. CDC news. Institutional salmonellosis. *J Infect Dis* 1973;128:357.)

have successfully prevented the healthcare-associated spread of multiply resistant Enterobacteriaceae and have reduced ICU infection rates *(332,333)*. The institution of barrier precautions (primarily gloving) resulted in a sustained 87% reduction in gentamicin-resistant Enterobacteriaceae in one hospital *(332)*. Even with the use of gloves, hand washing should be emphasized, as studies have shown that up to 50% of hands were contaminated after glove removal *(334)*. Use of gloves and gowns has been shown to reduce the incidence of healthcare-associated infections in the pediatric ICU as well *(335,336)*.

Elimination of common reservoirs of infection and proper care of invasive monitoring equipment are also important in prevention of healthcare-associated infection due to the Enterobacteriaceae. A variety of invasive devices have been implicated as sources of epidemic infections (Table 34-8). Care of all invasive devices should include removal of the device as soon as a patient's clinical condition permits and careful asepsis during use.

The environment is usually not a major source or vector in infections with Enterobacteriaceae. Contamination from environmental reservoirs that may come into contact with patients has been the cause of healthcare-associated outbreaks. These outbreaks have called attention to reservoirs that may warrant special care (Table 34-8).

Because broad-spectrum antibiotic therapy alters patients' microflora and may lead to colonization and to infection with multiply resistant microorganisms, restriction of broad-spectrum antibiotics has been cited as an important infection control measure *(93,337)*. Resistance rates generally diminish with antibiotic restriction, although most studies introduce several control measures simultaneously, making assignment of causality difficult.

With regard to infection control, two aspects are instrumental when attempting to control outbreaks of ESBL-containing Enterobacteriaceae or to prevent healthcare-associated epidemics *(93,337)*. First, as for all other healthcare-associated pathogens, enforcement of compliance with infection control measures is of key importance. Reinforcement of hand hygiene compliance *(338,339)*, glove use *(338)*, barrier precautions *(339,340)*, and appropriate room disinfection *(220)* have reduced the spread of resistant bacteria. A limited and rational use of broad-spectrum antibiotics, such as third-generation cephalosporins, is the second strategy to prevent and control outbreaks with these bacteria. ESBL genes can be transferred easily to other bacteria and even other bacterial species, especially in the presence of antibiotic pressure. In three studies, the use of ceftazidime was a risk factor for infection with ESBL-containing microorganisms *(217,218,340)*. Discontinuation of empiric ceftazidime and reduction of ceftazidime use in combination with barrier precautions resulted in a decline of resistant isolates, but they were not completely eradicated *(218,220)*. In a smaller outbreak in a pediatric cancer ward, no further cases of infection with resistant strains were detected after a change of empirical therapy from ceftazidime to a combination of amikacin, azlocillin, and nafcillin *(217)*. An outbreak of gentamicin-resistant Enterobacteriaceae (85 isolates comprising eight species) on neurology and neurosurgery wards was controlled following restriction of broad-spectrum β-lactams, cephalosporins, gentamicin, tobramycin, quinolones, and cotrimoxazole. Only after addition of the antibiotic restriction policy to infection control measures already in place (barrier precautions, educational sessions, and new hand hygiene products) did the incidence of multidrug-resistant Enterobacteriaceae decrease to half of the preintervention phase *(341)*. An experimental approach would be to use intestinal decontamination by nonabsorbable antibiotics, as a temporary adjunct to strict hygienic and antimicrobial control measures, to eradicate colonization with multiresistant bacteria *(342)*.

Efficacy of screening for multidrug-resistant Enterobacteriaceae in the absence of an outbreak was studied in patients admitted for organ transplantation. Of 287 patients (75% of whom underwent liver or kidney transplant), 69 (24%) were colonized with multidrug-resistant Enterobacteriaceae; 6 (9%) of 69 colonized patients developed clinical infections. These six isolates were all unique by PFGE. Of 995 other transplant ward patients who underwent passive clinical culture surveillance for multidrug-resistant Enterobacteriaceae, 12 (1.2%) were noted to be colonized; no clinical infections were detected in these patients. Typing of isolates included PFGE, plasmid, and integron analysis. There was no patient-to-patient transmission detected. The authors demonstrated a large cost for surveillance cultures and concluded that in a setting where multidrug-resistant Enterobacteriaceae are endemic, surveillance of clinical isolates was adequate for infection control purposes *(343)*.

Surveillance rectal cultures were part of an enhanced infection control program (among six total added measures) to limit spread of carbapenem-resistant *K. pneumoniae* in a New York City hospital. The mean number of new patients with positive cultures for KPCs per 1,000 patient days per quarter decreased significantly from 9.7 ± 2.2 before the intervention to 3.7 ± 1.6 after the intervention, though there was no decrease in the mean numbers of patients per quarter with cultures demonstrating other multidrug-resistant microoganisms. The investigators speculated that their intervention failed to control carbapenem-resistant *Acinetobacter* or *Pseudomonas* because these microoganisms frequently colonize the respiratory, rather than the gastrointestinal, tract, thereby trumping the value of rectal surveillance cultures, which had led to identification of 10 of 37 patients with carbapenem-resistant *K. pneumoniae (344)*.

Control and/or Eradication of Colonization

Conventional approaches to control of healthcare-associated infection due to the Enterobacteriaceae as outlined above are not always successful, in part because of lack of compliance. But even when compliance is total, endogenous oropharyngeal or rectal carriage of Enterobacteriaceae may create an "iceberg" effect (Fig. 34-1). Thus, conventional infection control methods aimed at reducing crossinfection may not work, because many patients arrive at the hospital already colonized. Studies have shown that isolation, barrier nursing, and strict antibiotic policies reduce rates of crossinfection and crosscolonization, but overall rates of infection, especially pneumonia, may be unchanged *(345)*. Thus, antibiotic prophylaxis has been studied repeatedly since the 1950s as a method to decrease rates of healthcare-associated infection, particularly pneumonia.

Early trials of systemic antibiotics in the 1950s showed no decrease in the risk of pneumonia and, furthermore, showed increased risk of gram-negative bacilli overgrowth

and increased risk of pneumonia, skin infection, and bacteremia *(346,347)*. Two later studies addressed the issue of systemic intravenous prophylaxis to prevent early-onset VAP. In one study, 570 patients were randomized to receive either 24 hours of penicillin G, cefoxitin, or no antibiotics, and the incidences of early-onset VAP were 6% in patients with and 7% in patients without antibiotics *(348)*. In the other study, two dosages of intravenous cefuroxime 12 hours apart after intubation resulted in a reduction in the incidence of early-onset VAP from 36% to 16% in comatose ICU patients *(349)*.

In the 1970s, use of topical antibiotics, either aerosolized polymyxin or endotracheal aminoglycosides, delivered directly to the site of potential infection, was studied as prophylaxis of gram-negative pneumonia. Use of polymyxin led to decreased rates of pneumonia but to increased rates of colonization with polymyxin-resistant *Serratia*, *Proteus*, and *Flavobacterium (350,351)*. Use of an endotracheal aminoglycoside, gentamicin, was also associated with decreased rates of pneumonia but with increased rates of colonization by gentamicin-resistant *Providencia* spp. *(352)*. Neither regimen had any effect on overall mortality rates.

More recently, topical application of chlorhexidine has been used to reduce bacterial colonization in the oropharynx as a way to prevent VAP, as a presurgical skin preparation, and for impregnation of devices and dressings *(353)*. Chlorexidine gluconate (2%)–impregnated cloths have demonstrated effectiveness in reducing CLABSIs in MICU patients *(354)*. Antiseptic solutions including iseganan, chlorhexidine, and povidone iodine have been proposed to achieve oropharyngeal decolonization and minimize promotion of antimicrobial resistance *(355)*. A double-blind RCT in noncardiothoracic ICUs using 2% of chlorhexidine compared to chlorhexidine and colistin against placebo showed a reduction in VAP with a 65% reduction for chlorhexidine-treated patients and 55% reduction for chlorhexidine/colistin-treated patients, the latter of which provided better decolonization of gram-negative microorganisms *(356)*. Daily baths with 2% chlorhexadine impregnated wipes were part of a bundled strategy (including point-prevalence surveillance, environmental culture, cleaning evaluation with powder detectable by ultraviolet light, cohorting colonized patients and healthcare providers, and staff education) which led to control of a monoclonal outbreak of KPC-3 producing *K. pneumoniae* in a 20-bed SICU (356a). A similar bundled strategy including daily bathing with 2% chlorhexidine gluconate controlled horizontal spread of KPC-producing *K. pneumoniae* at a long-term acute care hospital, despite continued admission of patients harboring KPC-producing pathogens *(229)*.

Novel experimental approaches to reducing bacterial adherence and biofilm formation on urinary catheters include devices to sense bacterial encrustation, application of biofilm inhibitors, hydrophilic coating or nutrient-scavenging materials on catheter surfaces, and use of low-energy surface acoustic waves *(47)*.

Selective Decontamination Selective decontamination of the digestive tract (SDD) has been investigated extensively as a method of pneumonia prophylaxis for ventilated patients in the ICU. SDD uses nonabsorbable antibiotics to eliminate potential gram-negative pathogens from the oropharynx and the gastrointestinal tract. The antibiotics chosen for SDD spare normal anaerobic flora that may help limit intestinal overgrowth by SDD-resistant gram-negative bacilli. The typical SDD regimen utilizes a sticky paste or gel mixed with polymyxin, an aminoglycoside, and an antifungal agent for topical oropharyngeal decontamination. The same antibiotics are also put into solution for gastric and intestinal decontamination. Some regimens also use systemic antibiotic therapy for the first few days to treat incubating community-acquired pneumonia. The effects of SDD (or selective oropharyngeal decontamination [SOD]) on infection rates and patient outcome are addressed in Chapter 22.

The most recent (and largest) trial on SDD was a crossover trial using cluster randomization in 13 ICUs of differing size and teaching status compared the effectiveness of SDD to SOD versus standard care over a 6-month period with the primary end point of mortality at 28 days. The SDD regimen included 4 days of intravenous cefotaxime and oropharyngeal/gastric topical application of tobramycin, colistin, and amphotericin B. The SOD regimen included only the topical application combination with no systemic antimicrobial therapy. The crude mortality in each group at day 28 for standard, SOD, and SDD was 27.5%, 26.6%, and 26.9%, respectively. In a random-effects logistic-regression model with covariates including age, sex, APACHE II score, intubation, and medical specialty, the odds ratio for 28-day mortality compared to standard care was 0.86 (95% CI, 0.74–0.99) for SOD and 0.83 (95% CI, 0.72–0.97) for SDD, respectively. These odds correspond to an absolute reduction in mortality at day 28 for SOD: 2.9% and SDD: 3.5% (357). SDD was, as compared to standard care and SOD, associated with a significantly reduced incidence of ICU-acquired bacteremia caused by Enterobacteriaceae.

The development of antibiotic resistance is the most feared complication of SDD. Initial studies in the 1980s showed no problems with overgrowth of resistant gram-negative bacilli. Now that gram-positive bacteria are re-emerging as important healthcare-associated pathogens in the last 2 decades, increased colonization rates with antibiotic-resistant gram-positive cocci, especially staphylococci and enterococci, have been reported from some ICUs using SDD *(342,358–362)*. Thus, ICUs with endemic or epidemic MRSA or enterococcal infection should avoid SDD. The crossover trial in 13 Dutch ICUs comparing SDD and SOD to standard care included monthly point-prevalence assessments with surveillance rectal swabs and endotracheal aspirates or throat swabs from all ICU patients (whether participating in the study or not) and did not find evidence of the emergence of antimicrobial-resistant pathogens or increased rates of *Clostridium difficile*. However, the study period may not have been long enough to determine the effect of the interventions on resident flora (357). In a separate analysis, the ecological effects of SDD and SOD were analyzed in time, by comparing point-prevalence rates of gram-negative bacteria resistant to certain marker antibiotics during the months of SDD and SOD to the months before and after intervention. For rectal carriage, lowest point-prevalence rates were observed during SDD, but rates rapidly increased after SDD, most notably for ceftazidime-resistant gram-negative bacteria. And for respiratory

tract carriage, point prevalence rates were lowest during SDD and SOD, but during these periods a steady increase in resistance, again most notably for ceftazidime-resistance, was observed *(363)*. Therefore, the clinical benefits of both interventions (as observed in units with low prevalence rates of antibiotic resistance) must be carefully balanced against the ecological effects on antibiotic resistance.

SDD may also be a useful short-term control measure for outbreaks of multiply resistant gram-negative bacilli when conventional infection control methods fail. Intestinal decontamination with orally administered nonabsorbable antibiotics (neomycin, polymyxin E, nalidixic acid) has successfully controlled ICU outbreaks of multiresistant Enterobacteriaceae (mainly *Klebsiella* and *Enterobacter*) *(342)* and of multiresistant *Klebsiella (364)*. In one outbreak, intestinal colonization with resistant strains decreased from 19% to 3%, and infection rates decreased from 9% to 0%. The infection rate for nonresistant strains was unchanged.

SDD may be of arguable benefit in reducing the risk of gram-negative pneumonia in a select patient population (e.g., ventilator patients with acute trauma or postoperative patients), although it is unclear whether the benefit of SDD reflects systemic antibiotic use as much as it does topical antibiotic use. Although there is accumulating evidence that SDD and SOD may decrease ICU mortality, these provocative results should be confirmed in various ICU settings and the relative importance of the individual components of SDD should be evaluated. Based on decreased mortality with SOD and SDD regimens demonstrated in the Dutch study (357), the SOD regimen may be preferable to the SDD regimen to avoid systemic antibiotic prophylaxis therapy, and the risk of increasing antimicrobial resistance. Oropharyngeal decontamination with antiseptic agents (chlorhexidine) could be an alternative to the antibiotic paste regimen and needs further study. Moreover, more studies should determine the relative benefits of SDD in specific patient populations (i.e., medical, surgical, or trauma) or subgroups of patients with different levels of illness. Nevertheless, SDD may increase the risk of colonization and infection with antibiotic-resistant gram-positive microorganisms, such as staphylococci and enterococci, in some ICUs, so that units having problems with such strains should avoid SDD. SDD has contributed to outbreak control in a few ICUs with epidemics of multiply resistant Enterobacteriaceae that had not been controlled by conventional methods.

Other Strategies Immunoprophylaxis has also been studied as an alternative approach to infection prevention in the ICU. Clinical studies have suggested that immunization of high-risk ICU patients with plasma from volunteers immunized with *E. coli* J5, a mutant in which core lipid A determinants are exposed *(365)*, failed to lower the infection rate but did prevent gram-negative shock.

Intravenously administered immunoglobulin reduced the infection rate when given prophylactically to selected high-risk patients in a surgical ICU in one study *(366)*, but did not reduce patient mortality. Prophylactic intravenous administration of immunoglobulin has been shown not to reduce the healthcare-associated infection rate in very low birth weight infants *(367)*. Passive immunization with intravenous hyperimmune globulin, derived from donors immunized with a 24-valent *Klebsiella* capsular polysaccharide plus an 8-valent *P. aeruginosa* O-polysaccharide–toxin A conjugate vaccine, was tested in 725 ICU patients and compared to albumin administered to 667 patients. Although there was some evidence that passive immunization decreased the incidence and the severity of vaccine-specific *Klebsiella* infections (from 2.7–1.2% and from 1.0–0.3%, respectively), the reductions were not statistically significant. Moreover, patients receiving hyperimmunoglobulin had more adverse reactions *(368)*.

Passive systemic vaccination with immune sera to bacteria-specific adhesins may be another approach for the future. Sera from animals vaccinated with adhesins from type 1 pili (FimH) inhibited UPEC from binding to human bladder cells *in vitro*. Immunization with FimH almost completely reduced *in vivo* colonization of the bladder in a murine cystitis model, and levels of immunoglobulin G to FimH could be detected in the urine samples of these mice *(369)*.

Less invasive and colonization-resistant devices are needed. These may very well be the most useful aids in controlling healthcare-associated infection by Enterobacteriaceae *(370,371)*.

CONCLUSION

Enterobacteriaceae, in part due to the increasing prevalence of antimicrobial-resistant strains, remain problem pathogens for healthcare facilities. Although the distribution of healthcare-associated pathogens continues to see a predominance of gram-positive bacteria at the end of the first decade in the 21st century, healthcare-associated infections due to the Enterobacteriaceae, especially strains that carry chromosomal- or plasmid-mediated antibiotic-resistance elements, still heavily impact infection control and treatment decisions. So, as the epidemiologic pendulum continues to swing, Enterobacteriaceae remain a challenging healthcare-associated and clinical problem.

The control of healthcare-associated infections due to the Enterobacteriaceae begins with our understanding of the basic epidemiology of these pathogens. Infection control measures including antiseptic-based decolonization and targeted active surveillance continue to be explored. The collaboration of public health and healthcare facility personnel at acute and long-term facilities is crucial to exploring regional epidemiologic patterns of spread and implementing measures to identify colonized and infected patients and to contain, reduce, and possibly eradicate transmission of these pathogens. Strides are being made in the development of safer and less invasive devices and surgical procedures and in our understanding of ways to control colonization and prevent invasive disease. And, as is said for most healthcare-associated infections, we must continue to make healthcare workers' adherence to hand hygiene a quality indicator (372).

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CHAPTER 35

Nonfermentative Gram-Negative Bacilli

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Nonfermentative gram-negative bacilli are a diverse array of microorganisms that have evolved in aquatic environments, have minimal growth requirements, and differ substantially in virulence. Included in this category are *Pseudomonas aeruginosa*, other *Pseudomonas* species, and genera such as *Stenotrophomonas*, *Acinetobacter*, *Burkholderia*, *Flavobacterium*, and *Achromobacter*. During the last half-century, nonfermentative gram-negative bacilli have become significant healthcare-associated pathogens because of the many reservoirs they inhabit in hospitals and the resistance of these microorganisms to commonly used antibiotics. Furthermore, the virulence of *P. aeruginosa* and its frequency as a healthcare-associated pathogen have been important factors impelling increased use of antipseudomonal β-lactam antibiotics and quinolones as presumptive therapy where *P. aeruginosa* is a potential pathogen.

MICROORGANISM CHARACTERISTICS

Pathogenicity

Like other bacterial pathogens, nonfermentative gram-negative bacilli must successfully navigate through a series of critical steps to cause disease. After entering the host, bacteria attach to host cells, breach host barriers, access nutrients to proliferate, evade local host defenses, and in some cases spread to regional or distant sites *(1)*. To accomplish these tasks, bacteria produce a number of cell-associated and secreted virulence determinants in a tightly regulated manner. Pathogenesis has been studied most extensively in *P. aeruginosa*, and this bacterium will be used as a model in our discussion of pathogenesis. However, it should be noted that each of the nonfermentative gram-negative bacilli has evolved its own unique set of pathogenicity factors and accomplishes the difficult process of causing infection by a different means.

Regardless of the type of infection, bacterial attachment to host epithelial cells is typically a prerequisite to the pathogenesis of bacterial disease. Attachment of *P. aeruginosa* (formerly *P. pyocyanea*) is accomplished by a number of surface structures including type IV pili (or fimbriae), flagella, lipopolysaccharide, and lectins. Of these, type IV pili have received the most attention as adhesins *(2)*. These polar filaments are composed of repeated monomers of the protein pilin and bind to the GalNacβ(1-4)Gal moiety of asialylated glycolipids found on epithelial cells *(3)*. Disruption of pilus biosynthetic genes results in decreased virulence in animal models of acute pneumonia *(4,5)*.

Despite producing a number of adhesins, *P. aeruginosa* attaches to the apical surface of intact epithelial cells quite poorly *(6)*. *P. aeruginosa* is thus blocked at this very early step in the pathogenic process, an observation that likely explains why healthy individuals are rarely infected with this ubiquitous bacterium. However, in a host in which skin and mucosal surfaces are disrupted by endotracheal intubation and mechanical ventilation, burn wounds, corneal abrasion, indwelling catheters, or cytotoxic chemotherapy, *P. aeruginosa* has all the virulence machinery necessary to proceed through the remaining steps of pathogenesis and to cause severe infection. Injury of epithelium leads to the loss of polarized distribution of cellular ligands for *P. aeruginosa*. In particular, heparin sulfate proteoglycans normally found only on the basal–lateral surface of epithelial cells are redistributed to the apical surface following tissue damage *(7)*. These proteoglycans are avidly bound by *P. aeruginosa* adhesins and allow this bacterium to efficiently bind to the apical surface of damaged epithelium.

Once *P. aeruginosa* bacteria successfully bind to a surface (living or inert), they are capable of forming biofilms under appropriate conditions. Biofilms are communities of microbes embedded in an organic polymer matrix at an air–solid or liquid–solid interface. The extracellular matrix of biofilms formed by *P. aeruginosa* consists of exopolysaccharides, proteins, and extracellular DNA. In particular, three exopolysaccharides play an important role in biofilm formation and maintenance: Psl, Pel, and alginate *(8)*. The extracellular matrix confers partial resistance to the host immune response by inhibiting antibody coating, phagocytosis, and intracellular killing by leukocytes *(9–12)*. Thus, even in individuals with normal cellular and humoral immune function, biofilm-related infections are rarely resolved by the host defense mechanisms *(9)*. Unfortunately, biofilms are also quite resistant to eradication by antimicrobial agents. Although the reasons for this are unclear, three mechanisms have been proposed. First, antimicrobial agents may diffuse slowly through the extracellular matrix of a biofilm, resulting in subinhibitory concentrations within the biofilm interior *(13,14)*. Second, bacteria in certain regions of the biofilm may assume a metabolically or otherwise inactive state

that allows persistence in the presence of antibiotics *(15)*. Third, zones of biofilms may accumulate waste products and have low oxygen tensions, conditions that antagonize the activity of some antibiotics *(16)*. More recently, it has been shown that mutations and horizontal transfer of genetic material occur more frequently during a biofilm mode of growth *(17,18)*. All these processes could contribute to the ability of *P. aeruginosa* biofilms to develop antimicrobial resistance and to persist despite antibiotic therapy. *P. aeruginosa* biofilms play important roles in the pathogenesis of central venous catheter–related infection, urinary catheter cystitis, contact lens–associated corneal infection, lung infection in cystic fibrosis, and ventilator-associated pneumonia (VAP) *(9)*. In these infections, antibiotic therapy typically eliminates the symptoms caused by the planktonic cells released from the biofilm but fails to kill the biofilm itself. As a result, biofilm infections typically show recurring symptoms until the sessile population of bacteria along with the infected catheter or prostheses is removed.

Once a focus of infection is established, *P. aeruginosa* employs its broad spectrum of metabolic pathways to utilize nutrients available within the host. One such essential nutrient is iron, which is tightly sequestered by a number of host factors. *P. aeruginosa* secretes two siderophores named pyoverdin and pyochelin to access these cellular stores *(19)*. Both are pigmented diffusable molecules that chelate iron in the environment and then transport it into the bacterium via specific outer membrane receptors. The yellow-green fluorescence of pyoverdine is sometimes apparent in wounds and dressings, allowing a presumptive diagnosis of *P. aeruginosa* infection to be made *(20)*. Interestingly, *P. aeruginosa* has the ability to hijack and utilize siderophores secreted by other microrganisms *(21)*.

After overcoming the initial obstacles to infection, *P. aeruginosa* employs a number of secretion systems to export toxic factors into the host environment. These factors function to impair host immune components or disrupt host barriers to facilitate dissemination. Here we will review each of these secretion systems in turn.

Type I secretion is a relatively simple three-component mechanism used by gram-negative bacteria to export a dedicated factor from within the bacterium to the extracellular environment. *P. aeruginosa* uses such a system to export alkaline protease, an enzyme that cleaves components of the complement cascade and the extracellular matrix *(22,23)*. Animal models of keratitis and burn infections have demonstrated that alkaline protease plays an important role in the pathogenesis of these infections *(24)*.

A number of *P. aeruginosa* virulence factors are exported by a type II secretion system, which similarly functions to move bacterial proteins across the inner and outer bacterial membranes. *P. aeruginosa* factors secreted by this system include exotoxin A, phospholipase C, and elastase. Exotoxin A is a secreted adenosine ribosyltransferase that inhibits protein synthesis in eukaryotic cells by modifying the structure of elongation factor-2 *(25)*. Exotoxin A is produced by most clinical isolates of *P. aeruginosa* and has potent local and systemic effects. These include necrosis of soft tissues into which sublethal doses are injected *(26)* and shock and hepatocellular necrosis following systemic administration *(27)*. Although experimental models of local infection have not consistently shown enhanced virulence of *P. aeruginosa* isolates that produce exotoxin A *(28,29)*, studies of bacteremic infection in humans suggest an important role *(30,31)*.

Elastase, a metalloprotease that accounts for the majority of the proteolytic activity of *P. aeruginosa*, cleaves elastin as well as a number of other host factors. One such factor is syndecan-1, a heparin sulfate proteoglycan found on the surface of respiratory mucosal cells *(32)*. It has been postulated that *P. aeruginosa* utilizes the shed portion of cleaved syndecan-1 to protect itself from host defenses *(32)*. Animal models support a pathogenic role for elastase, especially in the lung *(33)*.

P. aeruginosa produces two phospholipase C enzymes, sometimes referred to as Plc-HR and Plc-N. These enzymes can degrade surfactant in the lung and cause tissue destruction *(34)*. Mutants with disruptions in the genes encoding these phospholipases were defective in virulence in a mouse burn model *(35)*.

All *P. aeruginosa* strains also encode a type III secretion system, although this system appears to not function in some isolates. The type III secretion system uses a complex secretion/translocation mechanism to move toxins (called effector proteins) directly from the bacterium into host cells. Four effector proteins have been identified in *P. aeruginosa*: ExoS, ExoT, ExoU, and ExoY. ExoS and ExoT are related proteins that have ADP-ribosyltransferase and GTPase-activating protein activities. These activities are directed against a number of host proteins and are thought to inhibit phagocytosis, disrupt epithelial barriers, and cause apoptosis *(36,37)*. ExoU is a potent phospholipase that causes rapid necrotic cell death of a number of cell types, including neutrophils during acute pneumonia *(38–40)*. ExoY is an adenylate cyclase that elevates intracellular cyclic adenosine monophosphate levels *(41)*. ExoU and ExoS have been shown to be important virulence factors in several animal models *(40,42)*. Type III secretion itself has been associated with worse clinical outcomes in patients with VAP and bloodstream infection *(43,44)*.

P. aeruginosa does not harbor a type IV secretion system and the relationships between this bacterium's type V secretion systems and virulence have not been examined in detail. Recently, however, examples of a newly described type VI secretion system have been found in *P. aeruginosa* (45,*46*). One such system, designated H1-T6SS, has been shown to secrete three substrates: Tse1, Tse2, and Tse3 *(47)*. Work is ongoing to determine whether this secretion system is directed against eukaryotic microorganisms such as humans or competing bacteria, or both *(47)*.

P. aeruginosa produces a number of additional factors that have been implicated in disease pathogenesis, including rhamnolipids, pyocyanin, and leukocidin. The reader is referred to several recent reviews for more detailed information on these factors and *P. aeruginosa* pathogenesis in general *(48,49)*.

As would be expected, complex, integrated, and overlapping regulatory networks are required to ensure that many *P. aeruginosa* virulence determinants are activated at the appropriate time and place during infection. One such regulatory system is cyclic-diguanylate. This second messenger molecule is synthesized from guanosine triphosphate by diguanylate cyclases and degraded by

phosphodiesterases. Interestingly, more than 30 of these enzymes are believed to be encoded by the *P. aeruginosa* genome, suggesting complex regulation of this second messenger *(50)*. Cyclic-diguanylate levels within the bacterium, to a large extent, control biofilm formation by regulating matrix production and adhesion *(51,52)*.

A more global regulatory system employed by *P. aeruginosa* is quorum sensing. Quorum sensing allows bacteria to detect the density of their own species and alter their gene expression patterns to take advantage of this density. Small diffusible signal molecules called autoinducers are secreted by *P. aeruginosa*. At a specific cell density, the concentration of these molecules becomes sufficient to activate transcriptional regulator proteins and induce gene transcription. *In vitro*, quorum-sensing systems modulate expression of 6% to 10% of the genes in the *P. aeruginosa* genome *(53,54)*. *P. aeruginosa* produces several autoinducers, but two small acyl-homoserine lactone molecules referred to as PAI-1 and PAI-2 have been most extensively studied *(55)*. PAI-1 activates the LasR protein, which enhances the transcription of extracellular virulence factors including alkaline protease, exotoxin A, and elastase. The formation of a normal, dense biofilm is also dependent on the synthesis of PAI-1 (*56*,57). The autoinducer molecule PAI-2 binds RhlR and initiates transcription of several different genes involved in a variety of adaptations including biofilm formation. A further indication of the complexity of regulation is that the Las system itself regulates the Rhl system. *P. aeruginosa* strains with inactivated quorum-sensing systems demonstrate significantly diminished virulence in animal models of infection *(58)*.

Another global regulatory system used by *P. aeruginosa* consists of RetS and LadS. These two proteins are reciprocally activated hybrid sensor kinases/response regulators that form a molecular switch priming *P. aeruginosa* for either an acute (RetS) or a chronic (LadS) infection lifestyle. They activate downstream pathways that posttranslationally regulate a number of virulence determinants, including type III secretion, piliation, and a biofilm mode of growth *(59–62)*. Thus, RetS and LadS may sense environmental cues consistent with acute infection (e.g., VAP) or chronic infection (cystic fibrosis) and alter gene expression accordingly.

During pathogenesis, *P. aeruginosa* pathogenicity factors interact intimately with the host's immune system to cause pathology *(63,64)*. Key components of immunity to invasive infection are TLRs *(65)*, the inflammasome *(66,67)*, polymorphonuclear leukocytes *(68,69)*, and antibodies against the lipopolysaccharide cell wall *(70,71)*. A role for cellular immunity (in particular a Th17 response) is also suggested by reports of invasive pseudomonal infection in patients with cellular immune impairment *(72,73)* and is supported by experimental findings involving T cells *(74,75)*.

By most measures, *Stenotrophomonas maltophilia* (formerly *Pseudomonas maltophilia* and then *Xanthomonas maltophilia*) is not particularly virulent (reviewed in Ref. *76*). In the burned mouse model, inocula of 3×10^7 colony-forming units (CFU)/mL of *S. maltophilia* failed to establish lethal infection *(70)*. In contrast, only 2×10^2 CFU/mL of *P. aeruginosa* caused fatal infection in all the animals studied. Nevertheless, *S. maltophilia* can cause serious infection in compromised hosts. Genomic comparison of a clinical *S. maltophilia* isolate to an environmental isolate demonstrated that the clinical isolate encoded a unique filamentous hemagglutinin, a protein that functions as an adhesin in other bacteria, and a type IV pilus *(77)*. *S. maltophilia* also produces or carries genes encoding a number of putative virulence determinants, including protease, elastase, DNase, lipase, fibrinolysin, and zonula occludens toxin *(78–80)*. The latter is similar to an enterotoxin produced by *Vibrio cholerae*. Consistent with the production of these factors, *S. maltophilia* was cytotoxic toward a number of mammalian cell lines *(81)* and lethal in a *Caenorhabditis elegans* infection model *(82)*. Particularly, significant protease and elastase production was identified in a clinical isolate of *S. maltophilia* from a leukemic patient with bacteremia and ecthyma gangrenosum, mimicking both the clinical and virulence properties of *P. aeruginosa (83)*.

The *Burkholderia cepacia* complex group of bacteria was originally described in 1950 as a cause of soft rot in onions (Latin: *coepa*) and previously named eugonic oxidizer group 1, *Pseudomonas kingii*, *Pseudomonas multivorans*, *Pseudomonas P. alcaligenes* IVc, and *Pseudomonas cepacia*. More recently, they were given the name *B. cepacia*, but as these microorganisms were further characterized, it became clear that *B. cepacia* actually comprised a group of several related but distinct bacteria that have now been given species designations. Currently this group of bacteria is referred to as the *B. cepacia* complex and consists of more than 16 species *(84–87)* (reviewed in *88*). These bacteria are extremely versatile and capable of utilizing a wide variety of nutrients for growth. They thrive in natural water sources and can proliferate in tap or distilled water, presumably by utilizing trace elements and low concentrations of organic materials *(89–93)*. Like *S. maltophilia* bacteria, *B. cepacia* complex strains can cause significant disease in the compromised patient and produce a number of important virulence factors. The cable pilus, an adhesin, is used to tether bacteria to cytokeratin 13 on the surface of host cells *(94)*. *B. cepacia* complex bacteria can enter and survive intracellularly in cultured macrophages and pulmonary epithelial cells, which may provide a protected niche, allowing persistent infection *(95)*. Flagella are necessary for the invasion process, and mutants lacking functional flagella were defective in invasion *in vitro* and in lethality in a mouse model of chronic pulmonary infection *(96,97)*. *B. cepacia* complex bacteria also have a quorum-sensing system (CepIR), which is necessary for biofilm formation, secretion of putative toxins, and full virulence in a rodent model *(98,99)*. Interestingly, the *B. cepacia* complex quorum-sensing system also responds to autoinducers from *P. aeruginosa (100)*, demonstrating interspecies communication. Some strains within the *B. cepacia* complex contain a pathogenicity island named the cenocepacia island *(101)*. This island encodes a second quorum-sensing system (CciIR), metabolic pathways, and several transcriptional regulators. Mutations in specific portions of this island caused defects in bacterial persistence and inflammation in a rat chronic infection model *(101)*.

Acinetobacter, formerly classified as *Mima*, *Herellea*, *Moraxella*, *Neisseria*, *Bacterium*, *Alcaligenes*, *Achromobacter*, and *Pseudomonas*, is widely distributed in nature and is part of the normal flora of many animal species and humans

(*102*,*103*, reviewed in Ref. 104). By DNA hybridization, there may be as many as 17 species *(105)*, of which *Acinetobacter baumannii* is the most clinically relevant. *A. baumannii* is an uncommon pathogen *(106,107)* that usually infects immunocompromised or debilitated hosts and sometimes causes outbreaks in intensive care units (ICUs) *(108–110)*. A number of *A. baumannii* factors likely to be important in pathogenesis have been identified including siderophores for iron acquisition *(111,112)*, piluslike structures that facilitate adherence to host cells and biofilm formation *(113,114)*, and multiple quorum-sensing systems *(115)*. The sequencing of the *A. baumannii* genome identified a substantial number of genomic islands *(116,117)*, six of which were shown to enhance virulence in *C. elegans* and *Dictyostelium discoideum* models of infection *(117)*. The virulence-associated islands contained genes predicted to encode transcription factors, multidrug efflux transport systems, and a urease.

The pathogenesis or virulence properties of other nonfermenters have not been fully elucidated. *Sphingomonas paucimobilis* appears to have limited inherent virulence, but it does have endotoxin activity and produces alkaline and acid phosphatases and several esterases *(118,119)*. A report of *Shewanella putrefaciens* causing refractory ulcerative cellulitis and septic shock suggested possible exotoxin production *(120)*.

Resistance to Antimicrobial Agents

P. aeruginosa and other nonfermentative gram-negative bacilli are resistant to many common antibiotics, including first- and second-generation cephalosporins. Based on recent surveillance studies, piperacillin/tazobactam, carbapenems, piperacillin, ceftazidime, cefepime, and the polymyxins remain the most active antipseudomonal agents (104,*121–128*). Increased resistance across many classes of antimicrobial agents and multiclass drug resistance is a concerning trend exhibited by all the clinically important nonfermentative gram-negative bacteria *(121–123,129)*. Mechanisms of resistance to each class of antibiotics are diverse, and more than one mechanism may contribute to resistance to some antibiotics *(130)*. Antimicrobial resistance exhibited by the clinically important nonfermentative gram-negative pathogens is discussed below. Other nonfermenters that are less commonly encountered have varying antimicrobial susceptibility patterns *(127,131–134)*. Treatment of infections caused by these pathogens is typically guided by susceptibility testing of individual isolates.

For *P. aeruginosa*, inherent mechanisms such as outer cell membrane permeability factors and active drug efflux systems result in reduced susceptibility to many antimicrobial agents *(135,136)*. Efflux pumps play a role in reduced susceptibility to sulfonamides, tetracycline, macrolides, fluoroquinolones, penicillins, cephalosporins, meropenem, and even the aminoglycosides *(137)*. All *P. aeruginosa* inherently produce the AmpC β-lactamase that hydrolyzes penicillins and cephalosporins (*136*,138,*139*). In addition, acquired β-lactamases are responsible for penicillin, and first- and second-generation cephalosporin resistance *(136,139)*. Production of a number of extended-spectrum β-lactamases is reported with increasing frequency, resulting in resistance to advanced-generation cephalosporins, monobactams, and extended-spectrum penicillins, depending on the enzyme(s) present *(136,139)*. Changes in penicillin-binding proteins are a relatively uncommon mechanism of β-lactam resistance in *P. aeruginosa (130,135)*. Historically, reduced activity of carbapenems, when present, was attributed to reduced accumulation of the drug via downregulation of carbapenem-specific porin production *(137)*; however, carbapenemase production has been reported with increasing frequency *(124,140–142)*. Aminoglycosides are inactivated by enzymatic modification via the acquisition of plasmids carrying any of a number of such enzymes. The prevalence of fluoroquinolone resistance among *P. aeruginosa* is remarkably high *(121–123,128)*; mutations in the topoisomerase genes, *gyrA* and *parC*, are the genetic basis for such resistance *(143–146)* in addition to resistance caused by active efflux and membrane impermeability.

S. maltophilia demonstrates high-level resistance to many antimicrobial agent classes including the β-lactams, tetracyclines, and aminoglycosides *(127,147)*. As a rule, the carbapenems are hydrolyzed by a chromosomally encoded zinc-dependent β-lactamase possessed by most strains, thus rendering these agents ineffective for the treatment of *S. maltophilia* infections. The most reliable agents include trimethoprim/sulfamethoxazole, ticarcillin/clavulanate, and the newer generation fluoroquinolones such as levofloxacin, moxifloxacin, or gatifloxacin *(125,126,129,147–150)*. In addition, tigecycline demonstrates *in vitro* activity and polymyxin B has variable activity against *Stenotrophomonas (151,152)*.

B. cepacia complex strains are resistant to most antibiotics commonly used for treatment of gram-negative bacterial infections, including the extended-spectrum penicillins and aminoglycosides *(153)*. The most active antimicrobial agents are trimethoprim/sulfamethoxazole, the carbapenems, ceftazidime, and the fluoroquinolones (*127*,154). *Burkholderia* demonstrates *in vitro* susceptibility to tigecycline *(151)*. Most strains are resistant to polymyxin B *(127,152)*. Typically, serious infections are treated with combinations of antimicrobial agents.

Acinetobacter varies substantially in its susceptibility to specific antibiotics, and resistance has steadily increased over the last 3 decades (104,*123*,*124*,*128*,*140*,155). Multiple drug resistance has emerged (104), and outbreaks caused by *Acinetobacter* strains that are resistant to imipenem, ceftazidime, amikacin, and other routinely tested antibiotics are increasingly reported (156,*157–160*). The most appropriate therapy in such circumstances is unclear and should be guided by the results of antimicrobial susceptibility testing. Sulbactam exhibits antimicrobial activity against *Acinetobacter*, and thus, ampicillin–sulbactam may be considered for therapy *(105,157,161,162)*. Tigecycline possesses *in vitro* activity against *Acinetobacter (163)*, but data are limited regarding clinical efficacy and cases of tigecycline resistance have been reported *(164,165)*. The polymyxins, such as polymyxin B, colistin, and similar investigational peptides, demonstrate *in vitro* activity against *Acinetobacter* and *Pseudomonas* and offer a potential therapy for infections caused by strains that are resistant to all other agents *(157,166)*. Finally, there is limited data that support the use of combination therapy with agents such as colistin plus rifampin or colistin plus a carbapenem (104,*167*).

Antimicrobial resistance exhibited by the nonfermentative gram-negative bacilli creates an epidemiologic niche for these pathogens that facilitates colonization and

superinfection in antibiotic-treated patients. For example, multiple studies demonstrate that patients who receive antibiotics lacking anti-*Pseudomonas* activity are at risk for intestinal colonization *(168–171)* and bloodstream infections *(172)* caused by this bacterium. Similarly, administration of broad-spectrum antibiotics lacking activity against other nonfermentative gram-negative bacilli including *Acinetobacter* and *S. maltophilia* predisposes toward colonization and infection with these pathogens *(173–177)*.

Resistance to Biocides

Resistance to biocides is a feature of some nonfermentative gram-negative bacilli, most notably *P. aeruginosa* and *B. cepacia*. This problem was initially recognized in the 1950s when *Pseudomonas* contamination of dilute aqueous benzalkonium chloride was reported at several hospitals *(178,179)*. At these hospitals, the use of contaminated aqueous benzalkonium chloride to disinfect intravascular catheters and needles caused outbreaks of *Pseudomonas* bacteremia. The continued use of aqueous benzalkonium chloride alone or with other agents for antiseptic preparation of the skin or urethral meatus before catheter insertion resulted in further cases of bloodstream or urinary tract infection *(180–185)*. Most outbreaks involved aqueous benzalkonium chloride diluted in hospitals to an in-use concentration of 1:1,000; however, in several instances, *B. cepacia* was an intrinsic contaminant of commercially prepared swabs containing a 1:500 concentration of aqueous benzalkonium chloride *(183,186)*.

Other antiseptic preparations such as chlorhexidine *(187–190)*, chlorhexidine and cetrimide *(191,192)*, cetrimide *(193)*, hexachlorophene *(194)*, and green soap *(195)* have become contaminated with *Pseudomonas*, *Burkholderia*, *Ralstonia*, or *Stenotrophomonas*. While the presence of organic materials enhances survival of bacteria in these antiseptics *(178,193,196)*, *Pseudomonas* and related nonfermenters may proliferate substantially in antiseptics in the absence of such contaminants *(193,196)*. These bacteria may also contaminate phenolic disinfectants *(196–198)*. Even commercial preparations of poloxamer-iodine and povidone-iodine have become contaminated with *P. aeruginosa (199)* and *B. cepacia (200–202)*; in such reports, products from different manufacturers were implicated, and concentrations of free iodine, when tested, were sometimes in the same range as uncontaminated products *(201,202)*.

The susceptibility of *P. aeruginosa* and *B. cepacia* to commonly used antiseptics and disinfectants varies. Some strains are resistant to in-use dilutions of benzalkonium chloride, chlorhexidine, cetrimide, phenolic disinfectant, iodophor disinfectant, or quaternary ammonium disinfectant *(203–208)*. There are limited data regarding biocide resistance in other nonfermentative gram-negative bacteria. Two such studies examining *in vitro* susceptibility of *A. baumannii*, including multidrug resistant isolates, to biocides demonstrated no resistance to commonly used antiseptics such as chlorhexidine *(209,210)*. In contrast, *Acinetobacter* isolates possessing class 1 integrons were associated with both biofilm formation and resistance to biocides including benzalkonium chloride and chlorhexidine *(211)*.

It is evident that gram-negative bacteria may possess multiple intrinsic and acquired mechanisms for antiseptic and disinfectant resistance (212,213). *P. aeruginosa* and *B. cepacia* within biofilms are more resistant to biocides of all types, including antibiotics, than their free-living counterparts (9,*214–219*). Studies of iodophor contamination by *P. aeruginosa* and *B. cepacia* demonstrate the potential protective role of biofilm matrix *(220–222)*. The ways in which bacteria within a biofilm evade the actions of antimicrobials and disinfectants remain under investigation but appear identical to the mechanisms by which biofilms inhibit antibiotic activity. First, biofilms act as a permeability barrier to biocides (9,*215*,*223*). For example, *in vitro* resistance to povidone-iodine is mediated by the protective layering of *Pseudomonas* bacterial cells within a biofilm *(224)*. *In vitro*, higher concentrations of biocides can overcome this type of resistance *(225)*. Second, bacteria within a biofilm have slower growth rates that result in reduced efficacy of antimicrobials such as β-lactams.

Additional inherent and acquired mechanisms may allow evasion of biocide effects. The relative impermeability of the bacterial outer membrane may result in low-level resistance to hydrophobic compounds such as triclosan, and acquired alterations in bacterial outer membrane proteins may confer resistance to higher concentrations of such compounds (213,*216*,*223*,*226*). The expression of multidrug efflux pumps is another proposed mechanism of biocide resistance (*137*,213,*223*,*226–228*). Resistance of *Pseudomonas* species to other compounds such as phenols may be mediated by catabolic enzymes *(229–231)*. Plasmid-mediated resistance to silver has occurred in *Pseudomonas stutzeri (232)*.

Replication and Survival

Species of *Pseudomonas* and *B. cepacia* complex replicate in a wide range of moist environments because of their ability to obtain carbon and nitrogen from diverse substrates. Aliphatic amides or amino acids provide the source of both carbon and nitrogen. Alternatively, carbon may be derived from organic acids or esters of organic acids, whereas nitrogen is extracted from ammonium or nitrate. The range of substrates includes both antibiotics and germicides. For example, penicillin has served as a carbon source for *B. cepacia (233)* and *Pseudomonas fluorescens (234)*; chlorinated phenols were utilized by an isolate-designated *Pseudomonas* species B 13 *(235)*; and chlorhexidine and cetrimide were utilized by *B. cepacia (191)*. In addition, ammonium acetate–buffered benzalkonium chloride has supported the growth of *P. aeruginosa (236)*.

The minimal nutrient requirements of *P. aeruginosa* and *B. cepacia* complex permit their growth in tap water and distilled or deionized water up to concentrations of 10^5 to 10^7 CFU/mL *(185,237–239)*. Presumably, organic compounds absorbed in water from plumbing and storage systems are utilized as substrates. Naturally occurring pseudomonads in these minimal medium environments are more resistant to chemical inactivation by agents such as chlorine or iodine than are bacteria grown in enriched media *(191,201,237,238)*.

Pseudomonads are capable of prolonged survival in moist or dry environments. In laboratory studies, *P. aeruginosa* can survive in water for more than 300 days, on dry filter paper disks for up to 150 days, on hardened plaster of Paris bandages for at least 20 days, on plastics used in the hospital environment for up to 2 days, and in dried sputum for at least 5 days *(240–243)*. In the hospital environment,

P. aeruginosa was recovered from a dry floor 5 weeks after the ward was closed and from burn eschar tissue samples excised 8 weeks earlier *(244)*.

Acinetobacter demonstrates even better survival than *P. aeruginosa* under some conditions *(240,245–250)*. For example, *Acinetobacter calcoaceticus* survived an average of 9 days on a dry Formica surface compared with <1 day for *P. aeruginosa (247)*. Survival of *A. baumannii* at high colony counts for at least 16 weeks on dry surfaces has been shown using a strain initially isolated from dry environmental surfaces *(248)*. In addition, strains of *A. baumannii* survived on glass coverslips for an average of 27 days when incubated under conditions mimicking the hospital environment *(250)*.

B. cepacia achieved concentrations of 10^6 to 10^8 CFU/mL when inoculated into sterile 5% dextrose and normal saline solutions but appeared to exhaust its nutrient supply after 21 days of incubation *(251)*. *B. cepacia* did not multiply in 50% dextrose, 3% saline, or hyperalimentation solutions *(239)*. After prolonged storage of a contaminated solution of minimal inorganic salts containing benzalkonium chloride and ammonium acetate, cultures demonstrated viable *B. cepacia* after 14 years *(252)*.

DETECTION AND TYPING

P. aeruginosa grows readily on most standard laboratory media. For isolation from clinical specimens or sources with mixed flora, media that are selective for gram-negative bacilli, such as MacConkey or eosin–methylene blue agars, are utilized *(253,254)*. When culture surveillance of body sites or the environment is warranted, the detection of *P. aeruginosa* is facilitated by the use of selective media, and agar containing cetyltrimethylammonium bromide (cetrimide) is the most widely employed *(255–258)*. Other agents selective for *P. aeruginosa* include acetamide *(259)*, nitrofurantoin *(260)*, 9-chloro-9-(4-diethylaminophenyl)-10-phenylacridan (C-390) *(261–263)*, 1,10-phenanthroline *(264)*, C-390 and phenanthroline *(265)*, and 2,4,4-trichloro-2-hydroxydiphenyl ether (Irgasan) *(258)*. Before embarking on a culture survey with a selective medium, it is worthwhile to first confirm that the chosen medium inhibits competing species but not the strain(s) of interest. After isolation of bacteria on agar, characteristics that distinguish *P. aeruginosa* include a grapelike odor and production of a blue-green pigment (pyocyanin). Bacterial colonies exhibiting these features are definitively identified as *P. aeruginosa* by standard laboratory methods *(253,254)*.

Most nonfermenters also grow well on nonselective media and MacConkey agar *(266,267)*. For patients with cystic fibrosis, the isolation of *Burkholderia* species from culture is significantly enhanced by the use of selective media. *P. cepacia* agar and oxidation–fermentation polymyxin–bacitracin–lactose medium increase the yield of *B. cepacia* to three to four times that of MacConkey agar *(268,269)* and demonstrate evidence of growth 24 to 48 hours earlier *(270)*. *B. cepacia* selective agar, containing 1% lactose, 1% sucrose, polymyxin, gentamicin, and vancomycin, achieves better suppression of other respiratory tract pathogens than *P. cepacia* agar or oxidation–fermentation polymyxin–bacitracin–lactose while allowing the isolation of *B. cepacia (271,272)*. *S. maltophilia* has been misidentified as *B. cepacia* based on a false-negative DNase reaction. Because of the important clinical and prognostic implications in patients with cystic fibrosis, careful interpretation of such laboratory assays is essential *(273)*. Selective and differential media for the detection of *Acinetobacter* species, such as Leeds *Acinetobacter* medium, *Herellea* agar, and Holton's agar, were developed for use with clinical specimens and environmental testing *(267,274,275)*.

Because strain typing systems have become more sophisticated and accessible, epidemiologic investigations of *P. aeruginosa* are now more efficient and provide increasingly meaningful information. Early typing systems relied on phenotypic characteristics such as biochemical reactions, antibiotic susceptibility patterns, bacteriophage susceptibility, pyocin susceptibility, pyocin production, O serotype, and enzyme electrophoretic mobility. Because of the limited discriminatory power and sometimes cumbersome nature of such methods, these approaches have been largely replaced by DNA-based techniques *(276,277)*. Only serotyping, based on antigenic determinants on cell wall lipopolysaccharide (International Antigenic Typing System), remains a useful, widely available system *(276,278,279)*.

Plasmid profile analysis was among the first nucleic acid–based techniques applied to strain typing. This technique has been used infrequently *(280)*, and its interpretation is limited by the absence of plasmids in some strains and by potential transfer or spontaneous loss of plasmid(s) in others. Newer techniques have focused on chromosomal DNA (genotyping) to demonstrate genetic relatedness. Restriction endonuclease analysis of genomic DNA is the simplest approach and is useful as a screening tool *(279,281,282)*. Ribotyping has been employed successfully in epidemiologic investigations but is the least discriminatory of molecular methods *(281,283–287)*. A more precise approach is Southern blot analysis of chromosomal DNA in which restriction endonuclease fragments carrying a specific sequence are detected by a DNA probe. Probes encoding the exotoxin A gene have proven useful *(281,283,288–291)*, but not all *Pseudomonas* strains carry this gene. Probes encoding for phospholipase C or the pilin polypeptide also have been used alone or in combination with exotoxin A gene probes *(288,291,292)*. Restriction endonuclease analysis of genomic DNA using enzymes with infrequent recognition sites followed by pulsed-field gel electrophoresis (PFGE) has proven highly discriminatory in epidemiologic investigations involving *P. aeruginosa (255,281,293–297)*. This method is now considered the typing method of choice for *P. aeruginosa. P. aeruginosa* genotyping is also feasible by polymerase chain reaction (PCR) methodology such as random amplified polymorphic DNA analysis (RAPD) or enterobacterial repetitive intergenic consensus PCR *(285,292,298)*. Multilocus sequence typing (MLST), which involves the phylogenetic analysis of conserved regions of multiple housekeeping genes, is being investigated as a potential tool for the epidemiologic study of *Pseudomonas (299)*.

Similarly, for *B. cepacia*, the phenotypic typing methods *(300)* employed in the past are now considered unreliable (154). Ribotyping has documented patient-to-patient transmission *(301–303)*; however, PFGE and RAPD are now

the most commonly employed genotypic methods in epidemiologic investigations (154,*301–306*). Genotyping by repetitive extra-palindromic PCR is also reported *(307)*. MLST is emerging as a reliable and discriminatory tool to examine the global molecular epidemiology of *B. cepacia (308–311)*.

A variety of molecular techniques have been applied to the epidemiologic study of *A. baumannii*. Plasmid DNA electrophoresis and ribotyping both have limitations and thus largely have been replaced by PFGE or other PCR-based methods (104,*107*,*109*,*312–318*). The molecular epidemiology of *Acinetobacter*, particularly geographically remote clusters, can be undertaken with MLST *(319–320)*. Multilocus PCR followed by electron spray ionization mass spectroscopy is a rapid, high-throughput platform for MLST that is not widely available but has been successfully applied to the study of *Acinetobacter* and correlates with PFGE results *(321,322)*.

For other nonfermenters, older methods such as serotyping *(175,323)* and plasmid DNA electrophoresis *(313,314)* are sometimes helpful, and a variety of molecular techniques including ribotyping *(324)* and PCR-based systems *(325–333)* have been employed. However, PFGE of digested genomic or total DNA is most commonly used for molecular epidemiologic investigations, such as with *Stenotrophomonas (147,327,334–336)* and *Chryseobacterium (337,338)*.

CLINICAL AND EPIDEMIOLOGIC MANIFESTATIONS

Bacteremia

Bacteria may enter the bloodstream either because of microorganism virulence or because direct access is provided by contaminated intravascular devices or fluids. *P. aeruginosa* bacteremia usually arises by the former mechanism, whereas the latter mechanism accounts for most cases of bacteremia by other nonfermentative gram-negative bacilli.

The frequency of *P. aeruginosa* bacteremia largely depends on the population of patients studied. National statistics rank *P. aeruginosa* as the seventh leading cause of bloodstream infection, accounting for 4.3% of all bloodstream infections with an incidence of 2.1 per 10,000 hospitals admissions (155). At university teaching hospitals, the overall incidence has been about 10 cases per 10,000 admissions *(339,340)*. In patients with burn injuries or cancer, the incidence has been about 50 cases per 10,000 admissions *(341,342)*, and the incidence has exceeded 500 cases per 10,000 admissions in patients with acute leukemia *(342,343)*. The great majority of cases of *P. aeruginosa* bacteremia appears to be healthcare-associated.

The usual clinical picture of *P. aeruginosa* bacteremia is the same as that of bacteremia caused by other gram-negative bacilli. Fever is almost always present, except in infants, and tachycardia and hypotension are common findings *(342,344,345)*. Necrotizing skin lesions, called ecthyma gangrenosum, are considered pathognomonic of *P. aeruginosa* bacteremia *(346,347)*, but occasionally are seen in bloodstream infections by other pathogens, including *S. maltophilia* (83,*348*,*349*) and *B. cepacia (350)*. Ecthyma and other skin lesions were not uncommon in infected cancer patients treated in the 1950s and 1960s *(351,352)*, but are rare in later series *(342,344,345)*.

When present in the bloodstream of cancer patients, *P. aeruginosa* is virtually always the sole pathogen, and bacteremia is thought to arise from the alimentary tract. Gut colonization with *P. aeruginosa* has been associated with a risk of *P. aeruginosa* bacteremia exceeding 40% during neutropenia *(353–355)*. In other settings, about 20% of the cases of *P. aeruginosa* bacteremia are polymicrobial *(339,344,356)*. The most common primary sites of infection from which bacteremia arises are the urinary tract and respiratory tract *(339,340,344,356)*.

The outcome of *P. aeruginosa* bacteremia is poor, especially in neutropenic cancer patients. The mortality rate for these patients was about 90% until the 1970s, when it became common practice to administer combination therapy with gentamicin and carbenicillin presumptively for neutropenic fever *(343,351,357)*. Subsequently, the timely administration of more potent antipseudomonal antibiotics has lowered mortality rates below 40% *(358)*. In unselected patients at teaching hospitals, the mortality rate of *P. aeruginosa* bacteremia has remained about 40% to 50% *(349,359)* and exceeds that for other bacteria *(360)*. Some of this mortality can be attributed to the severity of underlying disease in patients with *P. aeruginosa* bacteremia. A matched cohort study of ICU patients with *P. aeruginosa* bacteremia reported an overall mortality of 62%, but an attributable mortality of only 15% *(361)*. Improved outcomes have been associated with resolution of neutropenia and the early use of appropriate antibiotics (*351*,*357–359*,*362*,363). Poor outcomes have been associated with inappropriate initial antimicrobial therapy (363,*364–366*). Historically, an emphasis was placed on the treatment of *P. aeruginosa* bacteremia with synergistic antibiotic combinations, typically an antipseudomonal β-lactam agent plus an aminoglycoside. Ongoing analysis suggests that combination therapy is no more effective than monotherapy, provided the single agent is not an aminoglycoside but is an antipseudomonal β-lactam with potent activity given at a suitable dosage *(364*,*365*,*367)*. Combination therapy may continue to have value as initial empiric therapy when the identity and the susceptibility profile of the infecting agent are unknown. In striking contrast to the life-threatening nature of most cases of healthcare-associated *P. aeruginosa* bacteremia, there are occasional examples of asymptomatic *P. aeruginosa* bacteremia *(368)* and of symptomatic intravenous catheter sepsis that resolves without specific antibiotic therapy *(369,370)*.

Cases of primary *P. aeruginosa* bacteremia occasionally have been linked to intravenous devices or infusion products that became contaminated during preparation in hospitals *(179*,*371–373)*. Bacteremia arising from contaminated endoscopes has been a more frequent problem (*374*,*375*,376), including episodes reported in association with endoscopic retrograde cholangiopancreatography *(377–380)*. Outbreaks of *P. aeruginosa* infection similarly have been traced to breaches in reprocessing of bronchoscopes (376) and cystoscopes *(381)*. In these cases, the onset of symptoms usually was a few hours to a few days after the procedure. Hemodialysis treatment also has been a source of *P. aeruginosa* bacteremia and has been associated with inadequate reprocessing of hemodialyzers

with benzalkonium chloride *(368,382)*, incorrectly diluted formaldehyde *(383)*, or contaminated dialysate waste drainage ports *(384)*.

In some centers treating neutropenic cancer patients, the overall incidence of *P. aeruginosa* bacteremia has declined *(385)*. However, other centers have reported outbreak or hyperendemic problems apparently linked to contamination of mouthwash *(386)*, environmental contamination *(355)*, or cross-transmission from patients *(171)*.

Pseudobacteremia due to *P. aeruginosa* contamination of blood culture specimens has been reported *(387,388)*. One outbreak of *P. aeruginosa* pseudobacteremia was traced to the use of contaminated disinfectant to clean blood culture bottles before use *(388)* (see also Chapter 9).

Although *P. aeruginosa* bacteremia is almost always life-threatening, bacteremia caused by other nonfermenting gram-negative bacilli is frequently self-limited. Outbreaks of *B. cepacia* complex bacteremia associated with common source exposure to contaminated fluids (89,*389–393*), including alcohol-free mouthwash *(394,395)*, skin moisturizer *(396)*, disinfectants *(186,202,397,398)*, or medical devices *(382–387,389–392,399,400)*, have been associated with significant morbidity, but there has been little or no mortality. Most reported cases of *B. cepacia* bacteremia have in common the direct introduction of contaminated material into the bloodstream. Pseudobacteremia due to *B. cepacia* has been reported rarely *(401)*.

S. maltophilia bacteremia generally arises secondary to respiratory tract or intravenous catheter–related infection in immunocompromised patients receiving broad-spectrum antibiotics. *S. maltophilia* bacteremia often occurs as a breakthrough infection *(402)*. Unlike *B. cepacia*, *S. maltophilia* bacteremia is often associated with signs and symptoms of sepsis and carries a mortality rate of 25% to 57% *(403–405)*. One case–control study reported an attributable mortality rate of 27% in patients with *S. maltophilia* bacteremia *(406)*. Mortality is increased when the patient is immunocompromised, the primary source is the lung, or antibiotic therapy is inappropriate *(402–405,407)*. Catheter-related bloodstream *S. maltophilia* infections respond well to early catheter removal; failure to remove the catheter is associated with a high risk of relapse (*408*,409,*410*). *S. maltophilia* has also been associated with outbreaks of pseudobacteremia *(411)*.

Acinetobacter species accounted for 1.5% of all healthcare-associated bloodstream infections in a survey of 49 US hospitals from 1995 to 1998 *(412)*. *A. baumannii* accounted for 86% of *Acinetobacter* isolates. *A. baumannii* bacteremia was more frequently observed in the ICU than bloodstream infections with other gram-negative bacilli (69% vs. 47%, respectively). *Acinetobacter* bacteremia has the potential to present as very low grade infection or as septic shock. Early reports emphasized the transient or benign nature of *Acinetobacter* bacteremia *(413–417)*. Bacteremia often cleared with removal of the associated intravenous catheter with or without antibiotic therapy. A report of catheter-related *Acinetobacter johnsonii* bacteremia described a similarly benign clinical course *(418)*. In other series, high fever, leukocytosis, and septic shock were present in 37% to 78% of cases, mortality rates ranged from 15% to 32%, and metastatic complications including endocarditis, septic thrombophlebitis, and intra-abdominal abscess were detected *(107,419–421)*. A case–control study of ICU patients with *A. baumannii* bacteremia found an overall mortality of 42%, but an attributable mortality of only 8%, reflecting the underlying severity of illness in patients with *Acinetobacter* bacteremia *(422)*. *Acinetobacter* infection tends to occur in patients with impaired host defenses. Almost all have intravenous catheters and are receiving broad-spectrum antibiotics *(107,413–421,423,424)*.

P. fluorescens is an important cause of transfusion-associated infection. This microorganism is psychrophilic (grows at 4°C) and utilizes citrate as a carbon source. Refrigerated citrate anticoagulated red blood cell units serve as an ideal growth medium. *P. fluorescens* can achieve peak concentrations of 10^6 to 10^7 CFU/mL within 1 week of storage at 4°C. Transfusion-related infection has been associated with severe illness and mortality rates exceeding 50% *(425–427)*. These infections are characterized by the sudden onset of fever, chills, and hypotension during red blood cell transfusion, and the source of infection has been confirmed by positive culture of untransfused blood. *P. fluorescens* bacteremia has also been associated with infusion of contaminated heparinized saline flush solution (428). In contrast to the high mortality rate reported with transfusion-related infection, there were no deaths among 80 cases reported, possibly reflecting a lower microorganism load in the infused flushes.

Bacteremia caused by *Ralstonia* (formerly *Pseudomonas*) *pickettii (189,361,420,421,423–427,429–441)*, other *Ralstonia* species *(442,443)*, *S. paucimobilis (118,438,443–448)*, *Pseudomonas* (formerly *Flavimonas*) *oryzihabitans (132)*, and *Rhizobium radiobacter* (formerly *Agrobacterium radiobacter* and *Agrobacterium tumefaciens) (449–452)*, *Ochrobactrum anthropi (453)*, or *P. stutzeri (454)* almost always results from either infusion of contaminated solutions or direct contact with contaminated ventilators or dialysis equipment. These infections have generally produced few symptoms, and many episodes of bacteremia have cleared without antibiotic therapy. Complications such as hematogenous infection of the central nervous system or bone have been reported rarely *(443)*, and catheter removal to resolve intravascular catheter–related bacteremia sometimes has been necessary *(448)*.

Pseudobacteremia has been reported with a variety of nonfermenting gram-negative bacilli including *O. anthropi (455)*, *Achromobacter xylosoxidans (456)*, and *P. oryzihabitans (457)*.

Pneumonia

Prior to the 1980s, *P. aeruginosa* was isolated from fewer than 10% of patients with healthcare-associated pneumonia (30,*458,459*). Thereafter, the proportion of cases attributed to *P. aeruginosa* nearly doubled, and *P. aeruginosa* has been the most common pathogen or the most common gram-negative bacterium isolated from patients with healthcare-associated pneumonia *(459–461)*. It remains uncertain whether detection of *P. aeruginosa* in sputum obtained by expectoration or tracheal aspiration necessarily indicates a causative role in lower respiratory tract infection since tracheal colonization may be present without causing pneumonia *(462)*. Nonetheless, *P. aeruginosa* has been the leading gram-negative pathogen in several studies in which selected patients underwent bronchial lavage or protected brush sampling *(463–466)*.

Factors that predispose to *P. aeruginosa* pneumonia include cystic fibrosis *(467–469)*, other underlying chronic pulmonary diseases *(462,468–471)*, mechanical ventilation *(470–472)*, and hematologic malignancies *(468,472)*. The pathogenesis of infection can involve microaspiration of microorganisms colonizing the oropharynx but more often appears to be due to direct contamination of the trachea with microorganisms from environmental or patient reservoirs *(473–476)*. Once initiated, *P. aeruginosa* infection of the lungs may progress to a necrotizing bronchopneumonia. Radiographically evident cavitation sometimes develops *(471,477)*, and pathologic features include diffuse small necrotic nodules, areas of hemorrhage, and vasculitis of small arteries *(288,470,471)*.

Survival of patients with *P. aeruginosa* pneumonia was infrequent prior to the 1980s, when potent antipseudomonal antibiotics became available *(468,472,478,479)*. Bacteremic pneumonia had an especially dismal prognosis. In later studies, survival rates have reached about 50% *(470,480,481)*. However, in patients with severe pneumonia, the prognosis remains poorest when *P. aeruginosa* is the bacterial pathogen isolated from initial respiratory tract cultures or blood cultures *(479–481)*. VAP also appears to have a worse prognosis when *P. aeruginosa* is the pathogen *(482,483)*. Specific problems in the treatment of *P. aeruginosa* pneumonia are recurrence, even after treatment for several weeks *(470)*, and emergence of resistance to the antibiotics used during treatment *(480,481)*. Even when potent antibiotics such as ciprofloxacin or imipenem–cilastatin have been used, resistance has emerged in more than one fourth of cases *(481)*.

During the 1960s and early 1970s, respiratory therapy equipment was recognized to be a potential source from which nonfermentative gram-negative bacilli could be introduced into the respiratory tract *(483–487)*. Contaminated nebulizers were the major problem and were shown in an experimental model to cause *P. aeruginosa* pneumonia in mechanically ventilated dogs *(487)*. Other devices that produce aerosols, such as room humidifiers *(488)* and oxygen humidifiers *(488,489)*, also have been identified as potential sources of pseudomonal respiratory infection. Investigations in specialized care units have shown that tracheal acquisition of *P. aeruginosa* sometimes is preceded by gastrointestinal tract colonization and that sources of *P. aeruginosa* include the inanimate environment and other patients *(476,490–496)*.

In cystic fibrosis centers, acquisition of *P. aeruginosa* is a significant concern. Contamination of the environment has been detected in some clinics *(242)* but not in others *(495,497)*. Where environmental contamination is minimized by routine or contact isolation precautions, transmission is infrequent *(497–499)*.

P. aeruginosa is a rare cause of community-acquired pneumonia. The clinical presentation is nonspecific, but the disease may be rapidly fatal. Patients with previous hospitalization or antimicrobial therapy and underlying pulmonary disease seem to be at highest risk *(500)*. In previously healthy persons with community-acquired pneumonia, *P. aeruginosa* should be considered in the differential diagnosis for anyone with a smoking history who presents with rapidly progressive pneumonia *(501)*.

B. cepacia complex is a rare pulmonary pathogen except in patients with cystic fibrosis or chronic granulomatous disease *(502)*. Epidemic recovery of *B. cepacia* from respiratory specimens has been reported when contaminated lidocaine, tetracaine, or cocaine was used in bronchoscopy or otolaryngology procedures, but pneumonia did not occur *(503–505)*. In one outbreak, there was no reported evidence of clinical illness among 18 patients with *B. cepacia* respiratory tract colonization despite instillation into the respiratory tract of 10 mL of contaminated anesthetic containing up to 10^{10} CFU/mL *(503)*.

B. cepacia is an important respiratory pathogen in individuals with cystic fibrosis. Persistent infection with *B. cepacia* has been associated with worsening pulmonary status and increased mortality when compared with uninfected controls (154,*506–508*). The response to acquisition of *B. cepacia* appears to take one of two forms: about 25% of patients develop fulminant infection characterized by high fever, leukocytosis, and severe progressive respiratory failure, whereas the remaining patients, usually those with mild cystic fibrosis, have persistent colonization without evidence of significant adverse effect (154,*507*). Risk factors associated with acquisition of *B. cepacia* include older age, more advanced pulmonary disease, and exposure to *B. cepacia* from previous hospitalization or a sibling with *B. cepacia* colonization *(506)*.

B. cepacia pneumonia is a serious illness in individuals with chronic granulomatous disease *(509)*. Of note, 6 of 10 cases reported in the literature were not known to have chronic granulomatous disease before the occurrence of *B. cepacia* pneumonia *(509)*. Isolation of this unusual pathogen from patients with community-acquired pneumonia should prompt an evaluation of phagocyte function and screening for cystic fibrosis.

S. maltophilia typically occurs as a late-onset healthcare-associated infection. *S. maltophilia* pneumonia has been associated with previous antibiotic therapy, in particular imipenem and cefepime, tracheostomy, and severity of illness *(510,511)*. *S. maltophilia* has been associated with increased morbidity, but the attributable mortality is uncertain.

The respiratory tract is the most frequent site of *Acinetobacter* infection. In surveys, *Acinetobacter* has ranked from third to the ninth most common cause of VAP accounting for 3.0% to 8.4% of VAPs *(512–514)*. Healthcare-associated pneumonia usually occurs in debilitated ICU patients receiving prolonged mechanical ventilation and broad-spectrum antibiotics (104,*107*,*515–518*). Distinguishing colonization from infection in these patients can be very difficult. Although some investigators have reported very low morbidity associated with the recovery of *Acinetobacter* from ventilated patients *(519)*, others have described severe illness with mortality rates of 36% due to infection (104,*107*,*515*). These latter patients present with fever, purulent sputum, leukocytosis, and multilobar patchy infiltrates on chest radiograph.

Acinetobacter demonstrates a unique seasonal variation in the United States with infection rates twice as high during July to October than during November to June *(520)*. In contrast, rates of *P. aeruginosa* show little seasonal variation. The cause of seasonal variation in *Acinetobacter* infection rates is uncertain and may be important for the design of prevention measures.

Acinetobacter occasionally causes severe community-acquired pneumonia, especially in individuals with

underlying alcoholism and chronic obstructive pulmonary disease*(521–523)*. The illness manifests as an acute, fulminant pneumonia and has a mortality rate of up to 50%. Mortality is strongly associated with inappropriate antibiotic therapy *(521,522)*, which has been linked to misidentification of the bipolar gram-negative rods of *Acinetobacter* as overdecolorized pneumococci.

Other nonfermenters have been associated with respiratory tract colonization but cause little morbidity and little or no mortality *(502,524–527)*.

Urinary Tract Infection

P. aeruginosa adheres well to bladder uroepithelial cells, but is not a common cause of urinary tract infection *(528,529)*. It accounts for only about 10% of healthcare-associated urinary tract infections and ranks fourth in frequency at this site behind *Escherichia coli*, *Enterococcus*, and *Candida (512)*. The pathogenesis of infection, as elucidated from case clusters, primarily involves retrograde introduction of microorganisms into the bladder via urinary drainage catheters or contaminated urologic instruments *(530–532)*. Colonization of the rectum, perineum, or urethra may precede *P. aeruginosa* urinary tract infection *(533,534)*.

P. aeruginosa bacteriuria in catheterized patients often resolves spontaneously within 2 to 3 months *(535)*. Necrotizing infection of the bladder or kidney is extremely rare, and pyelonephritis as a complication of bacteriuria is uncommon *(531)*. Rates of secondary bacteremia in patients with *P. aeruginosa* urinary tract infection were 3.1% in an endemic setting and 4.5% in an epidemic setting *(531,536)*. Urologic procedures have induced *P. aeruginosa* bacteremia, but there is no evidence that the procedure-related risk is greater than for other uropathogens *(381,537,538)*.

P. aeruginosa has been reported to be the most common cause of clustered cases of urinary tract infection *(539)*. Case clusters have been linked to contaminated urologic instruments *(530,532,540)*, urine collection or measuring devices *(531,541–543)*, and cross-transmission due to contamination of the hands of personnel *(544)*. Where infected urine is not well contained, *P. aeruginosa* contamination of the perineum and hands of infected patients and of bed linen has been noted *(544)*.

Efforts to prevent catheter-related urinary tract infection by instilling a disinfectant into the drainage system or by using a silver oxide–coated catheter have not clearly helped against *P. aeruginosa (545,546)*.

Urinary tract infection with nonfermenters other than *P. aeruginosa* is notable for the lack of significant morbidity. All episodes occur in patients who have undergone urologic procedures or bladder catheterization, and most infections are asymptomatic and resolve spontaneously with catheter removal (104,*186,547–549*).

Burn Wound Infections

P. aeruginosa is one of the most common burn wound pathogens, and it has colonized or infected more than one fourth of patients in several series *(550–553)*. An increased extent of burn has been associated with an increased risk of both colonization and burn wound sepsis *(551,554)*. *P. aeruginosa* colonization or infection is almost always hospital-acquired *(242,283,553,554)*. Culture surveys to identify reservoirs of *P. aeruginosa* in burn units have yielded positive cultures from sinks and hydrotherapy equipment *(283,550,553)*. Only hydrotherapy equipment has been compellingly linked to cases. Strains of *P. aeruginosa* acquired during hospitalization have been matched to those in hydrotherapy equipment, and disinfection of the equipment or suspension of its use has been associated with outbreak termination *(283,553)*. Dispersal of *P. aeruginosa*, presumably from colonized or infected patients, has resulted in the contamination of air *(554,555)*, the hands of personnel *(554)*, and surfaces such as bed rails *(550)*, counters *(550)*, food trays *(554)*, and transport equipment *(553)*.

Measures to control *P. aeruginosa* in burn units have included topical treatment of burn wounds, aseptic practices to prevent acquisition, and aggressive systemic antibiotic treatment of infections *(283,552,553)*. The use of selective bowel decontamination regimens to suppress aerobic gram-negative bacilli in the alimentary tract has been proposed *(556)* but may be of limited benefit against microorganisms such as *P. aeruginosa*, which multiply primarily in the burn wound (see also Chapter 25).

Eye Infections

P. aeruginosa is a highly destructive ocular pathogen (31,*557,558*), and it has been reported to account for about 8% of postoperative ocular infections at one center *(559)*. Superficial infection may lead rapidly to corneal or scleral perforation, and endophthalmitis can cause complete loss of vision. Keratitis typically presents as an acute, rapidly progressive corneal ulcer with greenish pus and hypopyon *(560)*. Extension from cornea to sclera may occur and is associated with a poor outcome *(561)*. Postoperative endophthalmitis usually becomes clinically evident within 1 to 2 days but may evolve over 5 to 10 days *(562,563)*.

Several risk factors for *P. aeruginosa* ocular infection have been identified, and most apply to healthcare-associated cases. Keratitis may be a consequence of corneal trauma, corneal surgery, or treatment with multidose eye drops or eyewash solutions that became contaminated during use *(560,562,564,565)*. Scleral irradiation has preceded scleral and corneal infection *(566)*, and neutropenia has been associated with blepharoconjunctivitis *(567)*. Endophthalmitis usually has been a consequence of surgery, and case clusters have been traced to contaminated solutions or implants *(562,563,568)*.

Sporadic cases and clusters of cases of *P. aeruginosa* conjunctivitis have been recognized in patients receiving respiratory care *(569–573)*. Almost all the patients were intubated, had *P. aeruginosa* in their respiratory secretions, and had frequent suctioning to remove respiratory secretions. Strikingly, infection involved primarily the left eye in almost all adult cases *(568,569)*. Hilton et al. *(569)* explained the left eye predominance by showing that *P. aeruginosa* in respiratory secretions was dispersed during suctioning and that nurses usually withdrew suction catheters diagonally across the left side of patients' faces. Cases of healthcare-associated conjunctivitis in newborn infants also have been reported and were traced to contaminated incubators *(574)* (see also Chapter 26). *S. maltophilia* is a rare cause of postoperative endophthalmitis after cataract surgery *(575,576)*. Other nonfermenters are occasionally isolated from conjunctival swabs but are rare causes of infection *(572,577,578)*.

Meningitis

Healthcare-associated meningitis caused by nonfermentative gram-negative bacilli is almost always a complication of neurosurgical procedures. *Pseudomonas* and *Acinetobacter* have been the predominant nonfermenters, accounting for about one fourth to one half of cases of postneurosurgical gram-negative meningitis in adults *(579–582)*. *P. aeruginosa* is also an important cause of meningitis in burn unit patients *(583)* and has caused healthcare-associated meningitis in patients hospitalized for cranial trauma *(584)*.

Investigations of cases of *P. aeruginosa* meningitis several decades ago implicated contaminated medications that had been injected intrathecally *(585,586)* and a contaminated shaving brush used in neurosurgical patients to prepare the site for incision *(587)*. The sources of *P. aeruginosa* causing recent cases have not been reported.

The first reported cases of *Acinetobacter* meningitis were community acquired *(588,589)* and the early genus name *Mima* ("mimic") arose from the frequent misidentification on Gram stain of the bipolar staining rod as *Neisseria meningitides (590)*. *Acinetobacter* meningitis was later reported almost exclusively in association with neurosurgical procedures or cranial trauma *(590,591)*. Occasional cases have occurred in neonates in the absence of invasive procedures *(592)*. Patients with *Acinetobacter* meningitis usually are receiving antibiotic therapy at the onset, and clinical features include fever (95%), mental status changes (50%), neck stiffness (25%), cerebrospinal fluid pleocytosis (100%), and low cerebrospinal fluid glucose (60%) *(591)*. Half of the recent cases have been polymicrobial. The overall mortality rate is about 20%, and survival is associated with prompt appropriate therapy. Sources of *Acinetobacter* causing healthcare-associated meningitis have not been identified. Other nonfermentative gram-negative bacilli have caused sporadic cases of meningitis *(593–598)*.

Surgical Site Infection—Osteomyelitis

Overall, *P. aeruginosa* has been isolated from about 9% of surgical site infections *(599)*. The relative frequency of *P. aeruginosa* as a pathogen is high at some sites such as sternotomy for cardiac surgery *(600–602)*, whereas *P. aeruginosa* accounts for only a few percent of infections following implantation of prosthetic joints *(603,604)*. Because of its virulence, the presence of *P. aeruginosa* in an incisional surgical site at the time of closure has been associated with a risk of subsequent surgical site infection exceeding 30% *(605,606)*. Administration of perioperative antibiotics directed against *P. aeruginosa* appears to diminish the risk *(606)*. Although an uncommon cause of osteomyelitis, *P. aeruginosa* was associated with more than a twofold risk of recurrence compared with infection with *Staphylococcus aureus (607)*.

The source of *P. aeruginosa* causing infection after intra-abdominal operations is generally considered to be the patient *(605,606)*. Exogenous sources in the operating theater have been sought to explain infections following other types of surgery, and positive cultures have been reported from a water bath *(371)*, a scrub sink faucet *(608)*, suction pumps for chest tubes *(608)*, and an arterial pressure monitoring system *(609)*. One cluster of cases of *P. aeruginosa* surgical site infections was attributed to the preparation of the skin incision site with a dilute solution of chlorhexidine contaminated with *P. aeruginosa (187)*, and another cluster, involving orthopedic patients, was traced to contaminated plaster-of-Paris bandages *(610)*.

Acinetobacter is a frequent isolate from skin, and recovery of the microorganism from surgical sites is not surprising. *S. maltophilia* and *B. cepacia* also have been recovered from surgical sites, but typically in mixed culture *(611,612)*. The clinical significance of these microorganisms in surgical site cultures is often uncertain. *Acinetobacter* has been reported as a frequent cause of wound infections complicating combat-related injuries in military personnel; the source of the *Acinetobacter* appears to be the medical facilities rather than the battlefield environment *(*613,*614)*.

EPIDEMIOLOGY

Rates of Healthcare-Associated Infection

The frequency of nonfermentative aerobic gram-negative bacilli as healthcare-associated pathogens has been characterized through the National Nosocomial Infection Surveillance system *(615)*. *P. aeruginosa* and *Acinetobacter* have become increasingly important causes of healthcare-associated pneumonia, surgical site infections, and urinary tract infection (see Table 35-1).

Inanimate Reservoirs

Extensive culture studies have been conducted, mostly during the 1950s and 1960s, to identify hospital sources of nonfermentative gram-negative bacilli. As summarized in Table 35-2, these microorganisms have been found in virtually every moist area of the hospital, many fluids, and an array of equipment and surfaces that were exposed to the hands, secretions, and excretions of patients. Recognition that these microorganisms are ubiquitous has prompted increased attention to aseptic practices, particularly in the use of respiratory equipment *(691)*. Nonetheless, nonfermentative gram-negative bacilli continue to test the adequacy of aseptic practices and to find deficiencies in product manufacturing (*183,186,201,222*,376,*434,664*) and in disinfection of medical devices for reuse *(179,374–380,382,383,568,632,665)*.

The major vehicles by which *P. aeruginosa* is conveyed into hospitals are tap water and food. Tap water is increasingly recognized as a potentially important reservoir for healthcare-associated acquisition of *P. aeruginosa* colonization and infection. One survey found that 14.2% to 50% of *P. aeruginosa* colonization or infection episodes were due to tap water genotypes (715,*716*). The use of point-of-use water filtration has been associated with a significant reduction in positive cultures for *P. aeruginosa* from tap water and a significant reduction in the incidence of infections due to *P. aeruginosa* and other nonfermenting gram-negative bacilli *(616,620,717)*. Vegetables are the most commonly contaminated foods, and rates of positive cultures of salads have ranged from 11% to 44% *(172,696–700)*. The concentration of *P. aeruginosa* in individual vegetables or in salads has ranged up to 10^3 CFU/g *(172,698–700)*.

Studies to ascertain whether environmental isolates of *P. aeruginosa* cause colonization or infection of patients have implicated most of the potential sources listed in Table 35-2. The major exceptions are sinks, drains, and

TABLE 35-1

Percentage and Rank Order of *Pseudomonas aeruginosa* and *Acinetobacter* Species Related to Healthcare-Associated Infection Reported to the National Nosocomial Surveillance System, 1975 and 2003

		Percentage of Isolates (Rank Order)	
Pathogen	***Site***	***1975***	***2003***
Pseudomonas aeruginosa	Pneumonia	9.6 (3)	18.1 (2)
	Bloodstream infection	4.8 (6)	3.4 (6)
	Surgical site infection	4.7 (5)	9.5 (4)
	Urinary tract infection	9.3 (3)	16.3 (3)
Acinetobacter species	Pneumonia	1.5 (8)	6.9 (5)
	Bloodstream infection	1.8 (9)	2.4 (8)
	Surgical site infection	0.5 (8)	2.1 (8)
	Urinary tract infection	0.6 (9)	1.6 (8)

suction apparatus. Typing of isolates from serial cultures of patients and sinks has shown that patients typically become culture-positive first and that there are at most a few occasions when the sink or drain might have been the source of patient colonization *(171,642,655,656,659)*.

Animate Reservoirs

Colonization of patients by *P. aeruginosa* constitutes an important reservoir, particularly in specialty care units where patients are exposed to broad-spectrum antibiotics, medical devices, and the hands of healthcare personnel. Culture studies have shown colonization rates of 4% to 58% in hematology–oncology patients *(171,172,718,719)*, 13% to 39% in ICU patients *(643,644,657,720–722)*, 19% to 43% in surgery patients *(639,721)*, and 2% to 51% in special care baby units *(723,724)*. Factors in individual studies that are associated with an increased risk of colonization include prior hospitalization *(639,644)*, age above 65 years *(676)*, endotracheal intubation *(639)* and mechanical ventilation *(635)*, tracheostomy *(722)*, broad-spectrum antibiotic therapy *(643,722)*, previous gastrointestinal surgery *(721)* including ileostomy or colostomy *(639)*, and anemia *(721)*. *P. aeruginosa* is often acquired after admission, and the proportion of patients with positive cultures usually increases by at least 50% during hospitalization *(172,639,643,644,721,723)*. The most common site from which *P. aeruginosa* is recovered is the rectum, and in most studies at least 80% of colonized patients can be detected by cultures of that site *(172,255,643,644)*. The pharynx is usually the second most common culture-positive site *(255,644,719,721)*, although higher carriage rates occasionally have been reported for the perineum or urine *(171,724)*. In a culture study of intestinal contents of 100 cadavers, Stoodley and Thom *(725)* demonstrated that when *P. aeruginosa* was present, it usually could be recovered from both the small intestine and colon and that rates of isolation were about half as high in the jejunum as in lower segments of the gut. The concentration of *P. aeruginosa* has reached 10^6 to 10^7 CFU/g of feces in a patient receiving broad-spectrum, orally administered, nonabsorbable antibiotics for total digestive decontamination *(255)*. In that patient, colonization persisted for at least 5 months.

Hospital personnel infrequently are a reservoir for *P. aeruginosa*. Rates of positive cultures from stool have been <13% *(587,643)*, and the concentration of microorganisms may be too low to be detected by rectal swab *(643)*. Other sites such as nose, throat, or skin may be culture-positive in up to 5% of personnel caring for colonized patients *(554)*. Hand colonization for at least 4 weeks has been reported in a nurse *(644)*.

Acinetobacter is present on the skin in up to one fourth of normal individuals and about one third of hospitalized patients *(726,727)*. Sites that are most frequently culture positive are intertriginous areas such as the toe web and groin. Oropharyngeal or rectal carriage is uncommon, except in patients in ICUs *(728,729)*. The hands of hospital personnel have been sampled for *Acinetobacter*, and the proportion of individuals with at least one positive specimen from serial cultures is about one third *(648,726)*. Persistent colonization of the hands of a respiratory therapist has been reported *(648)*. The frequency of hand colonization by *S. maltophilia* has not been investigated other than in response to outbreaks of infection. During an ICU epidemic, half of the hand cultures from nurses and respiratory therapists were positive *(175)*. *S. maltophilia* rarely is present in stool of outpatients with diarrhea but has been detected in feces of one third of hematologic malignancy patients *(349)*. *B. cepacia* is rarely recovered from sites other than the respiratory tract of patients with cystic fibrosis *(722,730)*. Prior broad-spectrum antibiotic therapy appears to be an important risk factor for colonization or infection by *S. maltophilia* or *Acinetobacter* *(175,404,422,423,731)*.

Transmission

Healthcare-associated transmission of *P. aeruginosa* almost always results either from contact with environmental sources or from patient-to-patient spread via the hands of healthcare personnel. Possible transmission from environmental sources usually has been examined in response to case clusters or unusual clinical events. Even though many

TABLE 35-2

Hospital Sources of Nonfermentative Gram-Negative Bacilli

Source	*Microorganism*	*References*
Tap water supply	*Pseudomonas aeruginosa*	*(355,359,386,616–618)*
	Pseudomonas fluorescens	*(619)*
	Stenotrophomonas maltophilia	*(245,620,621)*
Water for humidification	*Pseudomonas aeruginosa*	*(353,486,488,622–624)*
	Acinetobacter species	*(625–627)*
	Sphingomonas paucimobilis	*(628)*
	Pseudomonas fluorescens	*(526)*
	Stenotrophomonas maltophilia	*(629)*
Distilled water	*Pseudomonas aeruginosa*	*(624,630)*
	Burkholderia cepacia	*(300,628)*
	Acinetobacter species	*(631)*
	Pseudomonas fluorescens	*(526)*
	Ralstonia pickettii	*(632)*
Sterile water or saline	*Pseudomonas aeruginosa*	*(562,623,633)*
	Pseudomonas fluorescens	(428)
	Burkholderia cepacia	*(389,392,393)*
	Acinetobacter species	*(634)*
	Ralstonia pickettii	*(432,524,525,635,636)*
	Sphingomonas paucimobilis	*(637)*
	Stenotrophomonas maltophilia	*(638)*
Nonsterile water	*Pseudomonas aeruginosa*	*(372,633,639,640)*
	Burkholderia cepacia	*(188)*
	Acinetobacter species	*(641)*
Suction apparatus	*Pseudomonas aeruginosa*	*(476,491,623,642–646)*
Ventilator	*Pseudomonas aeruginosa*	*(476,485,486, 490,643)*
	Burkholderia cepacia	*(91,300,484,502,647)*
	Stenotrophomonas maltophilia	*(175)*
	Acinetobacter species	*(515,519,621,634,648–652)*
	Sphingomonas paucimobilis	*(631,653)*
	Pseudomonas fluorescens	*(619)*
Faucet aerator	*Pseudomonas aeruginosa*	*(623,654)*
Sink or wash basin	*Pseudomonas aeruginosa*	*(171,172,476)*
	Stenotrophomonas maltophilia	*(639,643,655–657)*
	Acinetobacter species	*(326,658)*
Sink drain	*Pseudomonas aeruginosa*	*(493,494,622,642,643,645,655,659,660)*
Showerhead	*Pseudomonas aeruginosa*	*(661)*
Water fountain or ice machine	*Pseudomonas aeruginosa*	*(662)*
Whirlpool or hydrotherapy tank	*Pseudomonas aeruginosa*	*(431,553,662,663)*
Urine collection or measuring device	*Pseudomonas aeruginosa*	*(531,541,543)*
Endoscope, cystoscope, or bronchoscope	*Pseudomonas aeruginosa*	*(374–380,530,532,664–667)*
Endoscope washer	*Pseudomonas aeruginosa*	*(374,664)*
Miscellaneous equipment	*Acinetobacter* species	*(668,669)*
	Sphingomonas paucimobilis	*(620,670)*
	Pseudomonas aeruginosa	*(540,568,574,587,644,671)*
	Burkholderia cepacia	*(400,609,672,673)*
	Stenotrophomonas maltophilia	*(307,674,675)*
Hemodialyzers or dialysis machines	*Pseudomonas aeruginosa*	*(384)*
	Burkholderia cepacia	*(399)*
	Stenotrophomonas maltophilia	*(399,676)*
	Acinetobacter species	*(384,399)*
	Pseudomonas stutzeri	*(453)*
Injected medication	*Pseudomonas aeruginosa*	*(371,585,586)*
	Pseudomonas putida	*(677)*
	Burkholderia cepacia	*(390,392,484,678–680)*
	Stenotrophomonas maltophilia	*(677)*

(*Continued*)

TABLE 35-2

Hospital Sources of Nonfermentative Gram-Negative Bacilli (*Continued*)

Source	*Microorganism*	*References*
	Sphingomonas paucimobilis	*(438)*
	Acinetobacter species	*(681)*
	Ralstonia pickettii	*(430,434–437)*
	Rhizobium radiobacter	*(451)*
Topical medications	*Pseudomonas aeruginosa*	*(201,503–505,676,682–684)*
	Burkholderia cepacia	*(684)*
Plasma expander	*Pseudomonas aeruginosa*	*(373)*
Infant formula bottles	*Pseudomonas aeruginosa*	*(685)*
Ultrasound gel	*Burkholderia cepacia*	*(686)*
Inhaled medication	*Burkholderia cepacia*	*(687,688)*
Linen, bedclothes, or mattresses	*Pseudomonas aeruginosa*	*(544,554,639)*
	Acinetobacter species	*(689,690)*
Objects or surfaces	*Pseudomonas aeruginosa*	*(243,476,553,645,691,692)*
	Stenotrophomonas maltophilia	*(175)*
	Acinetobacter species	*(160,649,690,693)*
	Pseudomonas fluorescens	*(619)*
Pericardial allograft	*Ochrobactrum anthropi*	*(694)*
Organ allograft	*Pseudomonas aeruginosa*	*(695)*
Blood products	*Burkholderia cepacia*	*(389,391)*
	Acinetobacter species	*(693)*
	Pseudomonas fluorescens	*(425–427,429)*
Foods (salads)	*Pseudomonas aeruginosa*	*(172,662,696–700)*
Enteral formula	*Pseudomonas aeruginosa*	*(640,701)*
	Acinetobacter species	*(702)*
Food dye	*Pseudomonas aeruginosa*	*(496)*
Mouthwash	*Pseudomonas aeruginosa*	*(386,642,696)*
	Burkholderia cepacia	*(289,394,395,703)*
Skin cream	*Pseudomonas aeruginosa*	*(704,705)*
	Burkholderia cepacia	*(396,706)*
Soap or detergent	*Pseudomonas aeruginosa*	*(243,476,623,640,645,707)*
	Burkholderia cepacia	*(609)*
	Acinetobacter species	*(708)*
	Pseudomonas stutzeri	*(195)*
Bath sponge	*Pseudomonas oryzihabitans*	*(709)*
Antiseptic or disinfectant	*Pseudomonas aeruginosa*	*(179,187,199,388,654,662,705)*
	Burkholderia cepacia	*(186,191,196,200–202,397,398,484,710–713)*
	Stenotrophomonas maltophilia	*(192)*
	Ralstonia pickettii	*(189,714)*
	Rhizobium radiobacter	*(456)*

of the early studies did not utilize rigorous epidemiologic methods or *P. aeruginosa* typing systems, plausible circumstantial evidence was provided for transmission from most of the sources listed in Table 35-2. Later studies in which patients and environmental isolates were typed confirmed that contaminated items, such as water *(386,553,716)*, food *(172)*, antiseptics *(199)*, endoscopes *(377,378,380)*, cystoscopes *(381)*, and bronchoscopes (376,*664*), can transmit *P. aeruginosa* to patients. Such transmission occurs infrequently when standard aseptic practices are followed *(171,644)*.

Patient-to-patient transmission of *P. aeruginosa* is documented by prospective studies in which periodic surveillance cultures of patients, personnel, and the environment were performed. Patient-to-patient transmission was considered to occur when a patient acquired a strain of *P. aeruginosa* that matched that of another patient and that was not present in any likely environmental source. Instances of apparent cross-transmission have been noted in increased risk settings, such as ICUs *(492,644,722,732)*, hematology/oncology units *(172,255)*, and pediatric units *(491,659,660)*. Contaminated hands of personnel are the likely vehicle of cross-transmission, and numerous investigations have demonstrated frequent *(476,494,554,644,660,733)* or occasional *(493,734–736)* positive cultures of hands. During routine care and in designed experiments *(491)*, the hands of personnel have become contaminated, especially after contact with heavily colonized patients *(644)*, exudates *(554)*, secretions

(476,644), or excretions *(622,734)*. The frequency of patient-to-patient transmission by personnel probably reflects the inadequacy of staffing, availability of gloves, hand disinfectant solution, and handwashing sinks, as well as attention to hand hygiene and other aseptic practices.

There is compelling evidence that when proper aseptic practices are observed, many apparent acquisitions of *P. aeruginosa* represent the emergence of strains carried in the alimentary tract at concentrations below the threshold of detection. Careful long-term studies in ICUs *(660,737)* and an oncology ward *(172)* showed that "acquisitions" often represent an array of *P. aeruginosa* types that do not match those isolated from environmental or patient reservoirs.

Clusters of cases of colonization or infection with other nonfermenters are usually caused by direct exposure to contaminated fluids or medical devices. Infection is facilitated by breaches in the normal host defenses by endotracheal tubes, intravenous catheters, hemodialyzers, peritoneal dialysis catheters, ventriculostomy tubes, or indwelling urinary catheters. Culture studies and epidemiologic findings sometimes suggest patient-to-patient transmission of *S. maltophilia* via the hands of personnel *(175,516,731)*. *S. maltophilia* is also found in tap water and tap water isolates have been linked to infection *(617)*. Investigations of ICU outbreaks of colonization and infection by *Acinetobacter* have demonstrated multiple likely modes of transmission involving the environment and the hands of personnel. Cultures of surfaces *(109,160,315,326,689,690,728,738–740)*, equipment *(109, 649,658,668,690,729,739)*, hands of personnel *(109,690,739,740)*, and latex gloves worn by personnel *(649,729)* are commonly positive. *Acinetobacter* is notably resistant to desiccation, persisting on dry surfaces for a mean of 27 days *(250)*. This remarkable durability along with intrinsic resistance to antibiotics and disinfectants undoubtedly contributes to persistent outbreaks. Barrier or contact isolation precautions have been at least partly effective in controlling outbreaks *(649,729,738,739)*; in addition, closure of units temporarily for cleaning, disinfection, and/or repainting has been useful in some *(315,690,738)* but not all *(729)* settings. Air samples taken near culture-positive patients have yielded *Acinetobacter (690,738)*, and transmission via droplets is plausible but airborne transmission has not been proven. Conflicting findings about a possible summer peak in the incidence of *Acinetobacter* infections have been reported *(223,312,422,500,516,591,690,741,742)*.

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CHAPTER 36

Legionella

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HISTORY

An explosive outbreak of community-acquired pneumonia occurred in July of 1976. The outbreak was among attendees of the American Legion Convention at a hotel in Philadelphia, PA *(1)*. Six months later, the causative agent was isolated from the lung tissue of Legionnaires' cases by scientists at the Centers for Disease Control and Prevention (CDC), Atlanta, GA *(2)*. The microorganism, an aerobic gram-negative bacterium, was named *Legionella pneumophila*. The pneumonia became known as Legionnaires' disease because the outbreaks occurred in attendees at the American Legion Convention. The first reported epidemic of healthcare-associated *Legionella* pneumonia was identified retrospectively. It occurred in July 1965 at St. Elizabeth's Hospital, a psychiatric institution in Washington, DC *(3)*. In this outbreak, 81 patients were afflicted, with an attack rate of 1.4%. It was not until 1980 that hospital water distribution systems were first implicated as the source for healthcare-associated Legionnaires' disease. Tobin isolated *Legionella* from showerheads in the hospital room of a patient with healthcare-associated Legionnaires' disease *(4)*. *Legionella* was subsequently isolated from potable water distribution systems of numerous hospitals experiencing outbreaks of Legionnaires' disease *(5–9)*.

MICROBIOLOGY

The Legionellaceae family has been characterized as one monophyletic family belonging to the gamma subdivision of the class Proteobacteria *(10)*. Although a single genus and species (*L. pneumophila*) was originally proposed for the family Legionellaceae *(11)*, the Legionellaceae family now contains >50 species and >70 serogroups in the genus *Legionella (12–14)*. Approximately half of these *Legionella* species have been implicated in human disease *(15)*. Among the species, *L. pneumophila* is responsible for 90% of infections (Table 36-1) *(15–17)*. These microorganisms are facultative intracellular gram-negative bacteria found in natural and man-made water systems. They are saprophytic water bacteria that can be intracellular parasites of protozoa (in water) and macrophages and epithelial cells in humans *(18)*. Most cases of legionellosis are caused by *L. pneumophila* serogroups 1, 4, and 6 *(13,17,19)*.

Other species implicated in human infection include *L. micdadei* (the Pittsburgh pneumonia agent), *L. bozemanii*, *L. dumoffii*, *L. tucsonensis*, *L. cincinnatiensis*, *L. feeleii*, *L. longbeachae*, and *L. oakridgensis (15,20)*. *L. longbeachae* is responsible for approximately 30% of Legionnaires' disease in Australia and New Zealand *(15)*. Most patients with nonpneumophila *Legionella* species infections have been severely immunocompromised because of corticosteroid therapy, organ transplantation, or malignancy (*21*,22,*23*,*24*).

Legionella species are small (0.3–0.9 μm in width and ~2 μm in length), faintly staining gram-negative rods with polar flagella (except *L. oakridgensis*) *(25)*. They generally appear as small coccobacilli in infected tissue or secretions, whereas long filamentous forms (up to 20 μm in length) can be seen when they are grown in culture media. Legionellaceae are obligately aerobic slow-growing nonfermentative bacteria. They are distinguished from other saccharolytic bacteria by their requirement for L-cysteine and iron salts for primary isolation on solid media and by their unique cellular fatty acids and ubiquinones. Differences among species have been assessed by phenotypic *(26)* and chemotaxonomic tests. Phenotypic tests include composition of lipopolysaccharides, electrophoretic protein profiles, monoclonal antibodies, fatty acid composition, and cellular carbohydrates. Genotypic tests include random amplified polymorphic DNA profiles, heteroduplex analysis of 5S ribosomal RNA (rRNA) gene sequences, and computer-assisted matching of transfer DNA–intergenic length polymorphism patterns, and sequence-based typing *(27–29)*.

The microorganism can be visualized, with some difficulty, with Gram stains of clinical specimens taken from normally sterile sites (e.g., pleural fluid). Both the Gram and Gimenez stains can be used for clinical specimens, whereas silver impregnation stains, including the Dieterle and Warthin–Starry stains, can be used for paraffin-fixed tissue sections. *L. micdadei* (Pittsburgh pneumonia agent) can stain weakly acid-fast in tissue with Kinyoun and Fite stains and on smears with a modified acid-fast stain in tissue or sputum specimens. These microorganisms are nutritionally fastidious and do not grow on standard bacteriologic media, which explains why the microorganism was so difficult to isolate in the original American Legion outbreak.

TABLE 36-1

Proportion of Legionnaires' Disease Caused by Species and Serogroups of *Legionella*

Species, Serogroup	*All Isolates (%) (n = 2,340)*	*Community-Acquired Infections (%) (n = 1,259)*	*Hospital Infections (%) (n = 890)*
Legionella pneumophila	91.4	90.7	93.6
Serogroup 1	50.5	49.6	52.5
Serogroup unknown	32.1	33.9	28.2
Serogroup 2	1.2	1.4	1.1
Serogroup 3	2.0	1.5	2.9
Serogroup 4	1.1	1.0	1.3
Serogroup 5	1.1	0.8	1.7
Serogroup 6	2.9	1.7	5.2
Serogroups 7–14	0.5	0.8	0.7
L. bozemanii	1.3	1.3	1.2
L. dumoffii	1.5	1.4	1.0
L. gormanii	0.2	0.2	0.2
L. micdadei	2.8	2.8	2.8
L. feeleii	0.2	0.2	0.2
L. longbeachae	2.2	3.3	0.7
L. jordanis	0.3	0.2	0.1

Note: Only isolates identified by culture are included.
(From Benin AL, Benson RF, Besser RE. Trends in Legionnaires' disease, 1980–1998: declining mortality and new patterns of diagnosis. *Clin Infect Dis* 2002;35:1039–1046, with permission.)

PATHOGENESIS

Legionnaires' disease can be acquired by the inhalation of aerosols containing *Legionella* or by aspiration of water or respiratory secretions containing *Legionella (12)*. Other possible modes of transmission include direct inhalation or hematogenous dissemination from other foci of infection *(30)*. Pneumonia is the presenting clinical syndrome in almost all cases of healthcare-associated legionellosis *(31)*. Although rare, extrapulmonary *Legionella* infection has been documented *(30,32–34)*.

Cigarette smokers, patients with chronic pulmonary disease, and alcoholics are at increased risk for Legionnaires' disease. For such individuals, mucociliary clearance is impaired and aspiration is common. As a barrier to entry, mucociliary clearance can be overcome by adherence of the microorganism to respiratory epithelial cells. After aspiration or inhalation, *Legionella* attaches to respiratory epithelial cells. Legionellae possesses pili that are known to mediate adherence to epithelial cells *(15)*. A gene has been identified that demonstrates homology to the type IV pilin genes in other bacteria. *Legionella* has also been detected in oropharyngeal secretions of transplant patients (35), and symbiosis has been shown *in vitro* between oropharyngeal flora and *Legionella (36)*.

Legionella is an intracellular pathogen both in humans and in aquatic environments (*15,37*,38). It has been suggested that the ability of *L. pneumophila* to replicate in protozoa is closely linked to its ability to replicate in human macrophages *(15)*. *Legionella* survives and multiplies as parasites of single-celled protozoa in freshwater and moist soil *(39)*. Virulence may be increased by replication in amoebae. In humans, cell-mediated immunity plays the central role in host defense against *L. pneumophila* as it does against other intracellular pathogens. *Legionella* replicates within mononuclear phagocytes, primarily monocytes, and alveolar macrophages *(40)*. Phagocytosis occurs through a process mediated by complement component C3 and outer membrane proteins such as the macrophage infectivity potentiator (Mip) protein. The uptake of *L. pneumophila* is considered a virulence-directed process that is a consequence of properties of the organism *(15)*. The macrophage readily phagocytoses *Legionella*, a process that is more avid in the presence of specific opsonizing antibody. Once inside the cell, the microorganism evades phagosome–lysosome fusion, converts to a replicative form that is acid tolerant, and multiplies until the cell ruptures (38). Liberated bacteria are phagocytosed by newly recruited cells, and the cycle of ingestion, multiplication, and liberation with cell lysis begins anew.

Although the resident alveolar macrophage normally degrades most microorganisms, *Legionella* is able to subvert this host defense. *L. pneumophila* evades destruction by inhibiting phagosome–lysosome fusion (38). Genes responsible for this survival mechanism have been identified as components of the Dot/Icm secretion system, which is required for intracellular replication and establishing the *Legionella*-containing vacuole *(41)*. Intracellular growth and formation of a replication vacuole requires the products of >26 *L. pneumophila dot/icm* genes *(42)*. This Dot/Icm type IV secretion system is used by *Legionella* to inject effector proteins into host cells to modulate host organelle function *(12,23)*.

Intracellular multiplication of *Legionella* within human monocytes also depends on the availability of iron *(45)*. The lymphokine interferon-γ (IFN-γ) stimulates human

alveolar macrophages and monocytes to resist *Legionella* infection by upregulating reactive oxygen production and downregulating cellular iron content. An analysis of Legionnaires' disease patients showed that they produced less IFN-γ than did non-Legionnaires' disease patients. Impaired IFN-γ response may increase susceptibility to the disease *(43)*. Other cytokines and hemopoietic growth factors, such as interleukin-10 (IL-10) and granulocyte-macrophage colony-stimulating factor, have not been shown to enhance anti-*Legionella* activity *(44)*. Significant rises in the T Helper-1 cytokines IFN-γ and IL-12 were detected in the serum of patients with Legionnaires' disease, supporting the importance of cellular immunity in this disease *(45)*. Neutrophils are less important, and neutropenic patients are not at undue risk for Legionnaires' disease. Nevertheless, *L. pneumophila* is susceptible to oxygen-dependent microbicidal systems *in vitro*. Neutrophils inhibit *Legionella* growth but lack the capacity to kill *L. pneumophila*. Lysis of infected macrophages by lymphokine-activated killer cells or natural killer cells may also be an important cell-mediated immune function for eliminating intracellular *Legionella*. It appears that *Legionella* is resistant to the direct bactericidal functions of neutrophils, but a requirement for neutrophils in the induction of IFN-γ by natural killer cells has been demonstrated *(46)*.

Humoral immunity plays a secondary role in host defense against *Legionella* infection. Patients with Legionnaires' disease have measurable type-specific antibodies (immunoglobulin M and immunoglobulin G) within several weeks of infection. Antibodies do not promote complement-mediated killing nor inhibit intracellular proliferation *(14,47)*. Moreover, immunized animals and patients develop a specific antibody response with subsequent resistance to *Legionella* challenge.

A number of factors have been postulated to contribute to the virulence of *L. pneumophila*: type I and type II secretion systems, a pore-forming toxin, type IV pili, flagella, a *Legionella* toxin, a 24-kd protein called Mip, a zinc metalloprotease, and proteases including enzymes that scavenge reduced-oxygenated metabolites *(15)*.

Strains of *L. pneumophila* differ in virulence. *L. pneumophila* serogroup 1 is known to cause most cases of Legionnaires' disease *(17)*. Although multiple strains of *L. pneumophila* serogroup 1 may colonize water distribution systems, only a few strains are likely to cause disease in patients exposed to the water *(48)*. Monoclonal antibody subtyping of strains of *L. pneumophila* serogroup 1 has shown that a surface epitope recognized by one particular monoclonal antibody (MAB-2/MAb3/1) may be associated with virulence. The immunodominant part of this virulence-associated epitope has been identified as the 8-0-acetyl group of the 0-specific polysaccharide chain of the lipopolysaccharides *(49,50)*. A correlation between virulence-associated MAB-2/MAb3/1 epitope and charge density of the *Legionella* envelope may be the factor that discriminates highly virulent from less virulent strains *(51)*.

Legionella species other than *L. pneumophila* appear to be less virulent and occur almost exclusively among immunocompromised hosts. They also respond more readily to antibiotic therapy *(20,52)*.

EPIDEMIOLOGY

Legionella is now the single most common cause of outbreaks involving drinking water *(53)*. Most legionellosis outbreaks associated with drinking water occurred in healthcare facilities, and nursing homes (54). Heffelfinger et al. *(55)* reported that 25% of 152 hospitals surveyed had reported cases or outbreaks of healthcare-associated Legionnaires' disease from 1989 to 1998. Although legionellosis is a reportable disease in many countries including the United States, the extent of this infection is still uncertain. Underestimates are likely due to cases that are overlooked because of the persistent lack of availability and utilization of the specialized laboratory tests needed to make the diagnosis *(16,56,57)*. The CDC has reported significant increases of legionellosis in the United States by analyzing data submitted to the National Notifiable Disease Surveillance System. There was an increase of 1300 cases in 2002 to over 2000 cases yearly through 2005 (58). The minimum number of *Legionella* cases annually is estimated at 18,000 and approximately 25% are healthcare associated (*16*,59). CDC also reviewed *Legionella* case report data from 2005 to 2007 submitted to the Legionnaires' Disease Supplemental Surveillance System and found that acute care hospitals accounted for 88% of the cases, with long-term care and rehabilitation facilities accounting for 12% of reported cases. The study documented that healthcare-associated Legionnaires' disease continues to have a high case-fatality rate (34%). In a study of reported cases of Legionnaires' disease in western Pennsylvania, Squier et al. also found a high mortality rate for healthcare-associated cases (38–53%), which is significantly higher than the 20% rate identified for community-acquired cases (*16*,59). Consequently, Legionnaires' disease should be considered in the differential diagnosis for all pneumonia cases with prior acute care facility exposure, particularly the elderly, smokers, immunosuppressed patients, and those with chronic lung disease *(60–62)*.

More extensive use of *Legionella* diagnostic testing has revealed that many patients with Legionnaires' do not fall into these typical risk groups. Squier et al. (59) found that 22% of the reported cases did not have any of the typical risk factors. This trend was also identified in a large study in the Netherlands *(63)*. These studies further emphasize the need for clinicians to include *Legionella* in the differential diagnosis of healthcare-associated pneumonia. The variable infection rates among individuals reflect a dependence on multiple variables. These include a contaminated potable water system with *Legionella*, exposure of the host to the contaminated water, susceptibility of the patient exposed, and recognition of the disease by the physician.

Since 1986, legionellosis has also been monitored in Europe. Reports show *Legionella* species to be a common cause of pneumonia, with *L. pneumophila* being the most predominant *(23)*.

Situations labeled as sporadic cases of *Legionella* may represent a chance discovery of the disease occurring at a low endemic period. Likewise, situations labeled as epidemic may represent a cyclical peak at a healthcare facility with endemic but previously undiscovered cases.

Cases surface because of a combination of circumstances: improved diagnostic methods, clinical suspicion of Legionnaires' disease by an individual physician, or

isolation of the microorganism from open lung biopsy or postmortem lung culture *(21)*.

Routine testing for Legionnaires' disease at autopsy identified eight cases of healthcare-associated *Legionella* at a regional transplant center in the southwestern United States *(64)*. The occurrence of three cases in early 1996 led to a retrospective review, which suggested that transmission had occurred for >17 years. An additional 14 cases were identified for a total of 25 culture-confirmed cases of Legionnaires' disease. Thus, situations labeled as sporadic or nonepidemic may merely represent chance discovery of disease occurring at a low endemic level. Likewise, situations labeled as "epidemic" may merely represent a cyclical peak at a hospital with endemic but previously undiscovered disease.

Consistently identified risk factors for Legionnaires' disease include advanced age, males, smoking, alcohol abuse, chronic pulmonary disease, and immunosuppression (malignancy, corticosteroid use). Males are affected at two to three times the rate of women; this may be related to cigarette smoking or underlying medical conditions (e.g., chronic obstructive pulmonary disease). Attributable mortality for Legionnaires' disease is approximately 20%; however, the likelihood of death from *Legionella* infection increases in patients who are younger than 1 year, elderly, or male, with healthcare-associated infection, renal disease, predisposing underlying conditions such as malignancy, or immunosuppression, or delayed administration of appropriate antimicrobial therapy *(23,56,64)*. Mortality can be as high as 40% for healthcare-associated cases *(16)*. When Jespersen et al. *(65)* compared mortality rates between community-acquired and hospital-acquired legionellosis, they found case-fatality rate to be three times higher in the hospital-acquired group.

Healthcare-associated infections due to *Legionella* occur most frequently in immunosuppressed hosts. The patients at highest risk are organ transplant and hematopoetic stem cell transplant recipients *(66)*. During an outbreak in an acute care hospital, 55% (5/9) of all patients undergoing kidney transplantation developed Legionnaires' disease over a 5-month period *(67)*. Healthcare-associated *Legionella* infection has been reported in renal *(67,68)*, heart *(64,69–71)*, and bone marrow transplant recipients *(64,71,72)*. Corticosteroids are an important independent risk factor. Neoplastic disease, diabetes, and renal failure are often cited as risk factors. The broader use of diagnostic testing may result in more patients being identified without these classic risk factors. A retrospective review of over 400 cases of Legionnaires' disease in the Pittsburgh area showed that 25% of reported cases did not have the classic risk factors *(73)*.

There is an association of Legionnaires' disease with surgery. In the past, up to 40% of cases reported in the literature occurred in surgical patients *(74)*. More recently, *Legionella* is mostly related to solid organ transplantation and to a lesser degree to head and neck surgery. Healthcare-associated *Legionella* infection increased with the use of general anesthesia and endotracheal intubation *(64,75,76)*.

Surprisingly, neutropenic or leukemic hosts appear to have an attack rate no higher than that of the general population. The exception is patients with hairy cell leukemia *(77,78)*. Likewise, the risk of *Legionella* infection in the HIV-infected patient appears to be no greater than other high-risk populations, with reports of <1% to 4% *(52)*. However, these patients are prone to extrapulmonary manifestations, bacteremia, and lung abscesses.

Increasing use of diagnostic tests for *Legionella* has led to new risk groups of patients being discovered as susceptible victims for Legionnaires' disease. They include immunocompromised children in pediatric hospitals colonized with *Legionella* and elderly patients residing in long-term care facilities and rehabilitation centers colonized by *Legionella*.

In a CDC survey of reported pediatric legionellosis cases, 72% were healthcare-associated; the source was related to exposure to tap water *(79)*. A review of published reports by Yu and Lee showed that an outbreak involving 11 neonates and another 2 related to "water-birth" delivery were all related to exposed to contaminated water. However, the percentage of tap water site positivity was not reported (80).

Healthcare-associated cases have been reported in immunosuppressed children *(71,81,82)* and children with underlying pulmonary disease (*30*,80,*83*). In three hospitals in which epidemiologic investigations were conducted *(81,83,84)*, a link to the hospital water supply was made.

Pneumonia in long-term care facilities has increased in recent years as the population of this group increases. However, it often is unclear if the cases should be considered community-acquired or healthcare-associated pneumonia. Increased reports of Legionnaires' disease has occurred in assisted-living and long-term care facilities (59). Legionellosis is not a diagnosis typically sought out in this setting. Implementing *Legionella* prevention guidelines in western Pennsylvania raised the index of suspicion, and as a result, the proportion of cases of healthcare-associated Legionnaires' disease diagnosed in long-term care facilities went up from 4% to 65% (59). One investigation in Canada identified *Legionella* in the potable water supply as the source for two outbreaks in nursing homes *(85)*. Aspiration was presumed to be the mode of transmission. In one outbreak, eating pureed food was a significant risk factor for *Legionella*, consistent with aspiration originating from a swallowing disorder *(85)*. In another prospective study, *L. pneumophila* serogroup 1 was isolated from a newly constructed long-term care facility *(86)*. Six cases of Legionnaires' disease were diagnosed over 2 years. DNA subtyping established that the patient isolates were identical to the environmental isolates from the water supply.

In a 10-year report of nursing home–acquired pneumonia by Polverino et al. *(87)*, 150 cases were analyzed. *L. pneumophila* was found in 5% of cases; etiology was reported in only 57 cases. The authors reported inadequate treatment and lack of aspiration assessment.

The CDC and the European Working Group for Legionella Infection have surveyed travel-associated Legionnaires' disease in the United States and Europe. They report an 85% increase from 2005 to 2008. Thus, a careful travel history is important to avoid the assumption that these cases might be related to a healthcare facility *(12)*.

Reservoir

The environmental ecology of *Legionella* is particularly pertinent in that Legionnaires' disease is a pneumonia

that theoretically could be prevented with eradication of the microorganism from its reservoir. The natural habitat for *Legionella* appears to be aquatic bodies including rivers, streams, and thermally polluted waters, although *L. longbeachae* has been isolated from moist soil in Australia *(88)*. Natural aquatic bodies contain only small numbers of *Legionella*. Since *Legionella* tolerates chlorine, the microorganism easily survives the water treatment process and passes into water distribution systems but, again, only in small numbers *(89,90)*.

Subsequent growth and proliferation also occur in man-made habitats, especially water distribution systems, which provide favorable water temperatures (25°C–42°C), physical protection (biofilm), and nutrients *(91)*. The single most important factor appears to be temperature. The microorganism is readily found at the bottom of hot water tanks—a relation that parallels its propensity for colonization in thermally polluted rivers. Interestingly, bacteria populating hot water tanks were more likely to demonstrate a symbiotic relationship with *L. pneumophila* than bacteria populating cold water tanks *(92)*. Bacteria, protozoa, and amoeba also colonize water pipe surfaces, some of which have been shown to promote *Legionella* replication. *Legionella* and other microorganisms attach to surfaces and form biofilms on pipes throughout the water distribution system *(93)*. Water pressure changes that disturb the biofilm may dramatically increase the concentration of *Legionella (94)*.

Healthcare facilities with hot water distribution systems colonized with *L. pneumophila* were significantly more likely to have lower water temperatures (<140°F), have a vertical configuration, be older, and have elevated calcium and magnesium concentrations in the water (*95*). Cold water sources, such as ice machines and fountains, have also been implicated as a source of healthcare-associated infection (*96*). *L. pneumophila* serogroup 8 infection was diagnosed by culture in 13 patients over an 8-month period (*97*). This was determined to be a "pseudo-outbreak" traced to immersing syringes containing saline for bronchoscopy directly into ice water. Molecular typing confirmed that patient isolates were indistinguishable from the strain recovered from the ice machine. Two hospitalized patients acquired their *Legionella* infections as a result of exposure to a contaminated water feature in a radiation oncology suite *(98)*.

The role of *Legionella*-contaminated potable water distribution systems as a source for healthcare-associated Legionnaires' disease has been well established. The British Communicable Disease Surveillance Centre reported that 19 of 20 hospital outbreaks of Legionnaires' disease in the United Kingdom from 1980 to 1992 were attributed to such systems *(99,100)*.

Cooling towers and, to a lesser degree, evaporative condensers were implicated in the earlier outbreaks prior to recognition of potable water as a reservoir. Surprisingly, air conditioners have never been directly implicated as a source of Legionnaires' disease, despite widespread belief that they are. The role of cooling towers in the dissemination of *Legionella* has been challenged *(101)*. Reports of cooling towers as reservoirs for healthcare-associated legionellosis have essentially disappeared. One notable exception was a report published in 1985 of a Rhode Island hospital in which cooling towers were cited as the source *(102)*, which was later linked to the potable water system; this now appears to be a typical scenario of water distribution system contamination in which the original epidemiologic investigation was flawed *(101)*.

Subtyping of *L. pneumophila* with molecular methods has proven invaluable in elucidating environmental sources, permitting application of rational methods for prevention. In fact, application of subtyping provided the first concrete evidence that water distribution systems rather than cooling towers were the actual sources of infection *(103)*. The subtype of *Legionella* isolates taken from patients were identical to the isolates taken from putative environmental reservoirs. Both phenotypic and genotypic methods have been used to demonstrate identity among strains of *L. pneumophila* in epidemiologic investigations. These methods include serotyping, monoclonal antibody subtyping, isoenzyme analysis, protein and carbohydrate profiling, plasmid analysis, restriction endonuclease analysis, restriction fragment length polymorphism of rRNA (ribotyping) or chromosomal DNA, amplified fragment length polymorphism, restriction endonuclease analysis of whole-cell DNA with or without pulsed-field gel electrophoresis (PFGE), DNA fingerprinting using polymerase chain reaction (PCR), and sequence-based typing *(29,90,104,105)*. However, PFGE has been the most widely applied. Maximum discrimination among isolates is achieved by combining both monoclonal antibody subtyping and PFGE (*106,107*,108).

Modes of Transmission

Multiple modes have been identified for transmission of *Legionella* to humans; there is evidence for aerosolization, aspiration, or even instillation into the lung during respiratory tract manipulation. Aspiration of contaminated water or oropharyngeal secretions appears to be the major mode of transmission in the hospital setting *(109)*. Colonization of oropharyngeal flora by *L. pneumophila* is a theoretical possibility *(110–113)*. The evidence for aspiration is impressive. *Legionella* was found to be the most common cause of healthcare-associated pneumonia in a population of oncologic head and neck surgery patients *(114)*; these patients had a propensity for aspiration as a result of their oral surgery and extensive cigarette smoking. Nasogastric tube placement has been shown to be a significant risk factor for healthcare-associated legionellosis in intubated patients; microaspiration of contaminated water was the presumed mode of entry *(109,115,116)*. In the original 1976 outbreak, consumption of water at the implicated hotel was associated with acquisition of disease—an association that has been generally overlooked *(1)*. Contaminated ice and water from an ice machine have been implicated as the source of healthcare-associated infection *(96,117,118)*.

Healthcare personnel frequently use tap water to rinse respiratory apparatus and tubing used for ventilators. If the tap water is contaminated with *L. pneumophila*, the microorganism could possibly be instilled directly into the lung of a patient *(119)*. In numerous studies, the risk of Legionnaires' disease was significantly greater for patients who underwent endotracheal tube placement more often or had a significantly longer duration of intubation than for patients who had other causes of pneumonia *(64,76,120)*. The use of a nasogastric tube, the presence of immunosuppression, and ventilator use were also reported to

be highly correlated with the acquisition of healthcare-associated Legionnaires' disease *(121)*. Use of sterile water for all nasogastric suspensions and for flushing tubes has been recommended to prevent *Legionella* infection. Intermittent positive pressure ventilators have been associated with healthcare-associated legionellosis, or more likely, the tubing attached to these ventilators. The use of such equipment was epidemiologically linked to Legionnaires' disease in 18 hospital patients over a 2-year period; again, it was noted that the equipment was rinsed with tap water between treatments *(109)*. Three cases of *L. pneumophila* pneumonia were acquired from contaminated transesophageal echocardiography probes *(122)*. Again, contaminated tap water had been used to rinse the probes.

Investigators from the CDC presented the first evidence to support the aerosolization theory when reporting the Legionnaires' disease outbreak in Memphis *(123)*. Tracer smoke studies indicated that aerosols from an auxiliary air conditioning tower could have reached an air intake supplying certain patient rooms. However, the attack rate for patients occupying rooms supplied with air from the air intake was not higher than the attack rate for patients occupying rooms in the same wing but receiving air from other sources *(124)*. Cases also occurred in hospital wings having no relationship to the cooling towers. Water was not cultured, since this investigation antedated the discovery that drinking water could be the source for Legionnaires' disease.

Because the first environmental isolation of *L. pneumophila* was from a showerhead *(4)*, it has been widely thought that aerosols from showers may be an important means for dissemination of this microorganism. However, simulation studies show that only small numbers of *Legionella* are aerosolized and only for short distances *(125,126)*. Although a few retrospective studies have suggested showers as a potential source *(127,128)*, an epidemiologic link between showering and acquisition of disease has never been shown in prospective studies; in fact, prospective studies have consistently shown that showers are not a risk factor *(64,109,129–132)*. However, the CDC recommends to restrict severely immunosuppressed patients from taking showers *(133)*.

Aerosolization by respiratory tract devices including the humidifier of oxygen therapy equipment, nebulizers, and room humidifiers has been documented *(119,134)*. Humidifiers are water-filled devices that add water vapor to air, oxygen, or other gases without producing particulate water. Guinea pigs exposed to a room humidifier contaminated with *Legionella* experienced subclinical infection as demonstrated by seroconversion. In a hospital setting, a portable room humidifier filled with *Legionella*-contaminated tap water disseminated the microorganism up to distances of 300 cm. Furthermore, recovery of aerosolized *Legionella* increased with proximity to the humidifier, and seroconversion of exposed animals was directly proportional to the concentration of *Legionella* in humidifier water. Humidifiers have been implicated in transmission of Legionnaires' disease in humans. Five of eight patients with healthcare-associated Legionnaires' disease in an Italian hospital had been exposed to bubble diffuser humidifiers filled with water containing *L. pneumophila (135)*. An immunosuppressed patient at the University of Chicago Hospital acquired Legionnaires' disease after exposure to a room humidifier that had been filled with contaminated tap water for 15 days *(136)*. The statistical association between disease and humidifier exposure was highly significant. Use of a room humidifier was also associated with 18 cases of healthcare-associated Legionnaires' disease in a 2-year period in a limited retrospective study *(137)*. Again, the room humidifiers had been filled with tap water.

A post-laryngectomy patient died from pneumonia following exposure to a room humidifier. *L. pneumophila* serogroups 4 and 5 were isolated from the patient's lung and from the tap water and containers used to fill the humidifier reservoir *(138)*. Distilled water in humidifiers has also been linked to hospital outbreaks of *Legionella* infection; one patient with *L. dumoffii* was exposed to a room humidifier presumably filled with contaminated distilled water *(139)*. Healthcare-associated pneumonia in a neonate was linked to the presence of *Legionella* in the humidifier of the incubator *(140)*. In one French hospital, the use of contaminated tap water to fill the humidifier of oxygen therapy equipment and for aerosol delivery of drugs led to five cases of Legionnaires' disease caused by *L. pneumophila* serogroup 1 *(134)*.

Nebulizers are devices that generate aerosols of uniform particulate size. Ultrasonic nebulizers can produce water particles ranging in size from 0.9 to 10 μm; water droplets of 1 to 2 μm in diameter can reach the alveoli. Medication jet nebulizers have been shown to aerosolize water particles containing *L. pneumophila* when the nebulizer water was seeded with the microorganism *(141)*; these particles were <5 μm in diameter, so it is likely they could bypass the pulmonary defenses and reach the alveoli. Jet nebulizers have been epidemiologically linked to healthcare-associated Legionnaires' disease *(136)*. Inhalation of contaminated tap water aerosols from jet nebulizers was found to be a highly significant risk factor for four patients who acquired Legionnaires' disease.

In addition to filling nebulizers with tap water, rinsing the chambers of hand-held medication nebulizers has been suggested as a source of contamination. In one study of 13 patients with healthcare-associated Legionnaires' disease due to *L. pneumophila* serogroup 3, there was a trend toward more frequent use of nebulizer medications in these patients. It was subsequently established that jet nebulizers were often rinsed with tap water *(141)*. Medication nebulizers have also been implicated in one of the few reports of pediatric healthcare-associated *Legionella* infection *(142)*. Two children with Legionnaires' disease received nebulizer treatments using equipment likely to have been rinsed under tap water.

Aerosolization via excavated soil was suggested as a possible mode of transmission for the outbreaks at the Wadsworth Veterans Administration Medical Center and St. Elizabeth's Hospital; in retrospect, contaminated water distribution systems were probably the actual reservoirs. Finally, person-to-person transmission has not been demonstrated *(143)*.

CLINICAL MANIFESTATIONS

Legionella infection presents as two clinical entities: Pontiac fever and pneumonia (Legionnaires' disease). Pontiac fever is an acute, self-limiting illness. Chills, high fever,

headache, and myalgias are typical. Pneumonia is not seen, and healthcare-associated cases of Pontiac fever have not been reported.

Pneumonia is the predominant clinical syndrome in Legionnaires' disease. The incubation period for Legionnaires' disease usually ranges from 2 to 14 days. One report demonstrated the onset of disease 63 days after discharge from the hospital, and molecular typing linked the hospital water supply as the source. This led to the speculation that oropharyngeal colonization with *Legionella* had occurred *(113)*. Subsequent studies have not been successful in demonstrating oropharyngeal colonization with *Legionella (111,144)*.

Legionnaires' disease encompasses a broad spectrum of illnesses, ranging from mild cough and low-grade fever to stupor, rapidly progressive pneumonia, and multiorgan system failure. Nonspecific symptoms including malaise, myalgias, anorexia, and headache are common in the first 48 hours. Fever is virtually always present, and temperatures in excess of 40°C should lead to the consideration of Legionnaires' disease. In earlier studies, relative bradycardia has been emphasized by some investigators, but this has been found to be a nonspecific finding *(145)*.

Initially, the cough is mild and only slightly productive. The character of the sputum is often nonpurulent. Although the sputum may be streaked with blood, gross hemoptysis is rare. Chest pain, often pleuritic, is common, and when coupled with hemoptysis, can masquerade as pulmonary infarction.

Gastrointestinal symptoms are more prominent in community-acquired pneumonia, but less so in healthcare-associated pneumonia; diarrhea, nausea, vomiting, and abdominal pain are common. The most common neurologic finding in Legionnaires' disease is change in mental status, although a wide variety of findings, including encephalopathy, have been reported *(146,147)*.

There has been a report of *L. pneumophila* cases associated with a widespread macular rash *(148)*.

In the pediatric population, fever, cough, tachypnea, and abnormal pulmonary findings are the most common signs and symptoms.

L. pneumophila microorganisms can disseminate from their pulmonary niche to various extrapulmonary sites, including spleen, liver, kidney, bone marrow, myocardium, and lymph nodes. Dissemination apparently occurs via the hematogenous or lymphatic system. Extrapulmonary healthcare-associated *Legionella* infections occurred in cardiothoracic surgical patients at Stanford University *(32,149)*. Seven patients presented with *Legionella* prosthetic valve endocarditis, three had sternal surgical site infections, and one patient manifested both infections. *L. pneumophila* serogroup 1 and *L. dumoffii* were isolated from clinical samples as well as from the potable water system of the hospital. The origin of the sternal surgical site infections was contaminated tap water used to remove the providone-iodine solution from the operative site.

Other reports have implicated tap water as the source for extrapulmonary *Legionella* infections. In one patient, an open hip wound infection due to *L. pneumophila* was linked to colonized water from a Hubbard tank used for rehabilitation *(150)*. Healthcare-associated extrapulmonary legionellosis involving hemodialysis fistula infections (two cases) *(151)* and a perirectal abscess *(152)* were probably secondary to hematogenous seeding from confirmed *Legionella* pneumonia; however, direct inoculation by contaminated water or equipment could not be excluded. Detection of the microorganism at extrapulmonary sites is problematic. Since selective media must be used to isolate the microorganism, the clinician must think of the possibility of *Legionella* as the cause of the infection. Other bacteria may also be isolated, thereby confounding the diagnosis.

TREATMENT

Originally, patients diagnosed with Legionnaires' disease were found to improve when prescribed erythromycin or tetracycline as compared to those treated with beta-lactam agents or aminoglycosides *(1)*. Presently, the preferred treatment for *Legionella* infection is either fluoroquinolone or azithromycin *(60,153)*. Dosage of quinolones should be maximal. Clarithromycin is an alternative choice for treatment in those countries where azithromycin is not readily available *(153)*. The dosages are usually as follows: levofloxacin 750 IV every 24 hours and then 750 mg p.o. daily for 10 days, moxifloxacin 400 mg IV every 24 hours and then 400 mg p.o. daily for 10 days, *or* azithromycin 500 mg IV and then 500 mg p.o. daily for 7 to 10 days. Combination therapy of quinolone and azithromycin can be considered for patients who are severely ill or have extrapulmonary infections *(153)*. Rifampin may be used in combination with fluoroquinolone or azithromycin in severely ill patients. However, the benefits of combination therapy are unclear *(154,155)*.

LABORATORY DIAGNOSIS

The prompt diagnosis of Legionnaires' disease in the hospital setting can save lives. Not only has early initiation of appropriate therapy been associated with improved outcome, but the diagnosis of a single case of healthcare-associated Legionnaires' disease can prompt the recognition of endemic Legionnaires' disease at the facility *(156)*. For patients with severe pneumonia, the Infectious Diseases Society of America recommends diagnostic tests for *Legionella (157,158)*.

The diagnosis of Legionnaires' disease based on a syndromic approach has been suggested *(31)*; however, most studies have shown that the clinical manifestations of Legionnaires' disease are nonspecific *(145)*. Laboratory abnormalities including abnormal liver function tests, elevated creatinine phosphokinase, hypophosphatemia, hematuria, hemolytic anemia, and thrombocytopenia have been reported. Hyponatremia with a serum sodium of <130 mEq/L occurs significantly more often in Legionnaires' disease than in other pneumonias; it appears to be more common in healthcare-associated Legionnaires' disease than in community-acquired disease. This syndrome probably is caused by salt and water loss rather than inappropriate antidiuretic hormonal secretion (V. L. Yu, unpublished data).

Specialized diagnostic laboratory tests are the key feature for diagnosing Legionnaires' disease because the clinical presentation is nonspecific. Most hospitals, including university and tertiary care hospitals, often do not have the most sensitive tests available, namely, culture on selective media and urinary antigen *(100)*, and up to 40% of hospitals send samples off-site for testing *(159)*. Data from a CDC survey showed that hospitals where *Legionella* diagnostic tests were available on-site were more likely to identify healthcare-associated Legionnaires' disease *(159)*.

Urinary Antigen

The *Legionella* urine antigen test is now the most common method for diagnosing Legionnaires' disease *(16)*. This test has a high sensitivity (90%), high specificity (99%), is relatively low cost, and the results can be available within hours of submission of the test *(160,161)*. The urine antigen test is available as an enzyme immunoassay (EIA) test or an immunochromatographic (ICT) test. The EIA test is available commercially from two US suppliers (Wampole Laboratories, a division of Carter-Wallace Inc., Cranbury, NJ; and Bartels, Issaquah, WA) and includes the Binax *Legionella* Urinary Antigen EIA and the Bartels *Legionella* Urinary Antigen EIA (Intracel, Frederick, MD). The BinaxNOW® *Legionella* urinary antigen test is a rapid ICT membrane assay for qualitative detection of *L. pneumophila* serogroup 1 antigen (Alere, Portland Maine). A swab is dipped in urine and inserted into the test device, and the reagent is added. The reaction is read after 15 minutes as the presence or absence of a visually detectable pink-purple colored line that results from the antigen–antibody reaction, giving the result (Fig. 36-1). The EIA and ICT tests have been shown to have comparable sensitivity and specificity *(162,163)*.

The success of the rapid urine test has prompted more companies to produce similar tests. These include the Legionella V-TesT (Coris Diagnostics, Inc., Calabasas, CA), Uni-Gold Legionella (Trinity Biotech Plc., Wicklow, Ireland), X/pect Legionella (oxoid, Basingstoke, United Kingdom), SAS Legionella test (SA Scientific, Inc., San Antonio, TX), and Accusay Legionella (Launch Diagnostics Ltd, Kent, England). These tests do not perform equally. In our comparative evaluation of seven different urine antigen tests, the Binax NOW gave the highest sensitivity *(164)*.

The fact that test positivity can persist for days, even during administration of antibiotic therapy, makes it useful in those patients who receive empiric anti-*Legionella* therapy *(165)*. A shortcoming of the test is that it can detect only serogroup 1 of *L. pneumophila (166,167)*. Since the other serogroups of *L. pneumophila* and other *Legionella* species are less common in the community *(17)*, this test is still extremely useful for community-acquired legionellosis. Unfortunately for healthcare-associated legionellosis, cases due to serogroups 4 and 6 are common. Culture of the drinking water should alert the infection preventionist (IP) to the usefulness of this test for diagnosis. Early diagnosis and treatment have resulted from the increased use of the rapid urinary antigen test. This, in combination with the increasing empiric use of quinolones for healthcare-associated pneumonia, may explain the decline in Legionnaires' disease-related mortality in the United States. The case-fatality rate for healthcare-associated Legionnaires' disease has decreased from 46% in 1982 to 14% in 1998 *(16)*.

Culture on Selective Media

When Legionnaires' disease is suspected, both a urinary antigen test and a *Legionella* culture of a respiratory specimen should be ordered. The single most important diagnostic test for Legionnaires' disease is isolation of the microorganism by culture. The availability of the clinical isolate from culture can be critical for subsequent

FIGURE 36-1 The NOW immunochromatographic test (ICT) is performed by dipping a swab in urine and inserting it into the test device. Two drops of a reagent are added and the card is closed and allowed to react for 15 minutes. A positive result is the presence of a visually detectable pink-purple colored line (next to the "Sample" line) resulting from the antigen–antibody reaction.

epidemiologic investigations *(168)*. Another reason not to rely exclusively on the urine antigen test is that the urinary antigen test may be negative if the infecting strain is not serogroup 1 or when the infecting strain is serogroup 1 but MAB-2 negative (Dresden Panel MAB-3/1 negative). Among 317 culture-proven cases of Legionnaires' disease, 67 (21%) were healthcare-associated cases. Only 45% of these cases were urine antigen positive, because 22% of the cases were caused by the MAB-2 negative serotype *(167)*.

To achieve a high yield from sputum, multiple media containing antibiotics and dyes are required *(25)*. Buffered charcoal yeast extract agar is the primary medium used for isolation of these microorganisms. The culture media can be made more selective by incorporating antibacterial agents (cefamandole, polymyxin B, vancomycin, aztreonam), antifungal agents (anisomycin), and inhibitors (glycine) into the media to suppress competing microflora. Pretreatment with acid is extremely useful for respiratory tract and environmental specimens, because *Legionella* microorganisms are acid-resistant whereas most other bacteria are not. The addition of dyes to the media enhances the visibility of the colonies because *Legionella* takes up the dye preferentially. The dye-containing media are especially important in detection of the nonpneumophila species. The microorganism grows slowly, taking up to 5 days for visible colonies to develop. Under a dissecting stereomicroscope, the colony surface shows a characteristic ground glass appearance.

Legionella culture is performed only when specifically requested. A physician often orders a *Legionella* urinary antigen test and only a routine microbiology culture. As a result, when the urine antigen test is positive, no sputum is available for *Legionella* culture. We refrigerate all respiratory specimens for 7 days by placing them in bins marked by the days of the week. This practice allows for subsequent retrieval of the specimen for *Legionella* culture if a urine test is positive. The isolate from the patient is now available if an epidemiologic investigation is performed to determine the source of the infection.

Transtracheal aspirate specimens that bypass contaminating oropharyngeal flora can achieve a sensitivity as high as 90% *(25)*. Sputum obtained by bronchoscopy can be useful, but does not provide any higher yield than a good sputum specimen. If sputum is not available, however, bronchoalveolar lavage can yield the microorganism. Bronchial washings, in which the volume of fluid instilled is notably lower than that of lavage, appear to be less sensitive. Transbronchial biopsy can yield the microorganism in tissue by direct fluorescent antibody (DFA) stains and culture and has been successful in identifying *Legionella* when sputum and bronchial washings were unrevealing. Percutaneous needle aspiration of a lung abscess has yielded the microorganism in culture from a patient who had negative sputum and bronchoscopy cultures.

Bacteremia is actually common in severely ill patients *(169)*. The microorganism can be isolated from blood by biphasic buffered charcoal yeast extract agar bottles, a radiometric system (Bactec, Johnston Laboratories, Towson, MD), or the Vacutainer tube (Becton Dickinson, Rutherford, NJ). In one study, 38% of cases of Legionnaires' disease had positive blood cultures when subcultures from Bactec bottles were plated onto buffered charcoal yeast extract agar *(170)*.

Direct Fluorescent Antibody Stain

The reported sensitivity of DFA stains has ranged from 25% to 75% *(180)*. It is highly specific, and the monoclonal antibody test (MONOFLUO, Bio-Rad Laboratories, Redmond, WA) has eliminated the rare occurrence of cross-reactivity with other gram-negative bacilli. Because of low sensitivity compared to culture, we do not perform the DFA on a specimen unless the direct culture is overgrown with competing flora and acid pretreatment of the specimen is required. Polyclonal DFA reagents are available from a number of suppliers for definitive identification of isolates of *Legionella* (Monoclonal Technologies, Atlanta, GA; Meridian Diagnostics, Inc., Cincinnati, OH; Zeus Technologies, Raritan, NJ).

Serology

Antibody tests have become less important with the advent of rapid diagnostic tests. Because the definitive criterion for diagnosis is a fourfold rise in antibody titer, repeat serology is required 4 to 6 weeks after the onset of infection. Sensitivity in the 1976 outbreak was 91% *(171)*, but sensitivity in studies of healthcare-associated pneumonia has been <50% *(172)*. Maximal sensitivity requires detection of both immunoglobulin G and immunoglobulin M antibody. Effective antibiotics and suboptimal timing of specimen collection are possible reasons for the decrease in sensitivity. Diagnosis of Legionnaires' disease by serologic testing has decreased significantly from 1980 to 1998 *(16)*.

Polymerase Chain Reaction

Rapid diagnostic testing is the key to reducing morbidity and mortality *(173)*. DNA amplification by PCR of *Legionella* has been reported from patients with pneumonia using throat swab specimens, bronchoalveolar lavage, urine, and serum *(174–176)*. The primer sequences of the *mip* gene of *L. pneumophila* and the 5S rRNA or 16S rRNA have been utilized in PCR assays. A real-time quantitative PCR assay has been used to detect *L. pneumophila* in respiratory tract secretions *(177)*. Although *Legionella* DNA has been detected in urine and serum samples from patients with legionellosis *(178)*, clinical experience has not shown PCR to be more sensitive than culture. Therefore, the CDC does not recommend the routine use of genetic probes or PCR for detection of *Legionella* in clinical samples *(179)*.

PREVENTION

There is a direct relationship between colonization of hospital water systems with *L. pneumophila* has been documented and the occurrence of healthcare-associated Legionnaires' disease *(180,181)*. *Legionella* species have been shown to colonize between 12% and 85% of hospital water systems *(182,183)*. Prospective studies have demonstrated cases of healthcare-associated Legionnaires' disease in colonized hospitals after environmental and clinical surveillance were initiated *(182)*. Knowledge of this relationship is the first step to prevention. The CDC recommends facilities should use two general strategies to prevent healthcare-associated legionellosis when no cases or sporadic cases have been detected. The first step is to do environmental surveillance for *Legionella* by periodically culturing the potable water system. If any sample cultures

are positive, diagnostic testing is recommended for patients with healthcare-associated pneumonia. In-house laboratory testing is recommended for facilities that have transplantation programs *(184)*. Decontamination of the facility's potable water system should be considered if 30% or more water outlet culture samples are positive. The basis for this approach is that if *Legionella* species is not in the potable water system, healthcare-associated legionellosis will not occur. Physicians should also be informed of water culture positivity so that appropriate diagnostic testing can be done. This proactive approach has been advocated by Pittsburgh investigators and the Allegheny County Health Department in Pittsburgh, PA, for many years *(182)*. This approach recommends proactively culturing the hospital water system as the initial step in making a risk assessment of the facility. Guidelines for *Legionella* prevention from the Allegheny County Health Department and from the state of Maryland specifically recommend routine environmental monitoring of the healthcare facility's water system *(185,186)* (Table 36-2). If any outlets yield *L. pneumophila*, diagnostic tests for *Legionella* are made available in-house. The presence of *L. pneumophila* serogroup 1 in the water supply necessitates the on-site availability of the urinary antigen test. If >30% of outlets are culture-positive for *L. pneumophila*, disinfection of the water system should be considered. This approach has now been adopted as a national guideline for all hospitals of the Veterans Healthcare System—the largest healthcare system in the United States *(186)*. The Texas Department of Health has also issued guidelines that recommend environmental surveillance for *Legionella* only if a risk assessment indicates that the facility has a significant risk of legionellosis transmission *(187)*. For example, a high-risk facility could be a multistory facility with multiple water distribution systems, supplied with water treated with chlorine, stored hot water at 51°C (124°F) and delivered at 43°C (110°F), and housing bone marrow or solid organ transplant recipients or cancer patients undergoing chemotherapy. Proactive approaches mandating routine environmental cultures within hospitals have now been adopted in Denmark, the Netherlands, France, and Taiwan.

The second strategy is the "clinical" approach. In this method, the clinician maintains a high awareness for legionellosis and orders the appropriate diagnostic tests for patients presenting with healthcare-associated pneumonia. If one case of definite or two cases of possible healthcare-associated *Legionella* occurs within 6 months of each other, then an investigation for the source, including the potable water system, should be initiated. However, hematopoietic stem cell transplant and solid organ transplantation recipients are at a high risk for legionellosis, thus culturing of the potable water system should be considered as a prevention strategy in these patient areas *(188,189)*.

The "Guideline for Prevention of Nosocomial Pneumonia" from the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) *(190)* was revised and continues to have no recommendation for routine culture of healthcare facilities' potable water systems with the exception of institutions housing transplant units *(179)*. Opposition to routine environmental cultures in the

TABLE 36-2

Guidelines for Control of Legionella in Healthcare Facilities: Veterans Healthcare System, Pennsylvania and Maryland Recommend Routine Environmental Culturing of the Hospital Water System for *Legionella*

State/Organization	*Diagnostic Testing*	*Clinical Surveillance*	*Routine Environment Testing*	*Approach to Prevention*
Veterans Healthcare System Directive 2008-001	Urine antigen testing and culture; all transplants	Active clinical surveillance	Yes: annual	If >30% sites positive, action plan for remediation
Allegheny County Health Department, Pennsylvania 1993/1997	Active: in-house urinary antigen (UA) testing	If environment positive, active clinical surveillance	Yes: annually; transplant hospital: more often	Consider disinfection if >30% sites positive; empiric antimicrobial therapy macrolide or quinolone
Maryland Health Department	Acute care: in-house; transplant hospitals: culture on site	Test pneumonia cases for *Legionella*	Yes: routine culture	If cases identified, disinfection recommended
Texas Department of Health	Acute and long term: UA in-house; transplant hospitals: culture on site	Active case detection after case identified	Routine: no; if high risk of cases: yes	Enhanced clinical surveillance and remediation if cases identified
Centers for Disease Control and Prevention	Routinely test without knowledge of environment colonization	Educate regarding diagnosis per 400+ beds equals UA/culture in-house	No: unless cases identified or transplant unit	Disinfect only if source identified

absence of documented disease is often based on the premise that *Legionella* colonization is ubiquitous, that *Legionella* can colonize water distribution systems without causing disease, and that environmental culturing is expensive *(190–192)*. However, these assertions have been refuted based on numerous studies in both the United States and the United Kingdom *(182,193,194)*.

As part of a comprehensive strategy to prevent Legionnaires' disease in transplant units, HICPAC recommends that facilities with solid organ transplant programs or hematopoietic stem cell transplant recipients should perform periodic culturing for *Legionella* in the transplant unit's potable water supply. This recommendation also appears in the "Guidelines for Prevention of Opportunistic Infections in Bone Marrow Transplant Recipients" *(195)*. If *Legionella* species are detected in the unit's water system, corrective measures (disinfection) should be performed until no *Legionella* is cultured. No such recommendation is made for healthcare facilities treating nontransplant patients or for disinfection of areas serving these patients.

One problem with this approach is that many cases of healthcare-associated Legionnaires' disease occur in nontransplant patients. In Yu's original report of endemic healthcare-associated Legionnaires' disease, none of the patients were transplant recipients and Legionnaires' disease constituted 22.5% (32/142) of the cases of healthcare-associated pneumonia *(196)*. In a Swedish hospital, 31 patients with healthcare-associated Legionnaires' disease were diagnosed over a 14-month period: 8 were from surgical wards, 16 from internal medicine or geriatric wards, 3 each from psychiatric and physiotherapy units, and 1 was from the maintenance department *(197)*.

Environmental Culturing

Routine environmental cultures for *Legionella* are necessary to assess the risk since *Legionella* colonization will vary over time *(198)*. The Allegheny County (Pittsburgh) Health Department recommends once a year culturing of water sites in patient units and wards housing high-risk patients, while the Maryland guidelines recommend flexibility with four times a year culturing if an outbreak has occurred. For those hospitals using systemic disinfection, the World Health Organization (WHO) recommends *Legionella* culture of the drinking water be performed every 3 months to verify efficacy (*199*).

Routine surveillance can be performed by collection of either swab and/or water samples from water outlets throughout the facility. Results will be affected by the type of sample collected and the method of sample collection. For example, swab samples should be collected first and after removal of the faucet aerator to achieve maximum recovery of *Legionella* from the biofilm within the fixture *(200)*. *Legionella* adheres to the biofilm lining pipes and fixtures. When doing a case investigation, two samples—water and swab—should be collected from the same water outlet(s) in the immediate environment of the suspected case *(200)*. Ongoing surveillance for monitoring the efficacy of disinfection efforts should include the previously positive locations for follow-up testing *(200)* (Fig. 36-2).

When collecting swab samples, aerators should be removed. The swab sample should be collected immediately after briefly turning on the hot water faucet or shower. The swab should be inserted into the faucet opening and rotated four times against the inner surface as it moves up into the opening. If a showerhead is cultured, rotate the swab over the entire surface of the showerhead four times. When collecting water samples, turn on the hot water and immediately fill the bottle with at least 120 mL. When culturing the hot water storage tanks, open the drain valve and collect at least 120 mL of the flowing water. Let the water drain for 15to 30 seconds and then collect another 120 mL sample in a second bottle. Label samples appropriately *(200)*. A minimum of 10 outlets plus the hot water storage tank should be cultured for the average 250-bed healthcare facility *(185)*. When taking a culture of the cooling tower, submerge an open bottle just under the surface of the water to obtain at least 120 mL. Swabs are not considered to be appropriate when culturing hot water tanks and cooling towers. If *Legionella* is isolated, specialized laboratory tests should be made available in-house. The urinary antigen is especially recommended as a cost-effective test if the *Legionella* isolated is serogroup 1. Prospective surveillance of healthcare-associated pneumonias should be initiated by the IP *(185,201,202)*. It has been well documented that unless the healthcare laboratory can isolate *Legionella*, healthcare-associated cases can be overlooked *(182)*. It has also been suggested that surveillance for healthcare-associated legionellosis can be targeted to select high-risk patients for cost-effectiveness *(115,201)*; high-risk patients include transplant recipients, immunosuppressed patients, patients with underlying pulmonary disease, and intensive care unit patients. Surveillance could be expanded to all patients with healthcare-associated pneumonia if cases of legionellosis were uncovered in the high-risk group. It is important to point out that if the frequency of contaminated sites is low, disinfection of the water supply is not necessarily required. Antibiotic prophylaxis of transplant patients with macrolides or quinolones has been used to stem outbreaks *(154)*. If the level of contamination increases, the option to disinfect the water supply can be exercised.

Contaminated Respiratory Devices

The use of sterile water for filling and rinsing humidifiers, nebulizers, and other respiratory equipment is recommended. Portable room humidifiers should be prohibited, because they are often filled with tap water and not routinely cleaned or disinfected. Even rinsing respiratory device tubing with tap water may create a secondary reservoir for *Legionella*. Subsequently, reattachment of the device to the patient could directly instill *Legionella*-containing respirable droplets into the respiratory tract. Devices such as medication nebulizers may retain water 12 hours after rinsing *(141)*.

DISINFECTION OF WATER DISTRIBUTION SYSTEMS

Healthcare-associated legionellosis has been effectively controlled by disinfection of the water distribution systems that are colonized by *Legionella*. In 1998, two reviews on disinfection methodologies were published: one for engineers and healthcare facility managers and another for physicians and infection preventionists *(194,203)*. At that

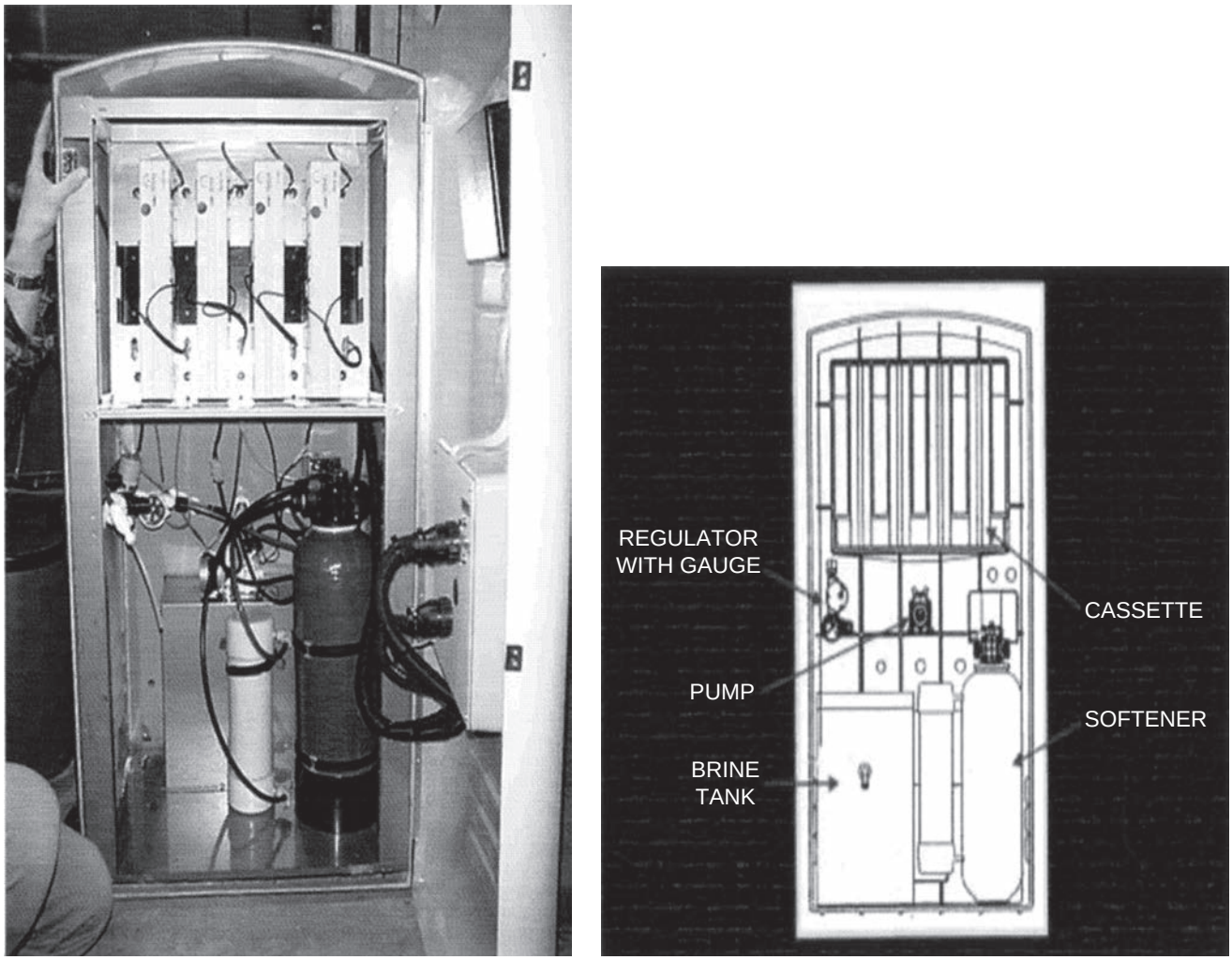

FIGURE 36-2 Chlorine dioxide is a *Legionella* disinfection option that has been used extensively in Europe but has recently been under evaluation in the United States. Chlorine dioxide is generated electrochemically from a sodium chlorite precursor within a self-contained unit. The electrochemical reaction occurs within removable cassettes. The unit generates a solution of concentrated chlorine dioxide (~500 mg/L), which is injected into the water stream to achieve a 0.5 mg/L target concentration. Photograph of generator on left; schematic of generator on right.

time, disadvantages of both hyperchlorination and ultraviolet (UV) light had become manifest and a new technology, copper–silver ionization, was under evaluation. Since then, additional methods have been introduced: use of chlorine dioxide, monochloramine, and point-of-use filters. In the spirit of evidence-based medicine, we have formulated evaluation criteria with the intent of "raising the bar" for manufacturers of disinfection methodologies. These objective criteria for demonstration of efficacy can assist hospitals in making a cost-effective decision.

There are two basic types of disinfection systems: focal and systemic. Focal disinfection is directed at only a portion of the water distribution system, usually the incoming water or individual outlets, but not at the entire water distribution system. Systemic disinfection is directed at the entire water distribution system and the biofilm throughout the system.

Focal modalities include UV light, instantaneous heating systems, and ozone. Focal modalities are not effective if the water distribution system has preexisting *Legionella* colonization, because the *Legionella* in the water distribution system remains unaffected. Focal modalities may work best in a virgin water distribution system (e.g., in a new healthcare facility) *(130)*. For maximal effectiveness, a heat and flush sterilization or shock chlorination prior to activation and intermittently thereafter is advisable. Localized disinfection of faucets or showers by physical cleaning and or chlorination has a short-lived effect and is not effective (204).

Systemic modalities provide a disinfectant residual that is bacteriostatic or bacteriocidal throughout the water distribution system; these modalities include hyperchlorination, copper–silver ionization, and chlorine dioxide (205). Superheat and flush is a systemic modality that cannot be applied continuously; however, maintaining hot water temperatures at 140°F (60°C) minimizes recolonization *(206)*. The duration of the flush must be 30 minutes, not the 5 minutes as recommended by the CDC. Failures have been reported if the shorter flush duration is used *(207)*.

In some hospitals with endemic legionellosis and a high-risk population (especially transplantation patients), multiple disinfection modalities may be needed so that if one modality fails because of human error or mechanical failure, the other modality can serve as a safety net *(208)*. Furthermore, a focal modality (UV light) can be combined with two systemic modalities (superheat and flush, copper–silver) to ensure maximal kill of *Legionella*. Routine continual surveillance with environmental cultures is critical, since mechanical failures and human error are expected with any system. Cultures performed at 2-month intervals are recommended. The endpoints for disinfection should be realistic and clinically relevant. Total sterility is extremely difficult to achieve with any disinfection modality, and zero positivity is not required to prevent healthcare-associated Legionnaires' disease *(209,210)*.

The efficacy of some modalities may vary depending on water use. For example, if superheated water or water containing metallic ions or chlorine cannot reach a site because the faucet is unused, disinfection cannot occur. Although the disinfection modality may remove the larger portion of the biomass of *Legionella*, small pockets of *Legionella* in protected niches may still be present but in insufficient amounts to cause infection. At our institution, *Legionella* infections did not occur until the percentage of colonized sites exceeded 30% *(211)*. The cut point of 30% distal site positivity as an indicator of increased risk of transmission of *Legionella* has not been universally applicable to all healthcare facilities. However, it does demonstrate that the concept of correlating environmental monitoring with predicting increased risk of disease is valid for Legionnaires' disease *(212)*. In a study by the CDC, increased risk was associated with the extent of colonization (percentage of outlets positive) and not the concentration of *Legionella* recovered from a given outlet *(213)*. The precise figure depends not only on the extent of *Legionella* colonization but also on the susceptibility of patient populations to *Legionella* infection. For example, patients on a transplant ward may become infected with *Legionella* with a much smaller inoculum of *Legionella* in the water than would ambulatory patients on a psychiatric ward. This may be the basis for the more stringent recommendations from the CDC for monitoring and disinfection of bone marrow transplant units *(179)*.

Options for Disinfection

It is important to apply a scientific method to the evaluation of disinfection methods. We have proposed that any disinfection method should be subjected to a standardized evaluation with the following steps: (a) demonstrated efficacy *in vitro* against *Legionella* microorganisms, (b) anecdotal experience of efficacy in controlling *Legionella* contamination in individual hospitals, (c) controlled studies of prolonged duration (years, not months) of efficacy in controlling *Legionella* growth and in preventing cases of healthcare-associated Legionnaires' disease in individual facilities, and (d) confirmatory reports from *multiple* healthcare facilities with prolonged duration of follow-up (validation step) *(210)*. Given the current reality of economic constraints, disinfection modalities should also be selected with the long-term goals of sustained efficacy at reasonable costs (Table 36-3). Important factors include the area requiring disinfection (one building or multiple buildings, number of floors), the number of hot water heating systems in place (one vs. multiple), the extent of colonization, and the age of the facility. Older healthcare

TABLE 36-3

Protection of Patients from Healthcare-Associated Legionnaires' Disease: An Evidence-Based Assessment of the New York State Guidelines

Healthcare Facility Function	*Strong Recommendation (Cost-Effective, Practical, Evidence-Based)*	*Weak Recommendation (Costly, Impractical, Not Evidence-Based)*
Infection control	1. Quarterly culturing of the potable water system of transplant units for *Legionella* species [a] 2. Sterile water for rinsing nasogastric tubes and for enteral nutrition for transplant recipients	1. Any *Legionella* spp. detected, decontaminate the water supply, remove aerators, restrict showering[b] (Not all species are pathogenic)
Engineering environmental care and maintenance	1. Complete eradication of *Legionella* is not feasible and regrowth may occur after system disinfection[b] 2. Disinfect dormant water lines in patient care areas prior to being returned to service[c] 3. Store hot water at 140°F (60°C)[b]	1. Routine thermal disinfection (at least semiannually) of the hot water system. Flush each outlet ≥5 min at 160°F (71°C) or ≥2 ppm free chlorine[b] (5-min flush ineffective) 2. Remove, clean, disinfect showerheads and faucet aerators monthly in transplant units[b] 3. Eliminate dead end or capped pipes[c]

Note: Recommendations grading system used in an online medical resource at www.uptodate.com.
[a]Consistent/reproducible evidence from controlled prospective studies.
[b]Consistent/reproducible evidence from case studies.
[c]Anecdotal reports that are not peer-reviewed.
(From Stout JE. Preventing legionellosis. *ASHRAE J* 2007;49(10):58–62, with permission.)

facilities generally pose a more formidable task in disinfection than newer facilities because of accumulation of scale and *Legionella* within biofilms, but new healthcare facilities may also colonize rapidly *(214)*. Disinfection efforts that target the hot water system have been effective in controlling *Legionella*. This would suggest that treating the cold water supply may not be necessary. Given the public health implications, any commercial vendor's history of experience and service commitment in *Legionella* disinfection should be reviewed. It would be prudent to obtain assessments from other healthcare facilities that have used the vendor's product.

It should be emphasized that appearance, degree of cleanliness, and regular preventive maintenance of the system have not been shown to minimize *Legionella* contamination (204,*215*). Plumbing modifications including "dead-leg" removal and cleaning or replacing showerheads have been overemphasized. Nevertheless, many engineering guidelines have advocated such unvalidated approaches despite evidence that they are tedious and ineffective (204). The only way to be certain that a system is free of *Legionella* is to obtain samples for environmental cultures.

Finally, a strong infection control program is critical if the approach is to be cost-effective and scientifically valid. We advise that each healthcare facility evaluate the utility of its modality scientifically. Baseline cultures prior to disinfection over an adequate period are critical, so that the efficacy of a new disinfection modality can be adequately evaluated.

Selection of the vendor for installation of a systemic disinfection method is an important decision. Review of our experience in which healthcare-associated Legionnaires' disease recurred after a disinfection system had been installed revealed one consistent finding: the decision for purchase and installation of the disinfection system was made by the engineers within the facilities management team, with minimal input from the Infection Control department. Given the proliferation of numerous companies that now offer such systems, failures have become commonplace with patients contracting Legionnaires' disease despite installation of an expensive disinfection system. As a result, we strongly advocate that the Infection Control Department lead the task force in both selecting the disinfection method and the vendor. Other members of the task force should include hospital engineers and members of the administration. The critical contribution by the infection control preventionist is the insistence for the use of evidence-based data in the selection of the vendor.

Copper–Silver Ionization

Copper and silver are bactericidal *in vitro* against *Legionella* and other waterborne pathogens including *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii*, and mycobacterial species. We recommend copper and silver ion concentrations of 0.20 to 0.80 mg/L copper and 0.01 to 0.08 mg/L silver, respectively, for *Legionella* eradication. Ionization is the only disinfection method that has fulfilled all four evaluation criteria *(210)*. The systems (Tarn-Pure, T.P. Technology, Buckinghamshire, UK; Liquitech, Lombard, IL; Enrich Products, Pittsburgh, PA) use copper–silver electrodes that generate ions when an electrical current is applied. The positively charged ions form electrostatic bonds with negatively hypercharged sites on bacterial cell walls. The distorted cellular permeability coupled with protein denaturation leads to cell lysis and death. Copper–silver ionization provides residual protection throughout the system. Theoretically, microorganisms are killed rather than suppressed, which should minimize the possibility of recolonization. Controlled studies have shown that this modality is highly effective in eradicating *Legionella* (*193*,205,*216*). Two healthcare facilities that switched from thermal eradication (superheat-and-flush) to copper–silver ionization reported that ionization was more effective for reducing the recovery of *Legionella* from their water system *(209,217)*.

Among the first 16 healthcare facilities to use ionization for *Legionella* disinfection, 75% had attempted disinfection with other methods *(210)*. All 16 hospitals were successful in preventing healthcare-associated Legionnaires' disease after installation of ionization systems. Although elevated pH can adversely affect the action of copper *(218)* and there has been speculation of ion resistance *(219,220)*, most facilities reported satisfactory control of *Legionella* within their hot water supply. The systems had been in place from 5 to 11 years. Cost depended on the number of systems installed, but the average cost was $20,000 to $40,000. The Environmental Protection Agency (EPA) sets a maximum containment level (MCL) for copper in drinking water of 1.3 mg/L and for silver 0.1 mg/L (nonenforceable). EPA now requires ionization systems to "register" as a biocide for use in potable water.

Chlorine Dioxide

Chlorine dioxide (ClO_2) is a registered biocide with the US EPA. EPA has set the maximum residual disinfectant level for ClO_2 of 0.8 mg/L, and the MCLs for its by-products chlorite and chlorate are 1.0 mg/L, and chlorate is currently not regulated due to the lack of health data to set an MCL. All chlorine dioxide products used in healthcare facilities must be EPA registered and American National Standards Institute/National Sanitation Foundation certified. Some states require regular monitoring of chlorine dioxide and chlorite. Such testing can be costly and this expense is often overlooked. Potential users should check with their local environmental protection agency for regulatory requirements.

Although this technology has been used to control *Legionella* in European hospital water systems for many years, it has only recently been introduced into the US healthcare market for this application *(221–223)*. New technology now allows for the safe generation of chlorine dioxide on a small scale. Methods for producing chlorine dioxide include controlled mixing of chemical precursors or electrochemical generation. One type of generation unit utilizes an electrical source and membrane technology to directly oxidize sodium chlorite (Halox, Inc., Nalco, Naperville, IL) (Fig. 36-2). These generators typically provide 5 g/h to 2.4 kg/d of chlorine dioxide. Chlorine dioxide can be fed into the water system at various points (cold water supply, hot water supply, reservoir), depending on where disinfection is desired. Preventative maintenance includes replacing various filters and tubing.

Several controlled evaluations of chlorine dioxide have been performed in the United States *(221–223)* and have shown that chlorine dioxide at a concentration of <0.8 mg/L was effective in reducing *Legionella* species

in the healthcare facility's water system. There was a significant reduction in the percentage of positive outlets; however, *Legionella* persisted at a low level in the treated systems and months were required to reach these levels. Difficulties were encountered in maintaining an adequate chlorine dioxide residual in the hot water system; the residual in the hot water was often <0.1 mg/L. This was attributed to a combination of loss of residual with increased distance from the injection point and increased decay of chlorine dioxide at higher water temperatures. Prospective studies of sufficient duration from different institutions are required to validate these results. Cost depends on the number of systems installed, but the average cost was $20,000 to $40,000 plus installation costs.

Point-of-Use Filtration

Point-of-use filters (0.2 μm) (AquaSafe, Pall Medical, East Hills, NY) have been used for prevention of healthcare-associated infections due to *Legionella* and *P. aeruginosa*, particularly in high-risk areas such as intensive care units and transplant units *(224–226)*. In a controlled study, the filter completely eliminated *Legionella* and *Mycobacterium* from the water *(225)*. Some healthcare facilities restrict water use during an outbreak by having patients use bottled water exclusively and restricting all patients from showering. Filters are usually more cost-effective and better tolerated by patients *(227)*. Filters must be changed every 30 days.

Superheat and Flush

If *Legionella* must be eradicated from the water distribution system immediately, the superheat-and-flush method warrants primary consideration. The basic method requires that hot water tank temperatures be elevated to >70°C (158°F), followed by flushing of all faucets and showerheads to kill *L. pneumophila* colonizing these sites (205,*228*).

All hot water tanks are shut down, drained, descaled with high-pressure steam, and then chlorinated to 100 ppm for 12 to 14 hours. The chlorinated water is drained and the tank flushed with water to remove the residual chlorine. The tanks are then placed back on line, and the temperature is elevated to 70°C to 80°C (158°F–176°F) for 72 hours. All distal water sites in patient care wards are flushed once a day for 2 days, whereas those sites located on patient units housing high-risk patients (intensive care units and transplant wards) are flushed once a day for 3 consecutive days. The outlets are flushed for 30 minutes. It is critical that temperatures of the flushed water be monitored to ensure that the temperature exceeds 60°C (140°F) distally. On the fourth day, selected distal sites are recultured; if no *Legionella* microorganisms are recovered, the procedure is considered completed. If *Legionella* is still isolated, the entire heat and flush protocol is repeated. Both maximum temperature and duration of the flush are important for successful decontamination. Healthcare facilities that have used shorter flush times have failed to eradicate *Legionella (207)*. Unfortunately, a minimum flush time of 5 to 10 minutes has been erroneously recommended by HICPAC *(133)*; although the 30-minute flush is tedious, it will be more successful than the 5- to 10-minute flush.

Recolonization can be delayed and minimized by maintaining hot water tank temperatures at 60°C (140°F). At the Pittsburgh Veterans Administration Medical Center, the heat-and-flush method was required only once every 2 to 3 years, making this method a cost-effective one. The costs are low except for personnel time; if overtime is required, the costs can quickly escalate. We used volunteers, when possible, for the flushing process. One healthcare facility reported overtime costs of approximately $20,000 (Table 36-3) (205). Ultimately, we abandoned this method of control in favor of the less labor-intensive copper–silver ionization system *(209)*.

The main disadvantage is that numerous personnel are involved to monitor distal sites, water tank temperatures, and flushing times. Scalding can occur, although such incidents have not been reported in numerous facilities using this method. It should be noted that the Joint Commission has rescinded its earlier standard for a maximum water temperature of 110°F and allows each healthcare facility to establish its own maximum temperature. However, many states have regulations for rehabilitation and long-term care institutions that prohibit temperature in excess of 43°C (110°F) at the tap *(229)*.

Monochloramine

Monochloramine is effective against *Legionella in vitro* and in biofilm-associated *Legionella* in model plumbing systems *(230)*. Two case–control studies suggested that healthcare facilities in municipalities that were supplied with domestic drinking water treated with monochloramine were less likely to report healthcare-associated Legionnaires' disease *(55,231)*. A 2-year prospective environmental study in a California municipality in which monochloramine replaced chlorine for water disinfection, *Legionella* colonization decreased from 60% to 4% with conversion from chlorine to monochloramine in 53 buildings. The median number of colonized sites per building decreased with monochloramine disinfection *(215)*.

The efficacy of on-site monochloramine treatment in individual healthcare facilities has not yet been studied over a prolonged period. A system for delivering monochloramine into building water distribution systems was evaluated at a hospital in Italy. A significant reduction in *Legionella* positivity was seen within 30 days of injecting 1 to 2 mg/L of monochloramine *(232)*.

Monochloramine provides a stable residual that penetrates biofilms and has a wider pH working range than copper–silver ionization and chlorine. Monochloramine can cause anemia in patients undergoing hemodialysis. The on-site generation of monochloramine can be complicated; injecting hypochlorous acid upstream and ammonia downstream in a flow-through pipe could result in coexistence of free chlorine, ammonia, and monochloramine due to incomplete mixing of the reactants.

If a municipality converts from chlorine to monochloramine as the primary treatment method, the healthcare facilities in that municipality become inadvertent beneficiaries if they have a water system colonized with *Legionella (198)*. The downside has been increased populations of other microorganisms (*Mycobacterium* spp.), nitrogen by-products, and increased lead leaching in drinking water. Wide-scale conversion to monochloramine for municipal water supplies appears unlikely today.

Monochloramine appears to be a promising approach in decreasing *Legionella* colonization. Long-term evaluations remain to be reported.

TABLE 36-4

Internet Web Sites Are a Valuable Resource for Information on All Aspects of Legionnaires' Disease

Web Address	*Publisher*
http://www.cdc.gov/ncidod/dbmd/diseaseinfo/legionellosis_g.htm	Centers for Disease Control and Prevention
http://www.legionella.org	Pittsburgh Legionella Group
http://www.osha-slc.gov/dts/osta/otm/otm_iii/otm_iii_7.html	Department of Labor and Occupational Safety and Health Administration
http://www.ashrae.org	American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE): Legionella Guideline 12-2000
www.awt.org/IndustryResources/Legionella03.pdf	Association of Water Technologies

(Adapted from Bassetti S, Widmer AF. Legionella resources on the World Wide Web. *Clin Infect Dis* 2002;34:1633–1640, with permission.)

Hyperchlorination

Hyperchlorination has proven disappointing as a long-term solution because of high expense, pipe corrosion (205), introduction of carcinogenic by-products into the drinking water *(233)*, and difficulty in maintaining high concentrations (2–4 ppm) of chlorine to sustain efficacy.

The advantages and disadvantages of sustained and continuous hyperchlorination have been reviewed in detail elsewhere *(194)*. This method widely implemented in the 1980s was found to be the most expensive and most unreliable disinfection approach. Inadequate penetration into piping biofilms, corrosion of the water distribution system leading to pinhole leaks, introduction of carcinogens into the drinking water, and unreliable efficacy led to its abandonment *(234)*. Corrosion can be minimized with the addition of silicate to the water—an additional cost.

Ultraviolet Light

UV light is an attractive option for disinfection since no chemicals are added to the drinking water. UV light kills *Legionella* by disrupting cellular DNA. Its point-of-entry application does not allow distal eradication of *Legionella* within the biofilms of the water distribution system that are distal to the point of entry.

These systems have proven to be effective if disinfection can be localized—for example, to a transplant or an intensive care unit *(154)*. Because UV sterilization provides no residual protection, areas distal to the sterilizer must be disinfected following installation and start-up. One effective approach is to use superheat and flush to disinfect most of the system and then to introduce chemical disinfection (metallic ion or chlorine) as an adjunct. Prefiltration is necessary to prevent the accumulation of scale on the UV lamps. One hospital reported successful control of *Legionella* in the water system after installation of UV units on the main water supply to a newly constructed hospital *(130,235)*. Depending on the size, these units can be installed for approximately $10,000 to $20,000.

GUIDELINES

In the absence of a national consensus policy or a guideline with specific recommendations for control and prevention, different organizations and state health departments have had to devise their own guidelines (Table 36-2) *(236)*. Control and prevention of Legionnaires' disease crosses many disciplines, and as such there are numerous guidance documents and resources for physicians, infection preventionists, engineers, and industrial hygienists. Unfortunately, many recommendations are not evidence-based, including those in the New York State guidelines that emphasize maintenance by engineers and prohibition of showering, leading to adoption of ineffective methods that are tedious, labor intensive, and expensive (Table 36-3) (204). Many of these documents are available via the World Wide Web (Table 36-4). The quality of *Legionella*-related Web sites maintained by private and state institutions, universities, professional organizations, and individuals has been reviewed *(237)*.

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CHAPTER 37

Clostridium difficile

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Clostridium difficile was identified as the etiologic agent of antibiotic-associated pseudomembranous colitis (PMC) in 1978 (1,*2*) and is now recognized as the most important identifiable cause of healthcare-associated infectious diarrhea. *C. difficile* may be the only pathogen sufficiently prevalent to warrant testing on a routine basis during the evaluation of healthcare-associated diarrhea *(3,4)*. It is estimated that each case of healthcare-associated *C. difficile* infection (CDI) costs between $10,212 and $13,675 and results in 3.0 to 6.4 excess hospital days *(5)*. Readmission for CDI costs $128,200 per hospital per year *(6)*. A conservative annual cost estimate for CDI in the United States is $3.2 billion *(5)*. Our present understanding of the pathogenesis of *C. difficile* disease and rationale for preventive and interventive measures is supported by (a) observations on antimicrobial use in patients who acquire this pathogen, (b) potential infectious reservoirs, (c) modes of *C. difficile* transmission, and (d) host risk factors.

PATHOGENESIS

The manifestation of enteric disease due to *C. difficile* depends on at least three critical events: disruption of the normal colonic microflora, exposure to a toxigenic *C. difficile* strain, and the presence of one or more host factors. Epidemiologic evidence also supports the order of these events in that, with most cases, exposure to antimicrobials with subsequent compromise of host colonization resistance is followed by *C. difficile* acquisition from exogenous sources (rather than reactivation from an endogenous source).

The normal colonic flora provides a profound resistance to infection with *C. difficile*. It appears that the host is susceptible to infection with this pathogen only after disruption of the colonic flora by antimicrobial therapy or by substances that act as antimicrobial surrogates such as antineoplastic agents *(7)*. The next critical event, exposure to toxigenic *C. difficile*, occurs most often in hospitals and chronic care facilities, which serve as the main reservoirs for this infection. With the recognition that asymptomatic carriage of *C. difficile* is very common among hospitalized patients, it might seem intuitive that these carriers are at high risk of subsequent CDI. However, a meta-analysis of four prospective studies that included 810 patients followed for 1,348 weeks with weekly surveillance cultures indicated that asymptomatic carriers were, conversely, at decreased risk of subsequent CDI (pooled risk difference –2.3% [95% confidence interval 0.3–4.3], *p* .021) *(8,9)*.

In our current hypothesis (Fig. 37-1), a patient is admitted to the hospital and, although exposed intermittently to *C. difficile*, is susceptible to colonization or disease only following antimicrobial therapy. The subsequent clinical outcome is determined shortly after acquisition (within a few days) and, like other enteric and infectious diseases, the majority of patients remain asymptomatic. These asymptomatic carriers are then at decreased risk for CDI when compared with noncolonized patients. Host risk factors comprise the third critical component to the pathogenesis of CDI and are discussed later in this chapter.

C. difficile elaborates two major toxins: toxin B, a potent cytotoxin; and toxin A, a potent enterotoxin that is also cytotoxic *(10)*. Although measurement of cytotoxicity in stool specimens is used to diagnose CDI, the enterotoxic effect of toxin A has been presumed to be critical in the pathogenesis of the disease. The early evidence implicating toxin A includes the observation that disease severity correlates more closely with toxin A production *in vivo (11)* and that toxin A alone, but not toxin B, given intragastrically reproduces the pathology of *C. difficile* cecitis in hamsters *(12)*. However, toxin B acts synergistically with toxin A in this model, and clinical data support virulence for variant strains that produce only toxin B, but not toxin A. Genetic knockout experiments indicate that toxin B, not toxin A, is the toxin essential for causing disease in the hamster model (13). Furthermore, a monoclonal antibody directed at toxin A was ineffective at reducing CDI recurrence, whereas two monoclonal antibodies directed at toxins A and B were effective in reducing CDI recurrence in patients (14,15).

Toxin A is a unique enterotoxin unrelated to cholera toxin or the *Escherichia coli* heat-labile toxin and causes extensive mucosal damage with hemorrhagic fluid response *(16)*. The receptor for toxin A involves a trisaccharide moiety, Gala1–3Galb1–4GlcNAc *(17)*, which is present on antigens within the brush border of human and hamster intestinal epithelium *(18)*. Subsequent toxic cellular events

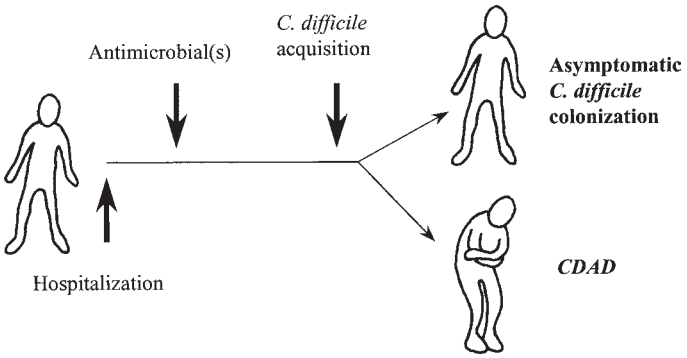

FIGURE 37-1 Hypothesis of the pathogenesis of *C. difficile* infection. Although patients are likely exposed to *C. difficile* throughout their hospitalization, we hypothesize that they are at negligible risk for CDI until exposed to an antimicrobial agent. Following antimicrobial exposure, the patient is now susceptible to infection, and when exposed to *C. difficile*, one of three outcomes ensues: the patient becomes colonized but remains asymptomatic, the patient develops CDI, or potentially the patient does not develop any detectable infection. Once the patient is established as an asymptomatic carrier, data indicate that the patient is at decreased risk for subsequent CDI (*7*). (Reproduced from Johnson S, Gerding DN. *Clostridium difficile*–associated diarrhea. *Clin Infect Dis* 1998;26:1027–1036, with permission.)

involve internalization of toxin A by receptor-mediated endocytosis and disruption of the cellular cytoskeleton. Toxin A (and B) induces glycosylation of small guanosine triphosphate–binding proteins that are important regulators of actin polymerization *(19)*.

Variant strains of *C. difficile* that do not produce toxin A have been recovered from clinical specimens around the world. These toxin A–/B+ strains were initially recovered from asymptomatic children and were not thought to be pathogenic. Recently, a particular toxin A–/B+ variant that has a 1.8-kb deletion in the toxin A gene (referred to as toxinotype VIII, serogroup F, restriction endonuclease analysis [REA] group CF) *(20)* has been recovered from multiple CDI cases, including a fatal case of PMC *(21)*. In addition, two well-documented hospital outbreaks with the A–/B+ variant *(22,23)* suggest that toxin B or some virulence determinant other than toxin A in these strains is sufficient to cause *C. difficile* disease, consistent with the observations in hamsters using toxin A knockout *C. difficile* strains (13).

In addition to toxins A and B, some strains of *C. difficile* (but not toxinotype VIII strains) also produce an adenosine diphosphate–ribosyltransferase (referred to as binary toxin) *(24)*. The role of binary toxin in the pathogenesis of CDI has not yet been determined, but during the first decade of the 21st century, there have been multiple outbreaks of a toxin-variant strain of *C. difficile* that has caused severe CDI in North America, the United Kingdom, and Europe (25,26). It is a toxinotype III strain variously known as type NAP1 by pulse field, type 027 by polymerase chain reaction (PCR) ribotyping, and group BI by REA and is collectively termed BI/NAP1/027 (25). The etiology of the high CDI rates and high severity of illness is not known, but the strains produce large amounts of toxins A and B *in vitro*, produce binary toxin, and have a deletion in the *tcdC* gene responsible for downregulation of toxin production *(27)*.

The other important aspect of *C. difficile* pathogenesis lies within the apparent host resistance of some patients to *C. difficile* disease. Infants in the first year of life frequently carry *C. difficile* in high numbers with high levels of both toxins in their stools *(28)*, yet *C. difficile* disease is rare in this group. Age-dependent expression of the epithelial cell receptor for toxin A may explain this apparent resistance in young infants *(29)*. Additionally, during outbreaks in adult settings, asymptomatic carriage is a more frequent outcome of CDI than is symptomatic infection *(8,30)*. Disease manifestation and severity are not solely strain-specific phenomena *(31)*; although the mechanism of this apparent host resistance in adult asymptomatic fecal excretors is not completely known, host antibody response to toxin A has been one factor implicated (32,33).

CLINICAL DISEASE SPECTRUM

Although the most common clinical manifestation of CDI is diarrhea, the disease spectrum ranges from asymptomatic colonization or fecal excretion to PMC to septic shock with and without toxic megacolon, which may present with signs of an acute abdomen but without diarrhea *(34)*. As with other enteric infections, asymptomatic colonization is two to five times more common than clinical disease associated with *C. difficile (8,30)*. Although colonized patients may carry epidemic strains responsible for illness in other patients, they are not at increased risk of CDI *(9)*, they are not at risk for subclinical protein-losing enteropathy *(35)*, and treatment of these patients with metronidazole or vancomycin is not advised *(36)*. Asymptomatic colonization is also very common in neonates, and it has been difficult to attribute any disease manifestation in neonates to *C. difficile*. However, the pathogenic role of *C. difficile* in children cannot be completely ignored, particularly in children over 1 year of age and especially in children with hypogammaglobulinemia *(37)*.

Diarrhea with or without demonstrable pseudomembranes in the colon is the most common manifestation of *C. difficile* disease. Although *C. difficile* is the most common recognized cause of antibiotic-associated diarrhea, *C. difficile* accounts for only 15% to 25% of these cases *(38)*. CDI may occur during antimicrobial administration or several weeks after discontinuation of the antimicrobial. In a prospective study of clindamycin therapy, one-third of the patients developed diarrhea or colitis several days to 3 weeks after completion of clindamycin treatment *(39)*. This marked variability of time between onset of diarrhea and antimicrobial exposure also supports exogenous acquisition as the major source of CDI. The incubation period for diarrhea after acquisition of *C. difficile* is less than 1 week, with a median onset of 2 days following acquisition *(8,30)*. However, the incidence of CDI in the first 30 days following hospital discharge is very high, suggesting the possibility of either acquisition of the microorganism in the community following discharge or a longer incubation period (40).

The severity and chronicity of diarrhea is also variable. In some cases, symptoms may be mild and respond to simply withdrawing the offending antimicrobial. CDI resolved spontaneously within 48 to 72 hours in 25% of patients in

one series *(41)*. More commonly, the diarrhea becomes chronic and severe if not diagnosed and treated with specific therapy. At presentation, symptoms may consist of only a few loose stools per day or multiple, large-volume, watery stools and signs of dehydration *(38)*. Stools may have mucus or evidence of occult blood but are rarely associated with visible blood *(42)*. Other findings commonly associated with CDI include abdominal pain (22%), ileus (21%), fever (28%), and leukocytosis (50%) *(42)*. CDI should be considered in any hospitalized patient with leukocytosis, particularly those with white blood cell counts >30,000 cells/mm^3, even without the presence of diarrhea *(43)*. Complications of severe disease include dehydration, electrolyte imbalance, hypotension, hypoalbuminemia with anasarca, toxic megacolon, colonic perforation, and sepsis, and in 1% to 7% of cases, death can result (26,*38*). Higher mortality rates have been particularly noted in CDI caused by the epidemic BI/NAP1/027 strain (26,44). A characteristic of CDI is the high rate of clinical recurrence following successful therapy, which may result from either relapse with the same strain or reinfection with a new strain *(45,46)*.

In distinction from antibiotic-associated diarrhea in general, *C. difficile* is responsible for nearly all cases of PMC that have been reported since 1978 *(38)*. The pseudomembranous intestinal lesions associated with *C. difficile* (which are present in only about half the patients who have diarrhea and *C. difficile* toxin in stool) have a characteristic gross and histologic appearance *(47)*. Early in the disease course, small (1–2-mm), raised, yellowish white plaques are noted, which may enlarge and coalesce *(48)*. These lesions, which are composed of fibrin, mucus, necrotic epithelial cells, and leukocytes, are restricted to the colon; therefore, this disease should be referred to as PMC rather than enterocolitis. Although PMC can be visualized by the sigmoidoscope in 90% of patients who have PMC, some patients have disease limited to the right colon, and the presentation may mimic appendicitis or Crohn disease *(49)*.

Fulminant *C. difficile* colitis and toxic megacolon are less common manifestations, but important syndromes to recognize, as they are associated with a high mortality rate and frequently require surgical intervention *(50,51)*. It is ironic that this most severe manifestation of CDI often occurs without diarrhea, and as a result, the diagnosis is frequently missed or delayed *(34)*. Risk factors for severe disease in one study included immunosuppression, prior CDI, and prior surgical procedures *(51)*. A rapidly increasing peripheral white blood cell count with a left shift may be an important clue to impending fulminant disease. A rising white blood cell count during medical treatment that is approaching 50,000/mm^3 or a lactic acidosis approaching 5 mmol/L are indication for colectomy in patients failing medical management *(52)*.

Extraintestinal CDIs are uncommon but include splenic abscess, bacteremia, wound infections, osteomyelitis, pleuritis, peritonitis, and urogenital tract infections *(53)*. As with other enteric infections, CDI has been associated with reactive arthritis *(54)*.

DIAGNOSIS

The diagnosis of CDI depends first on establishing the presence of clinical diarrhea or other gastrointestinal symptoms compatible with *C. difficile* disease such as abdominal pain or, rarely, ileus without diarrhea. Definitions for healthcare-associated CDI have been published and are summarized in Figure 37-2 (55,56). Two major avenues are available to establish the diagnosis in a clinically ill patient: endoscopic procedures to detect the presence of PMC and laboratory studies to document the presence of *C. difficile* or its toxins in the stool. The latter tests include (a) stool culture, antigen tests, and the PCR to detect the microorganism; (b) the cell cytotoxin test for toxin B; and (c) a variety of immunoassay tests for the presence of toxin A or toxins A and B in stool. The best way to establish the diagnosis of CDI remains controversial; however, the availability of commercial PCR tests for the detection of toxigenic *C. difficile* is likely to provide the best combination of sensitivity, specificity, and rapid results reporting for those labs equipped to do PCR (56,*57–60*). Advantages and disadvantages of each of the diagnostic modalities are discussed below. Sensitivity and specificity are summarized in Table 37-1.

Endoscopic Procedures

Endoscopic procedures indirectly indicate *C. difficile* disease by demonstrating PMC. The procedure may be

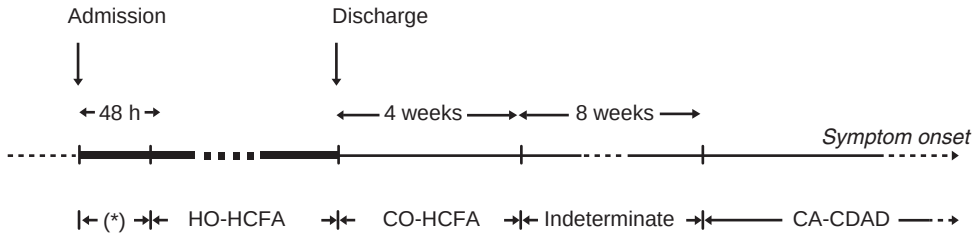

FIGURE 37-2 Time line for definitions of *Clostridium difficile* infection (CDI) exposures. Case patients with symptom onset during the window of hospitalization marked by an *asterisk* (*) would be classified as having community-onset, healthcare facility–associated disease (CO-HCFA), if the patient was discharged from a healthcare facility within the previous 4 weeks; would be classified as having indeterminate disease, if the patient was discharged from a healthcare facility between the previous 4 and 12 weeks; or would be classified as having community-associated CDI (CA-CDI), if the patient was not discharged from a healthcare facility in the previous 12 weeks. HO-HCFA, healthcare facility–onset, healthcare facility–associated CDI. (Adapted from McDonald LC, Coignard B, Dubberke E, et al. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol* 2007; 28:140–145.)

TABLE 37-1

Sensitivity and Specificity[a] of Diagnostic Tests for *Clostridium difficile*–Associated Disease

Test	*Sensitivity*	*Specificity*	*Comment*
Pseudomembrane detection			
Flexible sigmoidoscopy	+	+++++	Biopsy may be required
Microorganism detection			
C. difficile culture	+++++	+++	Most sensitive test
C. difficile culture with toxin testing of the isolate	+++++	+++++	Sensitive and specific for diagnosis of *C. difficile* infection
C. difficile GDH immunoassay	++++	+++	Detects GDH
PCR for *C. difficile*	++++	+++++	~90–95% as sensitive as stool culture
Toxin detection			
Cell cytotoxicity	+++	+++++	Highly specific
Immunoassay for toxins A and B	++	++++	Less sensitive than cell cytotoxicity
Immunoassay for toxin A	+	++++	Less sensitive than EIA for toxins A and B

[a]Relative sensitivity and specificity: +++++, highest; +, lowest. PCR, polymerase chain reaction; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase.

performed with a flexible fiberoptic sigmoidoscope or a fiberoptic colonoscope. The latter is the only device that permits visualization of the entire colon, but it is not routinely used for this diagnosis because of the need for extensive colon preparation and the high cost of the procedure. Flexible sigmoidoscopy is the most frequently employed of these procedures and allows visualization of the distal 60 cm of the colon. The diagnosis can be made by direct visualization of the pseudomembranes; biopsy may be required if the lesions are small *(48)*. The major deficiency of endoscopy is that it is highly insensitive. Pseudomembranes were seen in only 51% of patients who had diarrhea, a positive stool cytotoxin assay, and positive stool culture for *C. difficile (42)*. It is probable that PMC is a late manifestation of *C. difficile* disease that is more likely to occur in the proximal colon first, accounting for the low sensitivity of endoscopy for the diagnosis of CDI *(49)*.

Clinically, the major advantage of endoscopy is the rapidity with which a diagnosis can be made. This is particularly important in critically ill patients in whom the diagnosis of a surgical abdominal process is being considered. These patients often have symptoms of ileus or obstruction, which can be caused infrequently by *C. difficile*. Visualization of PMC by endoscopy can avert inappropriate emergency abdominal surgery and permit confident initiation of *C. difficile*–specific treatment. However, the vast majority of *C. difficile*–infected patients are not critically ill, and endoscopy has been almost totally supplanted by laboratory tests for the diagnosis of CDI.

Laboratory Diagnosis

Stool Toxin Tests

Cell Cytotoxin Assay The cell cytotoxin assay has been traditionally considered the most specific of stool diagnostic tests for CDI, albeit not the most sensitive when compared to stool culture *(61–63)*. A wide variety of cell types may be used for testing, but the test requires that laboratories maintain their own cell lines or purchase them in commercially available kits. For the test to be diagnostic, the cytopathic effect of the specimen (primarily due to the effects of toxin B) must be neutralized by specific *C. difficile* or *C. sordellii* antitoxin. Appropriate specimen dilution is critical to achieving test sensitivity and specificity. Sensitivity of the cell cytotoxin assay has ranged from 56% to 100% (depending upon the comparator test) when used to detect *C. difficile* disease in patients with clinically significant diarrhea *(61)*. Low sensitivity is thought to be due to the inactivation of toxins by proteases or other inactivating substances in stool, an occurrence that is more likely if the specimen remains at room temperature for a long period. Despite its relative insensitivity, stool testing for cytotoxin remains one of the gold standards against which *C. difficile* laboratory tests are evaluated. A major drawback of this test is the long (48-hour) turnaround time for results in most laboratories.

Immunoassay for Toxins A and B A variety of immunoassays are available that detect *C. difficile* toxin A, or toxins A and B. Enzyme immunoassays that detect only toxin A have been largely abandoned as they fail to detect clinically significant CDI caused by toxin A–/B+ strains *(21,22)*. These tests have now been widely adopted by clinical laboratories (and are often the only tests offered) because of the rapid turnaround time and decreased workload compared to cytotoxin assays. When compared only to cytotoxin testing, the sensitivity of a battery of immunoassays was 82.8% (range 66.7–91.7%) and the specificity was 95.4% (range 90.8–98.8%) *(64)*. The relative sensitivity of toxin immunoassays compared to culture with confirmation of toxin-producing isolates (also called toxigenic culture) was 75% (range 60–86.4%) and the specificity was 96.1% (range 91.4–99.4%) *(64)*. In an effort to overcome the low sensitivity of toxin immunoassays, clinicians may order multiple stool tests for toxin, but this practice, because of the lack of enzyme immunoassay specificity, leads to more false-positive test results than true positives and this practice should be discouraged by both laboratories and clinicians (56,65). Immunoassays that detect both toxins A

and B are more sensitive than assays that just detect toxin A and they also detect variant A–/B+ strains of *C. difficile* that are not detected by toxin A immunoassays *(66,67)*. The frequency of toxin A–/B+ variant strains has been low (0.2–3%) in most surveys *(67–69)* but may be considerably higher in A–/B+ hospital outbreaks *(22,23)*. Infections due to these A–/B+ variants are important to recognize clinically because of their propensity to cause clinically severe outbreaks worldwide *(21–23)*. Advantages of the toxin immunoassays are the relatively high specificity and rapid turnaround time (if the tests are not batched).

Tests for the Detection of the Microorganism in Stool

Stool Culture Stool culture for *C. difficile* on selective media (cycloserine-cefoxitin-fructose agar [CCFA]) has proven to be the most sensitive tests for CDI *(62,63)*. Special transport of stool specimens is not required for culture; however, CCFA media must be anaerobically reduced prior to inoculation so that residual oxygen in the media does not kill the microorganism when germinating from spores. Addition of taurocholate or lysozyme to CCFA enhances recovery of spores *(70)*. Clinical laboratories must exercise diligent quality control of commercially purchased media, as recovery rates have been shown to vary widely among manufacturers *(71,72)*. Culture is essential if epidemiologic investigation employing microorganism typing (including molecular techniques) is desired. The major criticism of culture as a diagnostic test for CDI is that it lacks specificity when compared with the cytotoxin assay because nontoxigenic *C. difficile* may be isolated and because many patients in hospitals may be asymptomatically colonized with toxigenic *C. difficile* and have diarrhea for reasons unrelated to the microorganism *(61,73)*. When culture and cell cytotoxin assay are both performed for CDI diagnosis, both tests yield positive results in well over half of patients with CDI, but stools are culture-positive and cytotoxin-negative in the remaining patients *(61)*. About 75% of the *C. difficile* isolates recovered from this latter group produce toxins *in vitro*. Patients with culture-positive, cytotoxin-negative stool specimens should be considered CDI cases if the isolated microorganism produces toxin *in vitro* (culture positive for toxigenic *C. difficile*) *(41,74)*.

Antigen Tests The latex agglutination test is a commercially available stool test that was originally thought to detect toxin A but was subsequently shown to detect a different *C. difficile* protein, glutamate dehydrogenase (GDH) *(75)*. The test is rapid, simple to use, and relatively inexpensive, but in its latex agglutination, detection format lacked both sensitivity and specificity and did not distinguish toxigenic from nontoxigenic strains of *C. difficile (62,63)* (Table 37-1). The detection method has been reformulated to use an enzyme-linked immunosorbent test or enzyme immunoassay for GDH, also referred to as "common antigen" *(76,77)*. Because the test is sensitive but not specific due to the lack of distinction between toxigenic and nontoxigenic strains of *C. difficile*, this test must be used in conjunction with a toxin-based assay or toxin gene detection of *C. difficile (77,78)*. Using this "two-step" method of GDH testing followed by cell cytotoxin testing for all positives, the GDH test can be used as a screening test to rule out CDI in the 80% to 90% of patients whose specimens test negative by GDH; however, up to 50% of the patients who test positive by GDH will not have confirmatory toxin found in the stool and will be ultimately reported as negative for *C. difficile* toxin *(77)*.

Polymerase Chain Reaction The use of PCR to detect *C. difficile* in stool is now commercially available and primers for amplification of conserved areas of the toxin B gene are used to detect toxigenic strains of *C. difficile* with a degree of sensitivity between 86% and 94% that of toxigenic culture *(57–60)*. For laboratories that have PCR amplification equipment, the use of PCR for clinical diagnosis will significantly improve sensitivity and specificity of diagnosis of CDI with rapid test results turnaround; however, the cost per test is substantially higher than for other tests. For laboratories that lack PCR capability, the GDH two-step algorithm may be the most effective diagnostic method *(*56*)*.

Diagnostic Summary

Testing of stools for fecal leukocytes *(42)* and examination by Gram stain for gram-positive bacilli *(79)* are of questionable utility as screening tests for CDI because of low sensitivity and low specificity. Of the available laboratory tests, the cell cytotoxin assay is the most specific whereas culture is the most sensitive. For epidemiologic purposes, there is no substitute for stool culture in the diagnosis and epidemiologic management of healthcare-associated CDIs. Because most clinical laboratories have abandoned culture and cytotoxin testing in favor of toxin immunoassays, alternative testing such as PCR or empiric treatment should be considered in patients with negative test results and high pretest probability for CDI (e.g., recent hospitalization and antibiotic exposure). The use of stool PCR for diagnosis in many laboratories is likely to significantly improve CDI diagnostic sensitivity in the future.

EPIDEMIOLOGY

Infection Rates and Epidemic Characteristics

Rates of *C. difficile* diarrhea and colonization vary markedly from one setting to another. The incidence of CDI in acute care hospitals has ranged from 0.3 cases per 1,000 patient admissions *(80)* to 22.5 cases per 1,000 patient admissions or higher (26). An extraordinary incidence of diarrhea (21%) and PMC (10%) was documented at one hospital in patients receiving clindamycin *(39)*, whereas CDI is only infrequently recognized at other hospitals. CDI has also been documented in chronic care facilities and nursing homes at the somewhat lower rate of 0.08 cases per 1,000 resident days *(81)*. Although CDI is rare in newborn infants, up to 60% of neonates are colonized, albeit at markedly different rates on different wards within the same hospital *(28)*. These differences in disease rates may reflect different diagnostic criteria and, particularly in regard to neonates, different clinical settings, but also likely reflect the endemic or epidemic status of *C. difficile* in different institutions, emphasizing the importance of healthcare-associated acquisition over endogenous activation in the pathogenesis of this disease.

C. difficile is only infrequently cultured from stools of healthy adults who have not had recent exposure to

antimicrobial agents *(82,83)*. Rates of *C. difficile* carriage among hospitalized patients, however, can range from 7% to 26% and the rate of acquisition increases linearly with the length of hospital stay *(73)*. Development and application of various typing schemes have demonstrated the importance of healthcare-associated acquisition and have clarified many aspects of *C. difficile* transmission within hospitals (*8*,*30*,*84*,85).

Among the numerous typing schemes that have been employed for *C. difficile*, PCR ribotyping, pulsed-field gel electrophoresis, and REA have been most widely used for epidemiological purposes (85,*86*). Among the newer genotypic methods, multilocus variable-number tandem-repeat analysis (MLVA) is more discriminatory than multilocus sequence typing, and MLVA and REA are best suited for discerning subtle strain differences and tracking outbreak strains geographically (85). We have used the high discrimination of REA to demonstrate the marked genetic diversity of *C. difficile*. Over 200 unique REA types were identified among *C. difficile* isolates from one hospital over a 10-year period *(87,88)*. High CDI incidence periods in this hospital were characterized by large clusters of specific REA types that changed yearly *(88)*. The large cluster outbreak strains at the beginning of the surveillance period had disappeared by the end of this study (1991) and, in retrospect, the current BI/NAP1/027 multicountry epidemic strain was also present in this hospital, but was only seen in isolated cases and the potential significance of this strain was not appreciated at that time *(88)*. In addition to outbreaks of CDI, silent clusters of *C. difficile* acquisitions occur in which few or no patients develop symptoms related to acquisition of that particular strain *(73)*. Even among clinical relapses of CDI in the same patient that occur within the hospital setting, half of the cases involve acquisition of new strains, emphasizing the importance of healthcare-associated transmission *(45,46)*.

Despite a good general understanding of the important aspects of control and treatment of CDI, there was a dramatic epidemiologic change in 2001 with increased rates of hospital-associated disease across the United States, increased reports of hospital outbreaks in North America and Europe, and increases in severe CDI cases. Nowhere was this change more dramatic than in Quebec in 2003 where a multihospital outbreak occurred in which the CDI incidence was 22.5 cases per 1,000 admissions and the CDI-attributable mortality at 30 days was 6.9% (26). It was estimated that 2,000 patients died directly as a result of CDI in Quebec from 2003 to 2004. One particular strain, now referred to as BI/NAP1/027, was responsible for 82% of the cases in these hospitals. The same strain was responsible for outbreaks in US hospitals during the same time period and was characterized by genes for binary toxin in addition to the genes for toxins A and B, polymorphisms in *tcdC* gene, a negative regulator of toxins A and B, as well as high-level fluoroquinolone resistance (25). This strain has been recovered from patients in at least 40 US states, multiple countries in Europe, as well as in Canada, and patients aged 60 to 90 years infected with this strain are twice as likely to die or have severe CDI compared to those infected with other strains (44). The virulence properties of this strain that are responsible for the increased disease severity as well as increased epidemic potential are not clear, but may include increased production of toxins A and B *(27)*, binary toxin production (25), increased sporulation potential *(89)*, and fluoroquinolone resistance (25).

Recent surveys of *C. difficile* isolates from patients with CDI in nonepidemic settings continue to show predominance of BI/NAP1/027 accounting for one-third of all isolates from North American subjects recruited to a large treatment trial conducted between 2005 and 2007 (90). Persistence of this epidemic strain is likely a major contributor to the increased incidence of CDI documented by hospital discharge diagnosis coding of patients in the United States since 2001 *(91)*.

Community-Associated CDI and Nontraditional Risk Populations

In 2005, reports of severe CDI among patients in the community without exposure to healthcare facilities (sometimes without antibiotic exposure) and reports of CDI in peripartum women and children highlighted concern that the epidemiology of CDI was expanding beyond traditional risk populations *(92)*. Community-associated CDI is well-documented, but many cases that are diagnosed in the community are associated with recent hospitalization. Chang et al. found that 78% of the CDI cases that were diagnosed in the clinic or emergency room of a large Veterans Affairs Health System were in-patients who had been recently discharged from the hospital and the antibiotic exposures were during the previous hospitalization (40). Kutty et al. also found many community-onset cases in North Carolina had recent hospitalizations, but they found higher rates of true community-associated CDI *(93)*. However, there is no suggestion of a community epidemic similar to that associated with the USA 300 strain of methicillin-resistant *S. aureus*. Cases of severe CDI among young, peripartum women and older children are well-documented, but other than age, the other traditional risk factors (hospital exposure and/or antibiotic exposure) are usually present.

Antimicrobial Use

Nearly all antibacterial agents given by either oral or parenteral routes have been associated with CDI. Historically, the most commonly implicated agents have been clindamycin, ampicillin, and cephalosporins *(7)*. The unique predisposition of patients treated with clindamycin has been repeatedly documented *(39,42,94,95)*. The mechanism of this unique propensity may be partially explained by the marked activity of clindamycin against anaerobic bacteria and a prolonged effect on the colonic flora. Clindamycin resistance was also a marker for *C. difficile* strains implicated in several CDI epidemics in the early 1990s *(94–96)*, and it was shown that clindamycin use was a specific risk factor for disease due to this highly clindamycin-resistant *C. difficile* strain, REA group J (97). Third-generation cephalosporins have been associated with CDI *(98)*, and studies have demonstrated a lower risk of CDI following treatment with ticarcillin/clavulanate or piperacillin/tazobactam than with ceftazidime or ceftriaxone *(99,100)*. Since 2000, fluoroquinolones have been recognized as a class of antimicrobials with a particularly high risk of CDI. Fluoroquinolones were the most frequently implicated antimicrobial associated with CDI during the multihospital outbreak in Quebec (26) as well as during recent outbreaks in the United States where BI/NAP1/027 was

predominant (101). Resistance to moxifloxacin and gatifloxacin was present in all of the epidemic BI/NAP1/027 isolates from recent US outbreaks, 42% of contemporary nonepidemic strains, and in none of the historic representatives of the BI strain (25). These data suggest that increasing fluoroquinolone use has facilitated dissemination of the once uncommon BI/NAP1/027 strain that has now developed high-level fluoroquinolone resistance.

Antimicrobial agents that are infrequently implicated include tetracycline, erythromycin, chloramphenicol, vancomycin, parenteral aminoglycosides, and metronidazole *(102)*. In addition, CDI can occur during or following antimicrobial therapy at any dosage, and cases have occurred after a few doses given for surgical prophylaxis *(103,104)*. However, prophylactic antimicrobials were not significantly associated with CDI in a prospective case-controlled study *(42)*.

Reservoirs and Modes of Transmission

Environmental Contamination Environmental surfaces contaminated with *C. difficile* spores are a potentially important source of healthcare-associated CDIs. The environment of patients with CDI is more frequently contaminated than the environment of other patients, and the degree of contamination has correlated with *C. difficile* outbreaks *(30,105,106,107)* as well as hands of healthcare workers caring for these patients *(96)*. Floors and bathroom sites tend to be most heavily contaminated *(108)*. In addition, commode chairs, sigmoidoscopes, bed pans, nursery baby baths, patient phones, and electronic thermometers have been found to be contaminated and can serve as reservoirs for healthcare-associated transmission of *C. difficile (109–111)*. Environmental contamination is highest around patients with active CDI, but skin and environmental contamination often persist following resolution of diarrhea (112). Although the environment of patients with CDI is heavily contaminated, the role of the environment in the transmission of *C. difficile* still needs clarification. Other potential modes of transmission, including airborne transmission *(113)* and foodborne transmission *(114)*, are as yet unproven.

Asymptomatic Patient Carriers Whenever patients with healthcare-associated CDI are identified, it can be assumed that higher numbers of asymptomatic *C. difficile* carriers (fecal excretors) are also on the same ward or in the same room *(8,30)*. Although these asymptomatic carriers are not at an increased risk for diarrhea themselves, they are potential reservoirs for infection in other susceptible patients *(8,9)*. Acquisition of *C. difficile* has been documented more frequently and earlier among patients exposed to roommates with positive cultures *(30)*. In one 9-month prospective surveillance study, healthcare-associated patient acquisitions of *C. difficile* were preceded by a documented introduction to that same ward of the identical REA-type strain by a newly admitted patient *(73)*. This sequence of events occurred in 16 (84%) of the 19 instances in which a specific *C. difficile* REA-type strain was isolated from more than one patient. These data suggest that asymptomatic carriers may be an important source of healthcare-associated CDIs.

Personnel Hand Carriage If either the environment or asymptomatic carriers are important sources of infections, *C. difficile* could be transmitted from those sources by direct contact or indirectly by the hands of patient care personnel. Hands are frequently contaminated with *C. difficile (30,106)*, and hand colonization rates as high as 59% after patient contact, which, in some instances, amounted to mere patient assessment and charting, have been documented *(30)*. Vinyl glove use by hospital personnel when handling body substances was also associated with a significant reduction in the incidence of CDI on acute care wards (101). Thus, direct and indirect evidence supports transient hand carriage by patient care personnel as a mode of *C. difficile* transmission.

Host Risk Factors

Before the etiology of PMC was elucidated, this disease was postulated to be an idiosyncratic host reaction to clindamycin. Since the role of *C. difficile* in antibiotic-associated diarrhea and colitis has been clarified, it is clear that CDIs frequently occur as outbreaks associated with unique strains *(8,100)*. However, the clinical manifestations and severity of CDIs are not solely attributable to specific *C. difficile* strains *(31)* but also depend on specific host factors.

Risks of Acquisition Asymptomatic fecal excretion is a more common outcome of infection with *C. difficile* than is diarrhea, and although antimicrobial exposure, the classic risk factor for CDI, has been associated with asymptomatic carriage *(8,42,115)*, this association is not as strong as it is with CDI *(116)*. Risk factors consistently associated with acquisition include advanced age, more severe underlying illnesses, and length of hospital stay *(8,116)*. Acquisition of *C. difficile* is highly correlated with the duration of hospital stay so that, by 4 weeks of hospitalization, 50% of previously uninfected patients may be culture-positive *(73,116)*. Stool softener and antacid use may also be risk factors for asymptomatic carriage *(116)*.

Risks of Illness Increased age, severe underlying illness, and length of hospital stay are the major risks for CDI *(30,42)*. Antimicrobials are highly associated with *C. difficile* disease. Clindamycin, multiple antimicrobials, and antimicrobials given for therapy rather than for prophylaxis have been significantly associated with CDI *(42)*. Failure to develop an anamnestic response to toxin A is a recognized risk factor for CDI (32,33). Shortly after exposure, serum antitoxin A immunoglobulin G levels predict subsequent clinical outcome (32). Asymptomatic carriers have higher levels than those who develop CDI, which may partially explain our previous observation that asymptomatic carriers are at decreased risk for subsequent CDI *(9)*. These antibody responses shortly after exposure also influence the risk of subsequent relapse among those who develop CDI (33).

Another repeated association with *C. difficile* disease has been the manipulation of the gastrointestinal tract by enemas, insertion of nasogastric and gastrostomy tubes, motility altering drugs such as atropine sulfate–diphenoxylate hydrochloride and codeine, and gastrointestinal surgery *(8,109,116)*. A well-controlled prospective cohort study

has demonstrated tube-feeding and, in particular, postpyloric administration as risk factors for acquiring *C. difficile* and developing CDI *(117)*. Insertion of nasogastric and gastrostomy tubes and enema administration may reflect increased contact with hospital personnel and with their potentially contaminated hands, which may be a partial explanation for these risk factors *(81)*.

CDI has also been reported in association with cancer chemotherapy, chronic renal disorders, HIV infection, and inflammatory bowel disease *(109,118)*. *C. difficile* has not been implicated as a cause of inflammatory bowel disease but may be responsible for some of the symptomatic relapses in patients with established inflammatory bowel disease *(119)*. Several recent studies have noted an association of proton pump inhibitor use with CDI, but this association is not consistent and, if validated, is likely much less important than antibiotic exposure (55,*120*). Also, for unknown reasons, women may have a higher rate of *C. difficile* disease than do men *(83)*.

PREVENTION AND CONTROL

No single infection control practice has effectively prevented and controlled healthcare-associated CDI. We postulate that CDI is at least a "three-hit" process that begins with (a) administration of antimicrobial or chemotherapeutic agents, (b) acquisition of the *C. difficile* microorganism, and (c) other factors such as the interaction with the host immune response that result in clinical illness in a minority of the large number of patients who both receive antimicrobials and acquire *C. difficile*. Prevention and control measures have focused largely on (a) interruption of the process of healthcare-associated microorganism acquisition and (b) measures to reduce the likelihood of clinical illness if a patient acquires *C. difficile*. The various interventive measures have been critiqued in terms of established evidence of benefit (Table 37-2). Clinical practice guidelines for prevention and control of CDI have recently been updated by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) (56).

Prevention of Acquisition of *C. difficile*

Barrier Precautions Cohorting, patient isolation, hand washing, and glove use are included under barrier techniques. A number of studies indirectly suggest that person-to-person spread of *C. difficile* occurs in the hospital, either from patient to patient or from personnel to patient. Hands of personnel are frequently contaminated with *C. difficile (30,42,121,138)*, and a prospective controlled trial has shown that vinyl glove use by hospital personnel

TABLE 37-2

Infection Control Practices to Prevent Healthcare-Acquired *Clostridium difficile*–Associated Disease

Practice	*Efficacy*	*Reference*
Barrier precautions		
Glove use when handling body substances	Proven	*121*
Hand washing before treating each patient	Probable	*122*
Isolation precautions and cohorting	Probable	*80*, *123–125*
Environmental cleaning and disinfection		
Rectal thermometers		
Substitution of disposables	Proven	*111*
Switch to tympanic thermometers	Proven	*126*
Gastrointestinal endoscopes	Accepted	*127*, *128*
Hypochlorite disinfection of patient rooms	Probable	*108*, *129–131*
Identification and management of asymptomatic carriers		
Vancomycin treatment of asymptomatic carriers	Possible	*36*, *132*
Metronidazole treatment of asymptomatic carriers	Ineffective	*36*, *124*
Isolation or cohorting of asymptomatic carriers	Untested	
Measures to reduce the risk of symptomatic disease		
Antimicrobial use restriction		
Clindamycin	Proven	*94*, *95*, *125*
Cefotaxime (switch to piperacillin/tazobactam)	Probable	*100*
Gatifloxacin	Possible	*133*
Moxifloxacin	Ineffective	*134*
All fluoroquinolones	Possible	*135*
Prophylaxis agents for patients receiving antimicrobials		
Saccharomyces boulardii	Possible	*136*
Actimel (yogurt drink)	Possible	*137*
Orally administered antibodies	Untested	
Colonization with nontoxigenic *C. difficile*	Untested	
Toxoid vaccination	Untested	

when contacting patient body substances was effective in interrupting transmission *(121)*. CDI rates declined from 7.7/1,000 patient discharges to 1.5/1,000 ($p = .015$) after glove use was instituted, whereas control wards in the same institution showed no significant change in rates. Hand washing following patient or body substance contact should also be an effective way to interrupt transmission via the hands of personnel, although the efficacy of soap in removing *C. difficile* from hands was questioned in one study, whereas chlorhexidine appeared effective *(30)*. Both agents were equally effective in removing seeded *C. difficile* from the hands of volunteers *(122)*. The widespread introduction of waterless alcohol-based hand hygiene products (that are not sporicidal) has raised concern about the effect on healthcare-associated transmission of *C. difficile*. Although introduction of alcohol hand gels have not been associated with increased healthcare-associated CDI rates *(139)*, these agents are not effective in removal of *C. difficile* spores from hands (140,141), and in the setting of an outbreak, consideration should be given to institution of hand washing with soap after care of patients with CDI.

The difficulty in implementing isolation techniques (private rooms, enteric isolation, cohorting) in the control of *C. difficile* transmission is that they cannot be employed rapidly (unless patients are isolated before infection is identified). Assessment of efficacy is difficult, because isolation methods frequently are not employed alone as control measures *(123–125)*. Whereas hand washing and glove use can be employed in the care of all patients, isolation techniques are directed at those patients who have been identified as infected. These patients are almost always symptomatic with diarrhea and have been diagnosed with CDI prior to being isolated. Aggressive patient identification and rapid isolation were employed by Struelens et al. *(80)* and were associated with a reduction in the rate of *C. difficile* cases from 1.5/1,000 to 0.3/1,000 admissions. However, patients were treated early with vancomycin and the environment was disinfected with formaldehyde and glutaraldehyde, making the contribution of isolation impossible to discern. Current SHEA/IDSA recommendations include placement of patients with CDI in private rooms with Contact Precautions or cohorting patients with a dedicated commode if private rooms are not available (56), although this was a C-III level recommendation.

Environmental Cleaning and Disinfection Numerous environmental sites and devices have been shown to be contaminated with *C. difficile (105,106)*. The rate of room contamination is proportional to the status of the patient in the room: highest for patients with CDI, intermediate for patients with asymptomatic *C. difficile* colonization, and lowest for patients without the microorganism *(30)*. Spread of *C. difficile* has been linked to contaminated environmental devices including commodes, electronic rectal thermometer handles, and baby baths *(28,142,143)*. Replacement of contaminated electronic thermometers with disposable thermometers *(111)* and subsequent replacement of all disposable thermometers (rectal and oral) with tympanic thermometers *(126)* showed a reduced incidence of CDIs. Flexible sigmoidoscopes and colonoscopes are frequently contaminated by *C. difficile* microorganisms following endoscopy in patients with CDI *(127)*. The potential for spread of *C. difficile* by contaminated endoscopes is real but has not been documented. The presently recommended regimen of endoscopic cleaning and disinfection with 2% glutaraldehyde immersion for as short a time as 10 minutes is sporicidal for *C. difficile (127,128)* and should adequately prevent transmission via endoscopes, provided the procedures are reliably followed.

Contamination of the patient's environment can be reduced significantly by employing a sporicidal disinfectant such as unbuffered hypochlorite solution (500 ppm available chloride), phosphate buffered hypochlorite (1,600 ppm chloride), or a combination of 0.04% formaldehyde and 0.03% glutaraldehyde (*108,125*). Three additional studies have documented reduced CDI rates on wards where hypochlorite environmental disinfection was introduced, but the results have not been uniformly effective and effectiveness of this intervention may be confounded by additional factors *(129–131)*. Wilcox et al. used a chlorine-containing agent (1,000 ppm available chlorine) in a cross-over study and showed a correlation with reduced CDI incidence on one of two wards *(130)*. Mayfield et al. used a hypochlorite-based solution (5,000 ppm available chlorine) and showed an effect of decreased CDI rates on one of three wards *(129)*. The ward with decreased rates was also the ward with the highest baseline rate of CDI. Newer technologies using vaporized hydrogen peroxide *(144)* and ultraviolet-C radiation *(145)* delivered by mobile devices in vacated patient rooms show promise for environmental decontamination, but additional issues of cost and practicality need further study.

Identification and Treatment of Asymptomatic C. difficile Carriers Asymptomatic patient carriers of *C. difficile* are a potential source of spread of the microorganism to other susceptible patients via contamination of the environment or the hands of personnel *(73,132)*. Although there is a decreased risk of CDI in the carriers themselves, they may be a source of transmission to other patients *(8)*. Identification of asymptomatic carriers requires extensive stool and/or rectal swab culturing, which is labor intensive for both infection control and laboratory personnel. The appropriate action following carrier identification is unknown *(73)*. No one has attempted a study of carrier isolation or cohorting. Intervention studies that involved treatment of asymptomatic colonized patients with metronidazole or vancomycin were ineffective *(124)*, inconclusive *(146)*, or the potential effect was confounded by other simultaneous interventions *(132)*. A randomized study that attempted to eradicate colonization found that whereas vancomycin was temporarily effective, treated patients were more likely to be colonized at the end of follow-up than were placebo-treated control patients *(36)*. Metronidazole treatment results were no different that placebo. Thus, whether to and how to address the asymptomatic colonized patient remains unresolved.

Reducing Risk of Clinical Illness

Antimicrobial Restriction Prior exposure to antimicrobials is virtually universal in patients who develop symptomatic *C. difficile* disease. Risk of CDI is increased for specific antimicrobials such as ampicillin, amoxicillin, clindamycin, cephalosporins, and fluoroquinolones (26,*42,147*). Risk is

higher if multiple antibiotics are administered, if the number of doses or days of therapy is higher, and if antimicrobials are administered to treat an infection rather than for prophylaxis (*42*,*94*,*116*,*125*). These observations suggest the opportunity to reduce *C. difficile* disease risk by reducing exposure and duration of antimicrobial therapy. There are three examples of a restricted clindamycin use policy that have reduced CDI rates *(94*,*95*,*125)*. In one instance, this intervention stopped an extended outbreak within a month of implementation *(94)*. Subsequent investigation showed that this outbreak was due to a highly clindamycin-resistant epidemic strain and that clindamycin use was a risk factor (97). The most convincing intervention strategy for cephalosporin restriction was a prospective, ward-based, crossover study replacing empiric cefotaxime therapy with piperacillin/tazobactam *(100)*. Piperacillin/tazobactam use was associated with a lower incidence of colonization and CDI; rates increased when cefotaxime was reintroduced. More environmental contamination was also documented during cefotaxime use.

Considering the strong association of fluoroquinolone use and recent outbreaks of the BI/NAP1/027 strain, the effect of fluoroquinolone restriction has been studied by several investigators *(133–135*,*148)*. Two studies have looked at the effect of "with-in-class" formulary switches of fluoroquinolone agents after documenting increased CDI rates when switching from levofloxacin to a newer fluoroquinolone. The first study noted a decrease in CDI rates when they switched back to levofloxacin from gatifloxacin in their long-term care facility *(133)*, whereas the second study did not see a decrease when they switched back to levofloxacin from moxifloxacin at their community hospital *(134)*. There is one study in which all fluoroquinolones were temporarily restricted and where decreased CDI rates were seen, but this study was somewhat confounded by a change in the environmental services contractor shortly after implementation of the antibiotic intervention *(135)*. Finally, reduction in the overall antimicrobial use was effective in controlling an outbreak in a Montreal hospital due to BI/NAP1/027 *(148)*.

Prophylactic Measures for Patients Receiving Antimicrobials Although as yet unproven, the hypothesis that patients receiving antimicrobials can be treated effectively with a prophylactic agent that will prevent CDI is an attractive one. Probiotics, orally administered antibodies, and active vaccination have been proposed as preventive agents *(136*,*137*,*149–151)*. *Saccharomyces boulardii* has been used in humans and was found to reduce antibiotic-associated diarrhea significantly ($p = .038$) when given during and for 2 weeks after antibiotic administration. CDI was also reduced, but this was not statistically significant ($p = .07$) *(136)*. A subsequent study failed to show efficacy of *S. boulardii* in elderly hospitalized patients receiving antibiotics *(150)*. There is one report of a randomized study in which a yoghurt drink was given to patients taking antibiotics and a decreased rate of both antibiotic-associated diarrhea and CDI was noted in the group taking yoghurt *(137)*. This study has been criticized because of several methodological issues including exclusion of patients with "high-risk" antibiotics and further study is needed to confirm these findings.

Whey protein in immunized cow's milk containing high levels of secretory IgA has been used in a trial of CDI recurrence prevention, but the results are inconclusive and the study was open label and uncontrolled *(149)*. Lactobacilli in yogurt and acidophilus milk have been used to reduce diarrheal side effects of antibiotics and to treat relapsing CDI, but efficacy remains questionable. A novel approach that has been highly successful in the hamster model and is undergoing phase I studies in humans involves colonization with nontoxigenic strains of *C. difficile* to prevent CDI *(151)*. A toxoid vaccine is currently undergoing phase II studies in prevention of CDI recurrences, but results are not yet available. No data are available as yet for whey protein, lactobacilli, nontoxigenic *C. difficile*, and vaccination use in the prevention of CDI.

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PART B. Mycobacterial Infections

CHAPTER 38

Mycobacterium tuberculosis

William R. Jarvis

Tuberculosis (TB) is a major global health problem. Worldwide, an estimated 8 million new cases occur each year and 2 million deaths are attributed to this disease annually *(1)*. TB case rates in the United States have been decreasing since the most recent peak in cases in 1992, but an increasing number of TB outbreaks in institutional settings, including hospitals, have been noted. Of greatest concern are outbreaks due to microorganisms resistant to multiple anti-TB drugs *(2)*.

THE ETIOLOGIC AGENT

Tuberculosis is caused by bacteria of the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, *M. bovis*, *M. bovis* [bacille Calmette Guérin (BCG)], *M. africanum*, and *M. microti*. *M. tuberculosis* is by far the most frequent and most important pathogen in this complex. It grows slowly and usually is identified by its rough, nonpigmented, corded colonies on oleic acid albumin agar; a positive niacin test; generally weak catalase activity, which is lost completely by heating to 68°C; and a positive nitrate reduction test. *M. bovis* is indistinguishable from *M. tuberculosis* except by culture followed by *in vitro* tests, restriction fragment length polymorphism (RFLP), or phage typing *(3,4)*.

MODE OF TRANSMISSION

M. tuberculosis is carried in airborne droplet nuclei, which are produced when persons with pulmonary or laryngeal TB cough, sneeze, speak, or sing. The nuclei also can be produced by irrigation or manipulation of tuberculous lesions (e.g., wounds) or processing of tissue or secretions in the hospital or laboratory. Droplet nuclei are so small (1–5 μm) and light that ambient air currents can keep them airborne for long periods of time and carry them substantial distances. Persons who breathe air contaminated with infectious *M. tuberculosis* droplet nuclei may inhale microorganisms into the alveoli of the lungs and become infected. The risk of infection is correlated with the concentration of infectious droplet nuclei in the air and the duration of exposure to the contaminated air. Airborne transmission of *M. bovis* also can occur.

PATHOGENESIS OF TUBERCULOSIS

Once tubercle bacilli become implanted in a respiratory bronchiole or alveolus, they are engulfed by macrophages, but they can remain viable and even multiply within the cells. Then, tubercle bacilli are spread via the lymphatic channels to regional lymph nodes and via the bloodstream to more distant sites. A specific cell-mediated immune response, which usually develops several weeks after infection, may limit further multiplication of the bacilli; the lesions heal, although the tubercle bacilli may remain viable. This results in a condition known as latent *M. tuberculosis* infection (LTBI), in which the person is asymptomatic and noncontagious. Bacilli deposited in some sites, for example, upper lung zones, kidneys, bones, or brain, may find an environment favorable for growth before specific immunity develops and limits multiplication. Hypersensitivity to *M. tuberculosis* components, as demonstrated by the development of a positive reaction to the tuberculin skin test (TST), develops 2 to 10 weeks after the initial infection.

At any point after this first infection, tubercle bacilli that have spread through the body may begin to replicate and produce active disease. In approximately 5% of all *M. tuberculosis*-infected persons, disease occurs within 1 year of infection. In another 5%, containment of the infection fails at a later time and *M. tuberculosis* active disease results. The most common site for this reactivation of *M. tuberculosis* infection is the upper lung zone, but foci anywhere in the body can be the sites of disease. The ability of the host to contain the infection is reduced by certain diseases, especially human immunodeficiency virus (HIV) infection, silicosis, or diabetes mellitus, and by treatment

with corticosteroids or other immunosuppressive drugs. In these circumstances, the likelihood of TB developing can be >10% per year *(5)*. For persons with LTBI, the risk of progressing to active TB is greatly reduced in persons with drug-susceptible strains by LTBI preventive therapy (e.g., isoniazid or rifampin).

CLINICAL FEATURES

Early symptoms of TB include fatigue, anorexia, weight loss, or low-grade fever. However, a few patients may present with an acute febrile illness. Erythema nodosum may occur with the acute onset of TB.

Pulmonary TB is the most common form of the disease and the most important from the perspective of hospital infection control. In pulmonary TB, there is insidious onset of cough, which usually progresses slowly over weeks to months to become more frequent and associated with the production of mucoid or mucopurulent sputum. Hemoptysis also may occur. Some patients present with the acute onset of productive cough, fever, chills, myalgia, and sweating similar to the signs and symptoms of influenza, acute bronchitis, or pneumonia. Hoarseness or a sore throat may suggest tuberculous laryngitis. Laryngeal involvement usually is associated with extensive pulmonary involvement, a large number of microorganisms in the sputum, and a very high degree of contagiousness. Physical findings of pulmonary TB may include crackles or signs of lung consolidation.

The infectiousness of a TB patient correlates with the number of microorganisms expelled into the air; this correlates with the site of disease (i.e., pulmonary, laryngeal, tracheal, or endobronchial TB being the most infectious), the presence of cough (or performance of cough-inducing procedures), the presence of acid-fast bacilli (AFB) on sputum smears, the presence of cavitation on chest radiograph, the duration of adequate chemotherapy, and the ability or willingness of the patient to cover his/her mouth when coughing.

Other clinical manifestations of the disease include tuberculous pleuritis, hematogenous dissemination (miliary TB), genitourinary tract TB, TB of the lymph nodes, skeletal TB, tuberculous meningitis, tuberculous peritonitis, or tuberculous pericarditis.

In addition to these sites, there are many other potential body sites where TB may occur less commonly. TB in most of these extrapulmonary sites, without pulmonary or laryngeal involvement, usually is not contagious. However, irrigation or other manipulation of tuberculous lesions can produce infectious droplet nuclei and result in transmission of *M. tuberculosis*, as can laboratory processing of specimens that contain *M. tuberculosis*. Standard textbooks can be consulted for information on disease at these sites.

DIAGNOSIS

Radiography

In patients who have signs or symptoms suggesting pulmonary or pleural TB, standard anterior–posterior and lateral radiographs of the chest should be obtained. Special imaging techniques, for example, computed tomography or magnetic resonance imaging, may be of value in defining nodules, cavities, cysts, calcifications, contours of large bronchi, or vascular details in lung parenchyma.

The radiographic manifestation of initial infection in the lung, whether in a child or an adult, usually is parenchymal infiltration accompanied by ipsilateral lymph node enlargement. The parenchymal lesion may be detected at any stage of development and in any portion of the lung, or it may be too small to be seen on the radiograph.

In adults with progression from LTBI to active TB disease, the common presentation is lesions in the apical and the posterior segments of the upper lobes or in the superior segments of the lower lobes. However, lesions may appear in any segment. Cavitation is common except in immunocompromised patients. Other findings include atelectasis or fibrotic scarring with retraction of the hilus and deviation of the trachea. Rarely, patients with pulmonary TB may present with normal chest radiographs, particularly patients with HIV infection or other conditions associated with severe cell-mediated immunosuppression.

Hematogenous TB is characterized by diffuse, finely nodular, uniformly distributed lesions on the chest radiograph. The word *miliary* is applied to this appearance because the nodules are about the size of millet seeds (~2 mm in diameter). Unilateral or, rarely, bilateral pleural effusion usually is the only radiographic abnormality evident with pleural TB.

Laboratory Procedures

The identification of *M. tuberculosis* microorganisms is of great importance for diagnosing TB. Therefore, careful attention should be given to the collection and handling of specimens. Specimens should be transported to the laboratory and processed as soon as possible after collection.

Because TB may occur in almost any body site, a variety of specimens may be appropriate to collect, including sputum (natural or induced), bronchial washings or biopsy material, gastric aspirates, urine, cerebrospinal fluid, pleural fluid, pus, endometrial scrapings, bone marrow biopsy, or other biopsy or resected tissue. All of these materials should be stained and examined by microscopy for the presence of AFB and should be cultured for mycobacteria.

The detection of AFB in stained smears is the easiest and quickest procedure that can be performed, and it provides preliminary support for the diagnosis. Also, the smear is of importance in assessing the patient's degree of infectiousness. The use of fluorescence microscopy allows the smears to be read much more rapidly than does standard microscopy. If necessary for confirmation, smears stained for fluorescence microscopy can be overstained and examined by standard light microscopy under an oil immersion lens.

All specimens from patients suspected of having *M. tuberculosis* disease should be inoculated (after appropriate digestion and decontamination, if required) onto appropriate culture media, such as Lowenstein-Jensen or Middlebrook 7H10. Nucleic acid amplification (NAA) testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.

Genotyping, or DNA fingerprinting, of *M. tuberculosis* is used to determine the clonality of bacterial cultures. Because this technology is useful for studying the molecular epidemiology of *M. tuberculosis* and investigating outbreaks, the Centers for Disease Control and Prevention (CDC) established a National TB Genotyping and Surveillance Network in the 1990s. This diagnostic technique in conjunction with traditional epidemiologic methods has enhanced TB surveillance and control programs *(6)* and has been instrumental in the identification of several pseudo-outbreaks of active TB caused by laboratory cross-contamination of sputum samples from patients without clinical signs of TB *(7–10)*.

Drug-Susceptibility Testing

The initial isolate from all patients with positive cultures for *M. tuberculosis* should be tested for susceptibility to anti-TB drugs. Drug-susceptibility tests for *M. tuberculosis* are important for choosing the most effective treatment regimen. The laboratory should report to the clinician the amount of growth on drug-containing medium as compared with growth on drug-free control medium. By counting the colonies on the drug-containing medium and on the control medium, the proportion of resistant cells in the total population can be calculated and expressed as a percentage. Generally, when ≥1% of a bacillary population become resistant to the critical concentration of a drug, then that agent is not, or soon will not be, useful for continued therapy, because the resistant population will soon predominate. If broth culture is used, results are reported as resistant or susceptible, and no colony percentage is reported.

Newer Diagnostic Techniques

Radiometric Technology Compared with standard culture methods using solid media, radiometric culture methods, which employ a ^{14}C-labeled substrate medium that is almost specific for mycobacteria, provide much more rapid detection of growth and rapid drug-susceptibility testing. These automated broth culture systems using Middlebrook 7H12 media with added material for detection of mycobacteria can detect growth in 1 to 3 weeks, compared to 3 to 8 weeks for solid media. However, at least one container of solid culture media should be used in conjunction with broth culture systems *(11)*. Combining radiometric culture with techniques for rapid species identification (e.g., genetic probes, high-performance liquid chromatography, or monoclonal antibodies) can further shorten the time required for species identification.

Genetic Probes Genetic probes offer tremendous promise for providing rapid identification. One such probe, an NAA test (Gen-Probe, San Diego, CA), has been approved by the U.S. Food and Drug Administration (FDA) for detection of *M. tuberculosis* in AFB smear-positive or smear-negative respiratory specimens in patients suspected of having TB. Another NAA test (Amplicor, Roche Diagnostic Systems, Branchburg, NJ) is approved by the FDA only for use on AFB smear-positive respiratory specimens. Interpret NAA test results in correlation with the AFB smear results (12). If the NAA result is positive and the AFB smear result is positive, presume the patient has TB and begin anti-TB treatment while awaiting culture results. The positive predictive value of FDA-approved NAA tests for TB is >95% in AFB smear-positive cases. If the NAA result is positive and the AFB smear result is negative, use clinical judgment whether to begin anti-TB treatment while awaiting culture results and determine if additional diagnostic testing is needed. Consider testing an additional specimen using NAA to confirm the NAA result. A patient can be presumed to have TB, pending culture results, if two or more specimens are NAA positive. If the NAA result is negative and the AFB smear result is positive, a test for inhibitors should be performed and an additional specimen should be tested with NAA. Sputum specimens (3–7%) might contain inhibitors that prevent or reduce amplification and cause false-negative NAA results. If inhibitors are detected, the NAA test is of no diagnostic help for this specimen. Use clinical judgment to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic testing. If inhibitors are not detected, use clinical judgment to determine whether to begin anti-TB treatment while awaiting culture results and determine if additional diagnostic testing is needed. A patient can be presumed to have an infection with nontuberculous mycobacteria if a second specimen is smear positive and NAA negative and has no inhibitors detected. If the NAA result is negative and the AFB smear result is negative, use clinical judgment to determine whether to begin anti-TB treatment while awaiting results of culture and additional diagnostic tests. Currently available NAA tests are not sufficiently sensitive (detecting 50–80% of AFB smear-negative, culture-positive pulmonary TB cases) to exclude the diagnosis of TB in AFB smear-negative patients suspected to have TB. Probes specific for the genus *Mycobacterium*, the *M. tuberculosis* complex, and the two species *M. avium* and *M. intracellulare* are available.

Diagnosis of Latent Tuberculosis Infection

Tuberculin Skin Test The TST is the standard method available for identifying persons infected with *M. tuberculosis (11,13)*. Currently available TSTs remain substantially <100% sensitive and specific for detection of infection with *M. tuberculosis*. Some causes of false-negative reactions are shown in Table 38-1. False-positive reactions can be due to prior infection with other mycobacteria, BCG vaccination, or problems with the antigen. Anecdotal reports also have raised concern that different commercially available reagents produce different degrees of induration *(14)*; however, a large-scale study of the two reagents available in the United States revealed comparable specificity in people at low risk for *M. tuberculosis* infection *(15)*.

The intradermal administration of 0.1 mL purified protein derivative (PPD) tuberculin into the skin of the volar surface of the forearm (Mantoux technique) is the preferred method of performing the TST. Tests should be read by a trained health professional between 48 and 72 hours after injection. The basis of reading is the presence or the absence of induration, which should be measured transversely to the long axis of the forearm and recorded in millimeters.

The positive predictive value of the TST varies widely in relation to the prevalence of true *M. tuberculosis* infection in any given population; furthermore, as already noted, the

TABLE 38-1

Factors Causing Decreased Ability to Respond to Tuberculin Skin Tests

Factors related to the person being tested
Infections
Viral (measles, mumps, chicken pox, HIV)
Bacterial (typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming tuberculosis, tuberculous pleurisy)
Fungal (South American blastomycosis)
Live virus vaccination (measles, mumps, polio, varicella)
Metabolic derangements (chronic renal failure)
Low protein states (severe protein depletion, afibrinogenemia)
Diseases affecting lymphoid organs (Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis)
Drugs (corticosteroids and many other immunosuppressive agents)
Age (newborns, elderly patients)
Stress (surgery, burns, mental illness, graft-versus-host reactions)
Factors related to the tuberculin used
Improper storage (exposure to light and heat)
Improper dilutions
Chemical denaturation
Contamination
Adsorption (partially controlled by adding Tween 80)
Factors related to the method of administration
Injection of too little antigen
Subcutaneous injection
Delayed administration after drawing into syringe
Injection too close to other skin tests
Factors related to reading the test and recording results
Inexperienced reader
Conscious or unconscious bias
Error in recording

(From American Thoracic Society/CDC. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med* 2000;161:1376–1395, with permission.)

risk of progression to disease from LTBI varies according to the characteristics of the infected person *(11,13)*. Thus, to increase the likelihood that a positive test represents true infection with *M. tuberculosis* and to improve the benefit-to-risk ratio of preventive therapy, the cut point used for defining a positive TST is varied in different populations. A reaction ≥5 mm is considered positive in persons with HIV infection or severe immunosuppression, persons with close contacts of infectious TB cases, or persons with abnormal chest radiographs consistent with TB.

A reaction ≥10 mm is classified as positive in persons who do not meet the above criteria but who have other risk factors for TB. These would include (a) recent (≤5 years) immigrants from countries with a high prevalence of TB; (b) intravenous drug users; (c) residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, healthcare facilities, homeless shelters, or mental institutions); (d) persons with medical conditions that have been reported to increase the risk of TB (e.g., silicosis, gastrectomy, jejunoileal bypass, being ≥10% below ideal body weight, chronic renal failure, diabetes mellitus), some hematologic disorders (i.e., leukemias, lymphomas, or carcinomas of the head, neck, or lung); (e) mycobacteriology laboratory personnel; (f) children <4 years of age or infants, children, and adolescents exposed to adults in high-risk categories; and (g) other high-risk populations identified locally as having a relatively high incidence of TB.

A reaction of ≥15 mm is classified as positive in persons with no risk factors for TB.

The TST can be valuable for identifying persons newly infected with *M. tuberculosis* when repeated periodically in surveillance of tuberculin-negative persons likely to be exposed to TB (e.g., healthcare workers) *(13)*. However, there are special considerations in identifying newly infected persons.

First, there are unavoidable errors in even the most carefully performed tests. For this reason, small increases in reaction size may not be meaningful. For persons whose previous reaction was negative, an increase in reaction size of ≥10 mm in diameter within 2 years should be considered a TST conversion. Healthcare workers with some degree of TST induration as a result of nontuberculous mycobacterial infection or previous BCG vaccination have converted, if induration increases by ≥10 mm over previous tests. For healthcare workers at low risk of exposure with a history of a negative TST, an increase of 15 mm within a 2-year period may be more appropriate for defining a recent conversion. Converters should be considered newly infected with *M. tuberculosis* and strongly considered for preventive therapy *(11,16)*.

A second problem in identifying newly infected persons is the so-called booster phenomenon *(17)*. Repeated testing of uninfected persons does not sensitize them to tuberculin. However, delayed hypersensitivity to tuberculin, once it has been established by infection with any species of mycobacteria or by BCG vaccination, may gradually wane over the years, resulting in a TST reaction that is negative. The stimulus of this test may recall the immune reaction, which results in an increase in the size of the reaction to a subsequent test, sometimes causing an apparent conversion that is then interpreted as indicating new infection. The booster effect can be seen on a second test done as soon as a week after the initial stimulating test and the booster effect can persist for a year and perhaps longer.

When tuberculin skin testing of adults is to be repeated periodically, the initial use of a two-step testing procedure can reduce the likelihood of interpreting a boosted reaction as representing recent infection *(18)*. In two-step testing, an initial TST is performed. If the reaction to the first test is negative, a second test should be given 1 to 3 weeks later. If the reaction to the second of the initial two tests reaches the appropriate cut point for a positive result in the patient, this probably represents a boosted reaction. On the basis of this second test result, the person should be classified as being previously infected and managed accordingly. If the second test result remains below the appropriate cut point, the person is classified as being uninfected. A positive reaction to a third test (with an appropriate increase) in such a person, within the next

2 years, is likely to represent the occurrence of new infection with *M. tuberculosis* in the interval.

Whole-Blood Interferon-γ Release Assays In 2005, a new *in vitro* test, QuantiFERON-TB Gold (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia), received final approval from the FDA as an aid in diagnosing *M. tuberculosis* infection, including both LTBI and TB disease. This enzyme-linked immunosorbent assay test detects the release of interferon-gamma (IFN-γ) in fresh heparinized whole blood from sensitized persons when it is incubated with mixtures of synthetic peptides simulating two proteins present in *M. tuberculosis*: early secretory antigenic target-6 (ESAT-6) and culture filtrate protein-10 (CFP-10). ESAT-6 and CFP-10 are secreted by all *M. tuberculosis* and pathogenic *M. bovis* strains. Because these proteins are absent from all BCG vaccine strains and from commonly encountered nontuberculous mycobacteria except *M. kansasii*, *M. szulgai*, and *M. marinum*, QFT-G is expected to be more specific for *M. tuberculosis* than tests that use tuberculin PPD as the antigen. QFT-G represents one type of interferon-γ release assay (IGRA). Tests such as QFT-G measure the IFN-γ released by sensitized white blood cells after whole blood is incubated with antigen. Tests such as ELISpot enumerate cells releasing IFN-γ after mononuclear cells recovered from whole blood are incubated with similar antigens. Two IGRAs have been approved by FDA for use in the United States: the original QuantiFERON-TB test (QFT) and the recently approved QFT-G. The two tests use different antigens to stimulate IFN-γ release, different methods of measurement, and different approaches to test interpretation. QFT was approved as an aid for diagnosing LTBI, whereas QFT-G is approved as an aid for diagnosing both LTBI and TB disease. QFT is no longer commercially available.

Each of the three tests (TST, QFT, and QFT-G) relies on a different immune response and differs in its relative measures of sensitivity and specificity. The TST assesses *in vivo* delayed type hypersensitivity (Type IV), whereas QFT and QFT-G measure *in vitro* release of IFN-γ. The TST and the QFT measure response to PPD, a polyvalent antigenic mixture, whereas QFT-G measures response to a mixture of synthetic peptides simulating two specific antigenic proteins that are present in PPD. The IGRA is less likely to be concordant with the TST in persons with a history of BCG vaccination and in persons with immune reactivity to nontuberculous mycobacteria *(19)*. The advantages of the IGRA test are that it requires only one patient visit, does not boost immune response like the TST, and is less subject to reader bias and error. Its disadvantages are that it requires phlebotomy, processing within 12 hours, and 16 to 24 hours of incubation.

QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of healthcare workers and others undergoing serial evaluation for *M. tuberculosis* infection. QFT-G usually can be used in place of (and not in addition to) the TST. A positive QFT-G result should prompt the same public health and medical interventions as a positive TST result. No reason exists to follow a positive QFT-G result with a TST. Persons who have a positive QFT-G result, regardless of symptoms or signs, should be evaluated for TB disease before LTBI is diagnosed. At a minimum, a chest radiograph should be examined for abnormalities consistent with TB disease. Additional medical evaluation would depend on clinical judgment on the basis of findings from history (including exposure to infectious TB), physical examination, and chest radiography. HIV counseling, testing, and referral is recommended, because HIV infection increases the suspicion for TB and the urgency of treating LTBI. After TB has been excluded, treatment of LTBI should be considered.

The majority of healthy adults who have negative QFT-G results are unlikely to have *M. tuberculosis* infection and do not require further evaluation. However, for persons with recent contact with persons who have infectious TB, negative QFT-G results should be confirmed with a repeat test performed 8 to 10 weeks after the end of exposure, as is recommended for a negative TST result. The CDC guidelines for use and interpretation of the interferon-γ test are listed in Table 38-2 (20).

GENERAL EPIDEMIOLOGY OF TUBERCULOSIS IN THE UNITED STATES

In the United States, TB affects certain segments of the population disproportionately because the factors that affect the likelihood of exposure to and infection with *M. tuberculosis* and the likelihood of progression from LTBI to disease are not homogeneously distributed throughout the population.

For 2008, 12,898 episodes of TB were reported to the CDC, reflecting a rate of 4.2 cases per 100,000 population *(21)*. This represents the 16th consecutive year that TB cases declined and the lowest rate recorded since national reporting began in 1953. However, the rate of decline has slowed; an average of 7.3% decline from 1993–2000 to 3.8% during 2000–2008. In 2008, the largest declines occurred in persons ≥65 years and older (from 17.7 per 100,000 in 1993 to 6.4 in 2008), in adults aged 45 to 64 years (from 12.4 to 5.0), in adults aged 25 to 44 years (from 11.5 to 5.1), and in children <15 years of age (from 2.9 to 1.3), each group having decreased more than 50% *(22)*. The rate declined by 32% in those 15 to 24 years of age (from 5.0 to 3.4). Six percent were children <15 years of age, 11% were age 15 to 24, 33% were age 25 to 44, 30% were age 45 to 64, and 19% were ≥65 years old.

The overall national trend reflects the impact of changes within population subgroups. Of the 12,824 incident cases of known origin, 5,283 (41.2%) were U.S. born and 7,541 (58.8%) were foreign born. From 1993 to 2008, there was a 72.6% decline in TB cases among U.S.-born persons of all age groups to a rate of 2.0 per 100,000 population. Among foreign-born persons in the United States, both the number and the rate of TB declined, 3.9% compared to 2007 and 69.7% compared to 1993; the 2008 rate was 20.2 per 100,000 population—a 2.6% decline from 2007 and a 40.6% decline since 1993. In 2008, four countries accounted for approximately half (50.1%) of foreign-born TB cases: Mexico (1,742), the Philippines (855), India (598), and Vietnam (580). U.S.-born non-Hispanic Blacks comprised the largest number of TB cases among US born (42.2%; 2,227/5,283).

TABLE 38-2

Interpretation of QFT-G[a] Results, from IFN-γ[b] Concentrations in Test Samples

ESAT-6–Nil[c] or CPF-10–Nil[d] or Both	*Nil*	*Mitogen–Nil[e]*	*QFT-G Result*	*Interpretation*
≥0.35 IU/mL[f] and >50% above nil	Any	Any	Positive	*Mycobacterium tuberculosis* infection likely
<0.35 IU/ml	≤0.7	≥0.5	Negative	*M. tuberculosis* infection unlikely but cannot be excluded especially when illness is consistent with TB[g] disease and likelihood of progression to TB disease is increased
<0.35 IU/mL	Any	<0.5	Indeterminate	QFT-G results cannot be interpreted as a result of low mitogen response
≤50% above nil	>0.7	any	Indeterminate	QFT-G results cannot be interpreted as a result of high background response

[a]QuantiFERON TB Gold test.
[b]Interferon-gamma.
[c]The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating early secretory antigenic target–6 (ESAT-6) minus the IFN-γ concentration in blood incubated with saline.
[d]The IFN-γ concentration in blood incubated with a mixture of synthetic peptides simulating culture filtrate protein–10 (CFP-10) minus the IFN-γ concentration in blood incubated with saline.
[e]IFN-γ concentration in blood incubated with mitogen minus the IFN-γ concentration in blood incubated with saline.
[f]International units per mL.
[g]Tuberculosis.
(From Centers for Disease Control and Prevention. Guidelines for using the QuantiFERON®-TB test for diagnosis of latent *Mycobacterium tuberculosis* infection. *MMWR Recomm Rep* 2003;52(RR-2):15–18.)

The geographic distribution of TB in the U.S. also is not homogeneous. In 2008, four states (California, Florida, New York, and Texas) reported approximately half (49.2%) of all TB cases and each reported >500 cases each. However, by 2008, 35 states had met the Advisory Council for TB Elimination interim goal of ≤3.5 cases/100,000 population. Cases of TB remained concentrated in urban areas: in 2001, 39% of TB cases were reported from 64 major cities *(23)*.

A total of 125 cases of multidrug-resistant TB (MDR-TB) were reported in 2007, the most recent year with complete drug-susceptibility testing data. Of those with drug-susceptibility results in 2006 and 2007, 97.4 (10,477/10,762) were susceptible to isoniazid and 97.8% (10,190/10,421) to rifampin. The percentage of TB cases that were MDR-TB for 2007 (1.2%; 125/10,190) was similar to that of 2006 (1.2%; 124/10,477). The percentage of MDR-TB cases among persons without a previous history of TB has remained stable at approximately 1.0% since 1997. In 2007, the percentage of MDR-TB cases among persons with a previous history of TB was 3.6%. In 2007, MDR-TB continued to disproportionately affect foreign-born persons, who accounted for 81.6% of MDR-TB cases. Foreign-born persons had a higher percentage of MDR-TB, both among those with (5.2%) and without (1.5%) a previous history of TB. Cases of extensively drug-resistant TB (XDR-TB) have been reported every year in the United States except 2003 since drug-susceptibility reporting began in 1993. Four XDR-TB cases were reported in 2006 and two in 2007. Provisional data indicated that four XDR-TB cases were reported in 2008.

Data on the HIV status of persons with TB reported to the national TB surveillance system at the CDC are limited. Reporting of HIV status has improved slowly since 1993, the year such information was first included on TB case reports submitted to the CDC. In 2001, 3,254/5,630 (58%) TB case reports for persons aged 25 to 44 years included information about HIV status *(22)*. In 2001, 26 states reported HIV test results for at least 75% of cases in persons in this age group. Of these 26 states, the percentage of TB cases in persons aged 25 to 44 years who were coinfected with HIV ranged from 0% (New Hampshire, South Dakota, and Wyoming) to >39% (District of Columbia and Florida). To help estimate the proportion of reported TB cases coinfected with HIV, state health departments have compared TB and acquired immunodeficiency syndrome (AIDS) registries. During 1993 to 1994, 14% of all TB cases (27% of cases in persons aged 25–44 years) had a match in the AIDS registry *(24)*. In 2008, among 7,625 persons with TB with a known HIV test result, 802 (10.5%) were infected with HIV. California, Michigan, and Vermont data were not available for this calculation. In 2007, excluding California and Vermont, among 8,289 persons with TB and an HIV test, 884 (10.7%) were infected with HIV *(21)*.

From 1953, when national reporting of incident TB cases was first fully implemented in the U.S., through 1984, the number of cases reported to the CDC decreased from 84,304 to 22,255. This average annual decline of 5% to 6% was interrupted only by a transient increase in 1980, which was attributed to cases arising from a large influx of refugees from Southeast Asia *(25)*. Between 1984 and 1992, there was a dramatic reversal of the long-standing decline in the number of TB cases.

From 1985 through 1992, reported cases increased 20.1%, from 22,201 to 26,673. Based on an extrapolation of the trend in cases observed from 1980 through 1984, approximately 52,000 excess cases of TB were reported to the CDC from 1985 through 1992 *(26)*.

Increases in the number of cases in the late 1980s were mainly due to the HIV/AIDS epidemic and the emergence of MDR-TB. Other contributing factors include (a) an increase in the number of cases occurring in persons who immigrate to the United States from areas of the world that have a high prevalence of TB; and (b) an increase in active transmission of *M. tuberculosis* caused largely by adverse social conditions and an inadequate healthcare infrastructure *(26)*.

The decline in the overall number of reported TB cases and in the level of MDR-TB since 1992 has been attributed to stronger TB controls that emphasize prompt identification of persons with TB, initiation of appropriate therapy, and ensuring completion of therapy. The declining TB trend among US-born persons reflects the reduction of community transmission of *M. tuberculosis*, particularly in areas with a high incidence of HIV *(27)*. In comparison, the relatively stable number of reported cases of TB among foreign-born persons indicates that most cases of active TB disease among foreign-born persons residing in the United States results from infection with *M. tuberculosis* in the person's country of birth (28). The CDC, in collaboration with state and local health departments, continues to focus on its comprehensive plan to reduce active TB disease among foreign-born persons residing in the United States. This plan includes strategies to (a) improve case finding and completion of therapy, (b) conduct contact investigations, (c) screen those at high risk for infection, and (d) ensure completion of preventive therapy in eligible candidates *(29)*.

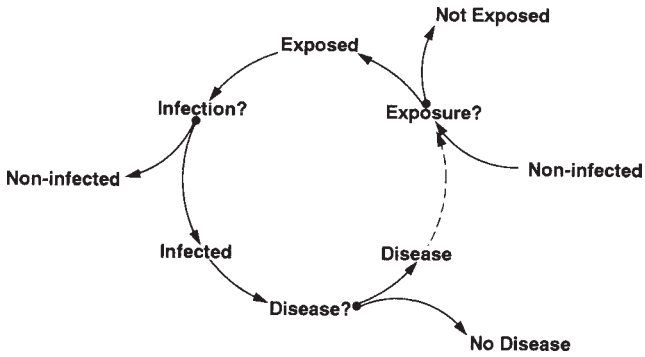

FIGURE 38-1 Schematic illustration of the steps involved in the acquisition of tuberculous infection and the development of active tuberculosis.

EPIDEMIOLOGY OF HEALTHCARE-ASSOCIATED TUBERCULOSIS IN THE UNITED STATES

Factors Influencing the Epidemiology of Healthcare-Associated Tuberculosis

The factors that influence the epidemiology of healthcare-associated TB are the joint probabilities that exposure to *M. tuberculosis* will occur, exposure will result in infection, and infection will lead to active TB (Fig. 38-1). In a healthcare facility, the likelihood of exposure to *M. tuberculosis* may be affected by factors such as the prevalence of infectious TB in the population served by the facility; the degree of crowding in the facility; the effectiveness of the facility's TB infection control program in rapidly identifying, isolating, and treating persons with infectious TB; and the effectiveness of engineering controls, such as directional airflow and booths for cough-inducing procedures, in preventing the spread of contaminated air throughout the facility.

Factors that may affect the likelihood that exposure to *M. tuberculosis* will result in infection are largely related to the effectiveness of the facility's infection control program. These factors include the effectiveness of the program in identifying and successfully treating persons with infectious TB, thereby rendering them noninfectious; the effectiveness of engineering controls, such as ventilation and ultraviolet germicidal irradiation (UVGI), in reducing the concentration of infectious droplet nuclei in the air; and the effectiveness of the respiratory protection program in preventing the inhalation of infectious droplet nuclei. Additionally, although supporting data are lacking, it is possible that medical conditions that cause severe suppression of cell-mediated immunity may increase susceptibility to infection with *M. tuberculosis*; thus, the prevalence of such conditions, either in patients or healthcare workers, may affect the likelihood that exposure of these persons will result in infection.

Factors that are likely to influence the risk that infection with *M. tuberculosis* will result in progression to active TB probably include the prevalence in the facility's patient and healthcare worker population of medical conditions that increase the likelihood of progression from LTBI to active disease (e.g., HIV infection). In addition, the infection control program's effectiveness in identifying persons who have been exposed and infected and providing them with appropriate preventive therapy is likely to influence the likelihood of progression to active disease. Events or conditions that alter any of these probabilities (the probability of exposure, infection, or progression to active TB) may result in changes in the epidemiology of TB in a healthcare facility.

Several types of information may be considered in describing the epidemiology of healthcare-associated TB. These include surveillance for active TB in healthcare workers, surveillance for LTBI (i.e., TST conversions or IGRA-positive) in healthcare workers, and reports of episodes of healthcare-associated *M. tuberculosis* transmission (such as reports of outbreaks).

Surveillance for Active Tuberculosis in Healthcare Workers

There are very few national data on the recent or current risk of active TB in healthcare workers. Information on the occupation of persons with TB was not collected in the national TB surveillance system until 1993, at which time limited variables on occupation were added to the data collection forms. However, without appropriate denominators, it is not possible to calculate incidence rates or relative risks for healthcare workers. In 2001, 50 of the reporting areas in the United States reported information

on occupation for at least 75% of TB cases. There were 414 reported TB cases among healthcare workers in 2001, a slight decline when compared to the 427 cases reported in 2000 *(22,30)*. The percentage of cases occurring among healthcare workers in 2001 ranged from 0% in the District of Columbia, Idaho, Indiana, Nevada, North Dakota, South Dakota, Utah, Vermont, West Virginia, and Wyoming to 6.6% in Massachusetts and 15.8% in New Hampshire.

In a questionnaire survey of medical school–affiliated physicians in California, Barrett-Connor *(31)* found that 3.5% had been treated for active TB. Seventy-five percent of cases of active disease began when the physicians were within 10 years of beginning medical school; 62% of cases of active disease followed infection acquired after beginning medical school. In the cohort of those who graduated between 1966 and 1975, disease rates after beginning medical school were 0% (0/54) among those who were TST positive at entry; 1.0% (7/669) among those who were TST negative at entry; and 10.0% (7/69) among those who became TST positive after entry.

A questionnaire survey of 1938 to 1981 graduates of the University of Illinois Medical School found that, for most years, the incidence of TB in the cohort of graduates was higher than that in the general population *(32)*. More than two thirds of all cases of TB occurred during medical school or within 6 years of graduation.

Finally, a review of the recorded occupations of persons with TB reported to the North Carolina TB control program found that TB case rates in hospital personnel in 1983 and 1984 were similar to or lower than rates in the general population *(33)*. However, these data were not adjusted for age or race, nor was a definition of the term *hospital employee* provided.

In summary, data concerning the recent or current risk of active TB in healthcare workers in the United States are very limited. Two questionnaire surveys suggest an increased risk among physicians, whereas a third study suggests that the risk for hospital employees in general is similar to that for the general population. The data from Barrett-Connor's survey suggest a protective effect of a previous positive TST. The incidence of TB is a relatively insensitive measure of the actual risk posed to healthcare workers by occupational exposure to *M. tuberculosis*. A more sensitive measure of this risk is the rate of TST conversions or IGRA positives among healthcare workers.

Surveillance for TST Conversions in Healthcare Workers

The annual rate of TST conversions in healthcare workers is the best potential indicator of the risk of becoming infected with *M. tuberculosis* through occupational exposure in the healthcare setting. However, there is no systematic national surveillance for such conversions in U.S. healthcare workers. In 1995, the CDC, in collaboration with selected state and local health departments, began a prospective TST surveillance project to estimate the incidence of occupational transmission of *M. tuberculosis* to healthcare workers. Participating sites (Florida, Massachusetts, Mississippi, New Jersey, New York City, San Francisco, and San Diego) were required to implement TST programs consistent with current CDC guidelines and to pilot test a CDC-developed microcomputer software system, staffTrakTB, to assist with collection, tracking, management, and analysis of data *(34a,34b)*. The project areas enrolled 26 facilities: eight hospitals, five health departments, two long-term-care facilities, three correctional facilities, and eight other facilities (including a state laboratory). From 1995 to 1997, a total of 29,004 healthcare workers were enrolled in the project; 9,088 (31.3%) were included in the analysis. TST conversions (i.e., ≥10 mm increase in reaction size on follow-up TST) were documented in 1.1% (104 of 9,088) of healthcare workers *(35)*. Conversion rates varied by project area, ranging from 0% in Florida to 4.2% in New York City, and by facility (correctional, 2.1%; health departments, 1.3%; hospitals, 1.0%; or nursing homes, 0.8%). TST conversion rates also varied by occupation of the healthcare worker (outreach worker, 4.2%; scientist, 2.7%; technician, 2.2%; nurse, 1.2%; housekeeper, 1.2%; clerical worker, 1.0%; administrator, 0.8%; attending physician, 0.6%; and social worker, 0.3%). TST conversion rates among nurses were highest in New York City (4.2%) and San Francisco (2.2%) and lowest in Mississippi (0.1%) and Florida (0%), probably reflecting an elevated risk of *M. tuberculosis* transmission in areas with high TB incidence such as New York City and San Francisco. Healthcare workers who were outreach workers, nonwhite, non–U.S.-born, or BCG-vaccinated were at a significantly higher risk of conversion. These data suggest that foreign-born status and certain occupations may be associated with an elevated risk of *M. tuberculosis* transmission, possibly reflecting more exposure to infectious individuals in the healthcare worker's household or community, and in certain healthcare settings.

There are several reports in the literature of the risk of TST conversion among U.S. healthcare workers (Table 38-3) (*18*,*31*,*33–50*,51,*52–59*). These reports suggest that, since 1980, the risk of TST conversion among hospital employees in general has been ≤1%.

One prospective study followed workers at an urban hospital in a high TB-incidence area where TST screening was required of all eligible employees every 6 months *(59)*. This study found an overall TST conversion rate of 0.38% per year. TST conversion was not associated with the degree of patient contact, but was associated with BCG vaccination, low annual salary, and increasing age. The researchers concluded that, in a hospital with an effective TB infection control program, TST conversion rates were low and that the most important risk factors for TST conversion among workers were not occupational.

At least two other studies have found a higher risk for TST conversion with increasing age of the workers *(40,43)*. A third study that examined age as a risk factor for TST conversion found an association with increasing age when two-step TST was not used to establish the employees' baseline skin test status; however, when two-step TST was used to eliminate apparent conversions caused by the booster phenomenon, there was no longer any correlation between age and the risk of conversion *(18)*. This finding suggests that the higher rate of apparent conversion sometimes observed in older workers may actually be the result of an increased level of boosting in older persons.

Race has been found to correlate with risk of TST conversion in two studies. One of these reported a higher risk among non-whites compared with whites, and a higher risk among employees in the lowest socioeconomic quintile *(40)*.

TABLE 38-3

Tuberculin Skin Test Conversion Rates in Healthcare Workers United States, 1960–1998

First Author (Reference)	*Institution Location*	*Time Period*	*Population*	*Annual Conversion Rate (%)*[a]
Levine (36)	Kings County Hospital Brooklyn, New York	1960–1967	Student nurses	1.05
Weiss (37)	Philadelphia General Hospital, Philadelphia, Pennsylvania	1962–1971	Student nurses	4.20
Atuk (38)	University of Virginia Hospital, Charlottesville, Virginia	1968–1969	Hospital employees	1.92
Gregg (39)	State Park Health Center, South Carolina	1969–1973	Hospital employees	4.08
Berman (40)	Sinai Hospital of Baltimore, Baltimore, Maryland	1971–1976	Hospital employees	1.41
Craven (41)	University of Virginia Hospital, Charlottesville, Virginia	1972–1973	Hospital employees	0.52
Vogeler (42)	LDS Hospital, Salt Lake City, Utah	1972–1975	Hospital employees	0.16
Ruben (43)	Montefiore Hospital, Pittsburgh, Pennsylvania	1973–1975	Hospital employees	3.07
Ktsanes (44)	Charity Hospital New Orleans, Louisiana	1972–1981	Hospital employees	1.04
Barrett-Connor (31)	Multiple institutions, California	1974–1975	Medical school–affiliated physicians	0.4–1.8
Weinstein (45)	Mount Sinai School of Medicine, New York City	1974–1982	Medical students	0.13
Chan (46)	Jackson Memorial Hospital, Miami, Florida	1978–1981	House staff	3.96
Bass (18)	University of South Alabama, Medical Center Mobile, Alabama	1979	Hospital employees	2.9
Thompson (47)	10 hospitals, 9 states[b]	1979	Hospital employees	2.9
Kantor (43)	Veterans Administration Medical Center Chicago, Illinois	1979–1986	Hospital employees	0.94
Price (33)	167 hospitals, North Carolina	1980–1984	Hospital employees	1.14
Aitken (49)	114 hospitals, Washington	1982–1984	Hospital employees	0.87
Malasky (50)	Multiple Institutions Multiple US cities	1984–1986	Pulmonary fellows	5.65
Raad (51)	Shands Hospital, Gainesville, Florida	1984–1987	Hospital employees	0.13
Raad (51)	Florida State Psychiatric Hospital, Chattahoochee, Florida	1985–1987	Hospital employees	0.42
Ramirez (52)	Humana Hospital, University of Louisville, Louisville, Kentucky	1986–1991	Hospital employees	0.68
Ikeda (53)	Health Science Center State, University of New York, Syracuse, New York	1989–1990	Hospital employees	0.84
Ramaswamy (54)	Bronx, New York	1990–1993	Hospital employees	1.40
Zahnow (55)	Multiple institutions providing HIV-related healthcare	1992–1993	House staff	3.00
Christie (56)	Children's Hospital Medical Center, Cincinnati, Ohio	1986–1994	Hospital employees	0.03–0.28
Panlilio (57)	5 hospitals, New York City, Boston, Massachusetts	1994–1995	Hospital employees	1.61
Manangan (58)	Multiple institutions multiple cities	1996	Hospital employees	0.27[a]
Larsen (59)	Grady Memorial Hospital, Atlanta, Georgia	1994–1998	Hospital employees	0.38

[a]In some cases, the annual conversion rate has been recalculated from data provided in the article referenced.
[b]The nine states are Pennsylvania, Colorado, Maryland, Texas, New Mexico, Ohio, Montana, New Hampshire, and Georgia.

The other found a higher risk of TST conversion among black employees than among non-blacks; however, among blacks, the risk was higher among nurses than among persons in other job categories *(44)*. In the one study that examined gender as a potential risk factor, no association was found between gender and the risk of TST conversion *(40)*. A survey that included multiple institutions throughout North Carolina found that the risk of conversion varied according to geographic region within the state *(33)*.

Few reported studies have examined the relationship between job category and risk of TST conversions. One study found a higher risk of conversion among persons

in laundry, housekeeping, and engineering and maintenance departments than among persons in other departments *(40)*. A second study found a higher conversion rate among nurses than among persons in other job categories *(44)*. A third study found higher conversion rates among admissions clerks, phlebotomists, and nurse technicians than among respiratory therapists, environmental services workers, or registered nurses *(52)*. A survey of self-reported TST conversions among medical fellows at multiple institutions found a higher reported rate of conversion among pulmonary fellows than among infectious diseases fellows *(50)*. Finally, a survey of self-reported TST conversions among medical school–affiliated physicians in California found that physicians in the major clinical specialties reported comparable infection rates before and during medical school, but that rates after medical school were highest in medicine, pediatrics, and surgery; intermediate in obstetrics and gynecology and orthopedics; and lowest in radiology and psychiatry *(31)*. In this survey, the cumulative percentage of TST-positive physicians was at least twice the estimated age-specific infection rate for the general U.S. population.

Several studies have found higher conversion rates among workers with a higher likelihood of exposure to patients with TB than among those with a relatively lower likelihood of such exposure *(38,39,41,42,57,58)*. In contrast, in a hospital in Pennsylvania, the reported conversion rates for groups with high or low degrees of exposure to patients with TB were not significantly different *(43)*. Similarly, in a multi-institution survey in Washington, reported conversion rates were not significantly different in hospitals that had admitted no patients with TB compared with hospitals that had admitted patients with AFB smear-negative TB or hospitals that had admitted patients with AFB smear-positive TB *(49)*. In this study, however, postexposure conversions were excluded from analysis, and there was no analysis by risk of exposure within the hospitals that did admit TB patients. A study from Florida reported a higher conversion rate among employees in a psychiatric hospital, in which there was presumably a low risk of exposure, than in a general hospital in which the risk of exposure was presumably higher (51). Again, this study did not examine the risk of TST conversion according to the likelihood of exposure within each hospital. Finally, a prospective study to assess the prevalence of TST positivity among healthcare workers providing service to HIV-infected persons found no association between the amount or the type of contact with HIV-infected individuals and the risk of TB infection *(55)*. Therefore, according to this study, caring for HIV-infected patients was not related to an increased rate of TB infections among healthcare workers in these settings.

These studies, in addition to being few in number, have substantial limitations. With the exception of one study *(59a)*, most are retrospective; the populations being studied often are not well defined; participation rates are not consistently reported but are variable and often quite low; the methods of applying and reading the tests are variable and often rely on employees' self-reporting of results; two-step TST to establish a baseline is rarely used; the definitions of positive skin tests or of TST conversions are not always specified and are variable; the classification of job categories and the definitions of exposure are inconsistent; there are essentially no data on background risk in the community or on the performance of serial TST in the general population from which to make estimates of attributable risk; the analyses often are insufficiently detailed to allow an estimation of relative risks for different job categories; and problems with the specificity and positive predictive value of the TST rarely are addressed adequately. Furthermore, the antigens used often are not described and appear to vary between, and possibly within, studies. It has been noted that a change in products can result in an increase in the conversion rate or pseudo-outbreak *(14)*. For these reasons, interpretation of the data is difficult, and comparison of data from different studies is problematic. In spite of all these limitations, it is interesting that the overall risk among hospital employees in general seems to be fairly consistent.

In summary, available data suggest that the risk of TST conversion among hospital employees in general is ≤1%. The data, although conflicting, also suggest that there may be substantial variation in risk according to the type of hospital, geographic location, occupational category, and a priori likelihood of exposure. Interpretation of the data is made difficult by methodologic limitations, by the lack of specificity and positive predictive value of the TST, by the difficulty of differentiating occupational risk from exposure in the community, and by an inadequate understanding of serial TSTs reflected in some studies. In international settings or domestic settings with large numbers of healthcare workers who have received BCG, the use of IGRAs may be more useful than TST for monitoring potential occupational exposures to *M. tuberculosis (59b)*.

Healthcare-Associated Outbreaks of Tuberculosis

A healthcare-associated outbreak of TB may be defined as transmission of *M. tuberculosis* in a healthcare setting, resulting in the acquisition of LTBI or the development of TB among exposed persons. There is no systematic national surveillance for healthcare-associated TB outbreaks; therefore, data on such outbreaks are limited to reports in the literature. Since 1960, at least 41 healthcare-associated outbreaks occurring in the United States have been reported in the literature (Table 38-4) (*48*,*53–55*,*60–64*,65,*66,67*,68,*69*,70,*71*,72,73,*74*,75,76,*77–96b*).

The reported outbreaks have occurred in a wide variety of geographic areas. Most have occurred in general medical-surgical hospitals; one occurred in a health department clinic, one in an outpatient methadone treatment program, one in an outpatient hemodialysis unit, one in a pediatric office, one at a children's hospital, one in two nursing homes and a community hospital, and one involved both a general hospital and a hospice. Outbreak settings within the hospitals have included emergency departments, inpatient medical wards, adult or neonatal intensive care units, a surgical suite, radiology suites, inpatient HIV wards and an outpatient HIV clinic, an inpatient renal transplant unit, an inpatient prison ward, an autopsy suite, a nursery, a maternity ward, and bronchoscopy rooms.

The earlier reports of outbreaks in this series primarily focused on transmission of *M. tuberculosis* from patients to healthcare workers, with an occasional secondary case

identified in another patient. The apparent infrequency of transmission to other patients in these outbreaks may be artifactual because of the difficulty often encountered in obtaining follow-up information on exposed patients and the natural history of TB. Because the interval from infection to disease is highly variable (ranging from weeks to decades), the occurrence of active TB is not likely to be attributed to a hospitalization in the more remote past. Thus, in the absence of temporal clustering of TB cases or the appearance of strains of *M. tuberculosis* with distinctive drug resistance or DNA fingerprint patterns, transmission to patients in a hospital may go unrecognized *(2)*. In contrast to the earlier reports, many of the more recently reported outbreaks have occurred in settings where many of the persons exposed were severely immunocompromised patients. These outbreaks have involved rapid propagation of active TB among relatively large numbers of patients.

A variety of factors have been identified as possibly contributing to the reported healthcare-associated TB outbreaks. In many cases, these factors represent empiric observations, and the actual contribution of any given factor cannot be calculated. In some instances, the analysis presented has allowed an estimate of the relative contribution of a specific factor. In general, potential contributing factors can be categorized into those that increase the likelihood of exposure to *M. tuberculosis*, those that increase the likelihood of infection occurring among persons who are exposed, and those that increase the likelihood of active disease in persons who become infected.

Factors That Affect the Likelihood of Exposure A major factor increasing the likelihood of exposure to *M. tuberculosis* has been failure to promptly identify and isolate a potential source of transmission, usually a patient with undiagnosed and untreated, or inadequately treated, TB (Table 38-4). In at least three outbreaks, healthcare workers also have been implicated as sources of transmission (70,*88,94*); in one, transmission only occurred from healthcare worker to healthcare worker in a setting where routine employee screening did not take place *(94)*. Failure to identify persons with infectious TB (including parents or visitors for pediatric patients) has resulted in these persons not being isolated and appropriately treated, thus increasing the number of persons exposed.

In most instances, transmission has occurred from patients with pulmonary TB. However, in two outbreaks, transmission occurred as a result of irrigation or manipulation of an undiagnosed *M. tuberculosis* abscess or skin ulcer *(64,71)*. The presence of drug-resistant microorganisms that are inadequately treated also may lead to prolonged infectiousness and an increased likelihood of exposure.

In some outbreaks, there often have been multiple sources, resulting in a web of possible transmissions, rather than a clearly defined single chain of transmission. In at least three recent outbreaks, DNA fingerprinting using RFLP has demonstrated the presence of more than one chain of transmission involving different strains of *M. tuberculosis*, when epidemiologic evidence seemed to suggest a single chain of transmission (68,72,*92*).

Inadequate ventilation also has increased the likelihood of exposure to *M. tuberculosis*. In some instances, the presence of positive air pressure in isolation rooms has allowed potentially contaminated air to escape from the isolation rooms into other areas of the facility. In most situations, the presence of other potentially contributing factors has made it difficult to assess the effect of positive air pressure alone; however, in one outbreak in which other aspects of the infection control program were adequately implemented, the role of positive air pressure was clearly demonstrated *(53)*. In other instances, recirculation of potentially contaminated air from sputum induction or isolation rooms into other areas of the facility has been implicated as a factor in transmission (*61,63,66*,72).

Lapses in isolation practices have increased the likelihood of exposure in several outbreaks. Such lapses have included not keeping isolation room doors closed, thereby allowing efflux of potentially contaminated air from the room into adjacent areas; not keeping patients with infectious TB confined to their rooms; not enforcing the use of masks by patients with infectious TB when they are out of their rooms; and not maintaining isolation for a period long enough to ensure that the patient is no longer infectious. Additionally, inadequate cleaning, disinfection, or leak testing of bronchoscopes after performing bronchoscopy in pulmonary TB patients led to transmission of infection and active TB disease *(86,94)* (see also Chapter 62).

Factors That Affect the Likelihood of Infection In general, factors that are likely to produce a relatively high concentration of infectious droplet nuclei in the air also are likely to increase the likelihood that an exposed person will inhale tubercle bacilli and become infected. Thus, patients identified as outbreak sources often have had chest radiographs showing extensive cavitary disease and sputum smears that were positive for AFB—factors suggesting a high bacterial burden. However, in outbreaks among immunocompromised persons, extensive cavitary disease has been relatively infrequent (67,68,72,73,75,*77,87,95,96*). Furthermore, in rare instances, high rates of transmission from persons with sputum smears that were negative for AFB have been documented *(48,62)*.

Inadequate ventilation rates and recirculation of potentially contaminated air within closed environments can lead to increased concentrations of infectious droplet nuclei in the air and have been implicated in several outbreaks (*48,61–63,66*,68,70,72,*74*,76,*77*). Patients in rooms in close proximity to a room housing a patient with infectious TB have been shown to be at increased risk when the isolation room is not under appropriate negative pressure (*64*,73,76).

Performing procedures that stimulate cough or generate aerosols in persons with TB also may lead to an increased concentration of infectious droplet nuclei in the air. A number of such procedures have been reported in association with outbreaks. These procedures have included endotracheal intubation and suctioning (*61–63*,68,*90*); bronchoscopy (*62*,68,*93*); surgical drainage and irrigation of a *M. tuberculosis* abscess, and surgical debridement of an *M. tuberculosis* skin ulcer *(64,71)*; administration of aerosolized pentamidine (*66*,72); and autopsy *(48)*. Finally, lack of or inappropriate use of respiratory protection also has been reported in some outbreaks (*63*,68,76,*77,90,93,94*).

Whether or not underlying HIV infection causes increased susceptibility to infection with *M. tuberculosis* is not yet

TABLE 38-4

Reported Healthcare-Associated Outbreaks of Tuberculosis (TB), United States, 1960–1999

Type of Facility, First Author (Reference)	*Setting*	*Patients (Including Source)*		*Healthcare Workers (Including Source)*		*Contributing Factors*
		Infection	*Active Disease*	*Infection*	*Active Disease*	
Medical school/medical center, northeastern U.S. 1962–1964	—	—	—	—	27	Undiagnosed, untreated pulmonary TB
Alpert (60) Municipal general hospital, Miami, Florida, 1969	Emergency department; inpatient medical ward; intensive care unit	—	1[a]	23/100 (23%)	2	Undiagnosed, untreated pulmonary TB
Ehrenkranz (61)						Positive pressure ventilation Endotracheal intubation Nasotracheal suctioning Air recirculation
University-affiliated hospital, San Diego, California, 1980	Intensive care unit	—	1[a]	14/45 (31%)	—	Undiagnosed, untreated pulmonary TB Bronchoscopy
Catanzaro (62)						Endotracheal intubation and suctioning Inadequate ventilation rate
General hospital, Dallas, Texas, 1983–1984	Emergency department, intensive care unit; radiology suite	—	3[a]	26/160 (16.3%)	7	Newly diagnosed, untreated pulmonary TB
Haley (63)						Endotracheal intubation and suctioning Air recirculation Inadequate respiratory protection
Community hospital, Arkansas (rural), 1985	Surgical suite; Inpatient medical ward; Intensive care unit	0%–67%	3[a]	59/492 (12%)	5	Undiagnosed, untreated tuberculous abscess
Hutton (64)						Positive pressure ventilation Surgical drainage of abscess Irrigation of abscess
Veterans Administration Medical Center, Chicago, Illinois, 1985	Inpatient medical ward; radiology suite; autopsy room	—	1[a]	8/55 (14.5%)	3	Undiagnosed, untreated pulmonary TB
Kantor (48)						No control of directional airflow Nasotracheal suctioning Inadequate ventilation rate Autopsy
Municipal general hospital, San Juan, Puerto Rico, 1987–1989	Inpatient HIV ward	—	8[a]	—	—	Undiagnosed, untreated pulmonary TB

Dooley (65)						Delayed isolation Positive pressure ventilation Immunocompromised patients (HIV)
Health department clinic, West Palm Beach, 1988	Outpatient clinic	—	1[a]	17/63 (27%)	—	Positive pressure ventilation
Calder (66)						Aerosolized pentamidine treatments Inadequate ventilation rate Air recirculation
Community general hospital, Amarillo, Texas, 1989	Inpatient medical ward; hospice	—	1[a]	30/158 (19%)	1	Undiagnosed, untreated pulmonary TB
Pierce (67)						
University-affiliated hospital, Pittsburgh, Pennsylvania, 1990–1991	Inpatient medical ward (renal transplant unit)	7	11[a]	2	0	Undiagnosed, untreated pulmonary TB
Jereb (68) Sundberg (69)						Bronchoscopy Endotracheal intubation Inadequate ventilation rate Immunocompromised patients (renal transplant)
Urban general hospital, Atlanta, Georgia, 1991–1992	Impatient medical ward	—	3	50/131 (38%)	8[b]	Undiagnosed, untreated pulmonary TB
Zaza (70)						Positive pressure ventilation Inadequate ventilation rate
Community hospital, Rochester, New York, 1992	Inpatient medical-surgical ward	—	1[a]	12/59 (20%)	2	Undiagnosed, untreated tuberculous ulcer
Frampton (71)						Surgical debridement of ulcer Dressing changes
Multidrug-resistant outbreaks						
Municipal general hospital, Miami, Florida, 1988–1990	Inpatient HIV ward; outpatient HIV clinic	—	29[a]	13/39 (33%)	—	Undiagnosed, untreated pulmonary TB
Beck-Sague (72)						Unrecognized drug resistance Lapses in isolation practices Positive pressure ventilation Aerosolized pentamidine treatments Air recirculation Immunocompromised patients (HIV)
Urban voluntary hospital, New York City, 1989–1990	Inpatient medical ward	—	18[a]	—	1	Undiagnosed, untreated pulmonary TB
Edlin (73)						Positive pressure ventilation Positive pressure ventilation Immunocompromised patients (HIV)
Urban voluntary hospital, New York City, 1989–1991	Inpatient HIV ward; Inpatient prison ward	—	17[c]	—	—	Undiagnosed, untreated pulmonary TB
						Unrecognized drug resistance

(*Continued*)

TABLE 38-4

Reported Healthcare-Associated Outbreaks of Tuberculosis (TB), United States, 1960–1999 (*Continued*)

Type of Facility, First Author (Reference)	*Setting*	*Patients (Including Source)*		*Healthcare Workers (Including Source)*		*Contributing Factors*
		Infection	*Active Disease*	*Infection*	*Active Disease*	
CDC (74)						No control of directional air flow Lapses in isolation practices Inadequate ventilation rate
Urban teaching hospital, New York City, 1989–1991	Inpatient HIV ward; inpatient medical ward	—	23[a]	11/32 (34%)	—	Undiagnosed, untreated pulmonary TB
Pearson (75)						Lapses in isolation practices Positive pressure ventilation Immunocompromised patients (HIV)
Urban teaching hospital, New York City, 1989–1991	Inpatient HIV ward; inpatient medical ward	—	23[a]	11/32 (34%)	—	Undiagnosed, untreated pulmonary TB
Pearson (75)						Lapses in isolation practices Positive pressure ventilation Immunocompromised patients (HIV)
General teaching hospital, Upstate New York, 1991	Inpatient medical wards	—	6[a]	46/696 (6.6%)	—	Positive pressure ventilation
Ikeda (53)						Prolonged infectiousness Immunocompromised patients (HIV)
Urban tertiary care hospital, New York City, 1990–1991	Inpatient medical wards	—	15[a]	—	1	No control of directional air flow
Coronado (76)						Lapses in isolation practices Inadequate ventilation rate Immunocompromised patients (HIV)
Veterans Administration Medical Center, New Jersey, 1990–1992	Inpatient infectious diseases ward	—	13[a]	5/10 (50%)	—	Positive pressure ventilation
Coronado (77)						Lapses in isolation practices Inadequate ventilation rate Inadequate use of respiratory protection by workers Immunocompromised patients (HIV)
Veterans Administration Medical Center, New Jersey, 1990–1992	Inpatient infectious diseases ward	—	13[a]	5/10 (50%)	—	Positive pressure ventilation
Coronado (77)						Lapses in isolation practices Inadequate ventilation rate Inadequate use of respiratory protection by workers Immunocompromised patients (HIV)

Urban general hospital, New York City, 1991–1992	Inpatient HIV ward	—	37	—	—[a]	Undiagnosed, untreated pulmonary TB
CDC (78)						Lapses in isolation practices Positive pressure ventilation Immunocompromised patients (HIV)
Teaching hospital, New York City, 1989–1992	Inpatient medical ward	—	—	88/352 (25%)	6	Lapses in isolation practices
Jereb (79)						
Multiple hospitals, New York City, 1990–1993	—	—	256	—	15[b]	Lapses in isolation practices
Frieden (80)						
Community hospital, La Mirada, California, 1992	Emergency room; medical intensive care unit	—	1	13/20 (65%)	3	Undiagnosed TB
Griffith (81)						Positive pressure ventilation Lack of respiratory protection by workers
Urban hospital, New York City, 1993–1994	Nursery; medical ward	—	4	—	3	Undiagnosed TB
		—	17[b]	—	—	Lapses in isolation practices
Nivin (82)						
Community hospital, South Carolina, 1994	Inpatient medical ward	—	1	12/28 (43%)	—	Unrecognized TB
Luby (83)						
Private hospital, Chicago, IL, 1994–1995	Inpatient medical ward	—	6	11/74 (15%)	1	Immunocompromised patients (HIV)
Kenyon (84)						
General hospital, South Carolina, 1995	Bronchoscopy room	—	4[b]	—	—	Contaminated bronchoscope
Agerton (85)						
Teaching hospital, Baltimore, MD, 1996	Bronchoscopy room	—	4	—	—	Contaminated bronchoscope
Michele (86)						
Urban teaching hospital, Tennessee, 1992	Inpatient medical ward	—	2	35/172 (20.3%)	1	Undiagnosed pulmonary tuberculosis, immunocompromised patients (HIV)
Haas (87)						
Outpatient clinic, New Jersey, 1992–1993	Pediatric office	3	—	2	1	Undiagnosed TB
Askew (88)						
General hospital, New York, 1996–1997	Neonatal intensive care unit	—[e]	1	2/260 (0.8%)	—	Undiagnosed TB, positive pressure ventilation, suctioning
Lee (89)						
Community hospital, Arizona, 1996	Nursery	—	1	1/119 (0.8%)	—	Undiagnosed TB, inadequate use of respiratory protection during endotracheal intubation
Spark (90)						

(*Continued*)

TABLE 38-4

Reported Healthcare-Associated Outbreaks of Tuberculosis (TB), United States, 1960–1999 (*Continued*)

Type of Facility, First Author (Reference)	*Setting*	*Patients (Including Source)*		*Healthcare Workers (Including Source)*		*Contributing Factors*
		Infection	*Active Disease*	*Infection*	*Active Disease*	
Nursing homes, community hospital, Arkansas, 1995–1998 Ijaz (91)	Two nursing homes; one community hospital ward	24/98 (24%)	2	48/320 (15%)	2	Undiagnosed TB
Community hospital, California, 1998 Linquist (92)	Outpatient hemodialysis unit	12/89 (13%) No prior TST	—	1/23 (4%)	1	Anergy of case patient
Community hospital, Wisconsin, 1999	Bronchoscopy suite	10	2/10 (20%)	1	—	Contamination of bronchoscope in procedure on TB patient, inadequate bronchoscope reprocessing procedure, inadequate use of respiratory protection by worker
HIV dental clinic, New York City, 1990–1991	Clinic	—	—	—	2[b]	Undiagnosed TB, inadequate use of respiratory protection by workers, immunocompromised patients and workers (HIV), lack of screening program for workers
Urban hospital Chicago, 1994–1995 Kenyon (95)	Inpatient medical ward	—	6[b]	11/74 (15%)	1[b]	Immunocompromised patients (HIV), lapses in isolation practices, undiagnosed TB
Outpatient clinic, Chicago, 1994–1995 Conover (96)	Methadone treatment program	51/302 (17%)[d]	13	5/29 (17%)	—	Undiagnosed TB, immunocompromised patients (HIV)
Children's hospital; Lee et al. *(96b)*	Pediatric ward	1/16 (6.7%)		6/293 (1.9%)		

[a]Includes source(s) of outbreak.
[b]See also Table 37-5.
[c]For multidrug-resistant outbreaks, the number of cases in patients and the number of healthcare workers listed in this table include only those identified in the initial investigation.
[d]Although the initial report of this outbreak notes several "skin test conversions" in healthcare workers, the criteria used to define a skin test conversion in that report did not meet the general accepted definition.
[e]All exposed neonates presumptively treated with isoniazid for 6 months.

clearly established. In an MDR-TB outbreak in the New York state prison system, HIV infection was not found to be associated with an increased risk of becoming infected with *M. tuberculosis*; however, the small numbers included in this analysis limited the power of the analysis to detect such a risk *(97)*. In two studies, patients with HIV hospitalized for active TB caused by drug-susceptible microorganisms developed secondary infection with a hospital-acquired MDR-TB *(98,99)*.

Factors That Affect the Likelihood of Active Tuberculosis Although, hypothetically, the virulence of the infecting microorganism may increase the likelihood of progression from LTBI to active TB, this issue remains unresolved *(100)*. Profound suppression of cell-mediated immunity in the infected host is the only factor that has been definitively identified in the outbreaks as increasing the likelihood of active TB. In most cases, immunosuppression has resulted from coinfection with HIV (Table 38-4). In one outbreak, the cause was pharmacologic immunosuppression in renal transplant recipients (68). In each of these cases, immunosuppression has increased both the risk of developing active disease and the rate at which it developed, leading to rapid and widespread propagation of the outbreak.

In summary, at least 41 healthcare-associated outbreaks of TB in the U.S. have been reported in the literature since 1960. Because there is no systematic national surveillance of such outbreaks, it is unknown how many other outbreaks may have occurred but have not been reported, nor is it known whether those that have been reported are representative of all outbreaks. A multiplicity of factors potentially contributing to the reported outbreaks has been identified. Although it is difficult to estimate the quantitative contribution of each of these factors to the outbreaks, it is clear that failure to identify and appropriately isolate and treat persons with infectious TB is one of the most important factors.

Healthcare-Associated Outbreaks of Multidrug-Resistant Tuberculosis In the 1990s, several large, healthcare-associated outbreaks of MDR-TB were reported (Tables 38-4 and 38-5) (2). Outbreaks of MDR-TB are not a new phenomenon, having been reported in at least three communities, a residential substance-abuse treatment center, and a homeless shelter since 1976 (*82,85,94–96,101–105*). However, in contrast to these earlier outbreaks, which were relatively small and propagated slowly, the healthcare-associated outbreaks of the early to mid-1990s involved large numbers of patients in institutional settings and propagated rapidly.

From 1990 through 1992, the CDC collaborated with officials from state and local health departments, hospitals, and prisons to investigate eight outbreaks of MDR-TB in hospitals and in the New York state prison system (*53*,72,73,*74*,75,76,*77–97*,*106–110*). In addition to the initial investigations, follow-up investigations were conducted in some of the hospitals to evaluate the effectiveness of infection control interventions that were initiated after the outbreaks were detected (111,*112*,113,114). The total number of cases identified in each of the outbreaks has ranged from approximately 8 to 70, with the total for all the outbreaks combined >300 cases.

All of these outbreaks involved the transmission of MDR *M. tuberculosis* from person to person, including from patient to patient, patient to healthcare worker, and healthcare worker to healthcare worker. In each instance, the epidemiologic evidence of healthcare-associated transmission was compelling. For patients, factors associated with an increased risk of MDR-TB have included previous hospitalization in the associated outbreak hospital, previous hospitalization on the same ward as a patient with infectious MDR-TB, physical proximity to a patient with infectious MDR-TB during a previous hospitalization, or previous exposure to patients with infectious MDR-TB in an outpatient clinic. For healthcare workers, exposure to patients with MDR-TB has been associated with a higher risk of TST conversion than has exposure to patients with drug-susceptible TB (72). This is probably explained by prolonged infectiousness of patients with inadequately treated MDR-TB rather than by increased infectiousness of such patients. In all of the outbreaks, the epidemiologic evidence of healthcare-associated transmission was corroborated by laboratory evidence in the form of DNA fingerprinting using RFLP.

Nearly all patients in these outbreaks have had *M. tuberculosis* isolates resistant to both isoniazid and rifampin, the two most effective anti-TB drugs available. Most isolates also have been resistant to other drugs. In four hospitals and the New York state prison system, the outbreak strain was resistant to seven anti-TB drugs. Mortality among patients with MDR-TB in these outbreaks was extraordinarily high (43–93%) and has been associated with rapid progression from diagnosis of TB to death (range of median intervals: 4–16 weeks). The high mortality rates observed in these outbreaks are probably explained by the severe degree of immunosuppression in many of the patients combined with ineffective treatment for unrecognized drug-resistant disease.

In all but two of these outbreaks, >85% of cases have occurred in persons infected with HIV. This high proportion of HIV infection can be explained in two ways. First, the outbreaks have occurred predominantly in settings, for example, HIV wards and clinics, in which most of the persons exposed to and infected with *M. tuberculosis* have been HIV infected. Second, once infected with *M. tuberculosis*, HIV-infected persons are highly likely to develop active TB, especially when they are profoundly immunosuppressed, as often was true of the persons exposed in these outbreaks.

Healthcare workers at hospitals experiencing outbreaks of MDR-TB also have been affected. In some instances, it has been difficult to document infection of healthcare workers, because results of baseline TSTs were not available. However, in several of the facilities, it was possible to document TST conversions in healthcare workers in association with exposure to patients with MDR-TB (Table 38-4) (*53*,72,75,*77,95,96,109*). At least 23 healthcare workers at these facilities developed active MDR-TB; at least 11 of these workers died with MDR-TB.

The factors contributing to the MDR-TB outbreaks are essentially the same as already described for other outbreaks, including delayed diagnosis and isolation of patients with TB. Of particular importance has been delayed recognition of drug resistance leading to delays

TABLE 38-5

Reported Healthcare-Associated Outbreaks of Multidrug-Resistant Tuberculosis, United States, 1988–1995

Facility First Author (Reference)	*Location and Year(s)*	*Total Cases*[a]	*Drug Resistance Pattern*[b,c]	*Prevalence of HIV*[d] *Infection (%*[a]*)*	*Mortality Rate (%)*[e]	*Median Interval from TB Diagnosis to Death (Weeks)*
Hospital A Beck-Sagué (72) CDC (106) CDC (74) Wenger (111) Fischl (107) Fischl (108)	Miami 1988–1991	65	INH, RIF (EMB, ETA, SM, CYC)	93	72	7
Hospital B Edlin (73) CDC (74) Stroud (112)	New York City 1989–1991	51	INH, SM (RIF, EMB)	100[f]	89	16
Hospital C CDC (74) Jereb (109)	New York City 1989–1992	70	INH, RIF, SM (EMB, ETA, KM, RBT)	95	77	4
Hospital D Pearson (75) CDC (74) Maloney (113)	New York City 1990–1991	40	INH, RIF (EMB, ETA, SM, PZA, KM, RBT)	91	83	4
Hospital E Ikeda (53)	New York City 1991	8	INH, RIF, SM (EMB, ETA, KM, RBT)	63	43	4
Hospital F Coronado (76)	New York City 1990–1991	16	INH, RIF, SM (EMB, ETA, KM, RBT)	88	88	8
Hospital I Coronado (77)	New Jersey 1990–1992	13	INH, RIF (EMB)	100	85	4
Hospital J CDC (78)	New York City 1991–1992	37	INH, RIF, (SM, EMB, ETA, KM)	96	93	4
Prison system Valway (97) Valway (110)	New York State 1990–1992	42[g]	INH, RIF (SM, EMB, ETA, KM, RBT)	98	79	4
Hospital K Nivin (82)	New York City 1993–1994	24	INH, RIF, SM	—	—	—
Hospital L Agerton (85)	South Carolina 1995	4	INH, RIF, SM (EMB, ETA, KM, RBT)	—	—	—
Hospital M Cleveland (94)	New York city 1990–1991	2	INH, RIF	100	100	—
Hospital N Kenyon (95)	Chicago 1994–1995	7	INH, RIF	100	—	—
Clinic O Conover (96)	Chicago 1994–1995	13	INH, RIF	85	69	—

[a]Includes cases identified during initial investigation and cases identified during subsequent follow-up.
[b]All cases resistant to drugs listed outside of parentheses; some cases resistant to drugs listed in parentheses.
[c]INH, isoniezid; RIF, rifampin; EMB, ethambutol; ETA, ethionamide; SM, streptomycin; CYC, cyloserine; KM, Kanamycin; RBT, rifabutin; PZA, pyrazinamide.
[d]HIV, human immunodeficiency virus.
[e]Includes only cases for which outcome information has been ascertained.
[f]HIV infection was part of the case definition in this outbreak.
[g]Includes 24 cases also counted with Hospital C.

in initiating effective therapy that, in turn, resulted in even more prolonged periods of infectiousness. In several instances, the delays that occurred in identifying persons with TB and recognizing drug resistance were exacerbated by delays in performing and reporting the results of laboratory tests.

Also of particular importance is the observation that each of the MDR-TB outbreaks occurred in a setting where many HIV-infected and often profoundly immunosuppressed patients were exposed. In one outbreak, 21/346 (6.1%) patients with AIDS hospitalized on the same ward as ≥1 patients with infectious MDR-TB were subsequently diagnosed with active MDR-TB, demonstrating the very high disease attack rate that can occur in such a setting (73). In several of the outbreaks, the interval from exposure to onset of active TB (i.e., incubation period) was estimated (72,73,76,*77,97*). Although different methodologies used in these calculations make summary and comparison difficult, all documented remarkably short incubation periods, possibly as short as 3 to 4 weeks. As a result of the short incubation period, as many as three complete generations of transmission and onset of clinical TB were observed in one outbreak in a 12-month period (CDC, unpublished data). Thus, the amplifying and accelerating effect that HIV has on the pathogenesis of TB has contributed substantially to the propagation of these outbreaks.

Healthcare-associated MDR-TB outbreaks also have been reported from countries other than the U.S. *(99,115–122)*. Clinically and epidemiologically, these outbreaks are similar to those reported in the United States. Many episodes occurred in HIV-infected patients with short onset of active TB after exposure, and high mortality rates *(99,115–122)*.

In summary, MDR-TB outbreaks in hospitals and correctional facilities illustrate the tremendous rapidity and extent of spread that can occur when persons who have undiagnosed or untreated (or inadequately treated) TB, caused by drug-resistant microorganisms, are brought together with highly vulnerable, immunosuppressed persons in an enclosed and relatively densely populated environment in the absence of adequate infection control precautions.

Special Settings

Pediatric Settings Healthcare-associated transmission of *M. tuberculosis* in the pediatric setting usually has involved exposure of hospitalized infants or children to hospital employees or adult visitors with active TB *(88,96b,123–129)*. Transmission from infants and young children is generally regarded as unlikely because an infant's microorganism load is low, cavitary disease is usually absent (indeed, many cases of TB in children involve primary disease with minimal pulmonary involvement), and infants have a reduced ability to expectorate *(130–132)*. However, TST conversion occurred in two healthcare workers who cared for an infant on a ventilator with widely disseminated congenital TB diagnosed at autopsy *(89)*. In another case, possible transmission to healthcare workers from a 5-year-old child with cavitary TB was reported *(133)*. In a third case, TST conversions occurred in 3.7% (5/134) of hospital employees identified as contacts of a 7-year-old child with cystic fibrosis who was hospitalized for 2 months with undiagnosed, disseminated pulmonary TB *(38)*. In a fourth case, TST conversion occurred in one healthcare worker not using respiratory protection who intubated a neonate with congenital TB *(90)*. Thus, although transmission of *M. tuberculosis* from infants and young children probably is uncommon, there are circumstances in which it may occur. In addition, parents have been associated with potential transmission of *M. tuberculosis* to patients and healthcare workers *(96b)*.

Nursing Homes and Chronic Care Facilities Transmission of *M. tuberculosis* in nursing homes and chronic care facilities has been well documented. Several outbreaks of TB in such facilities have been reported *(91,134–139)*. These outbreaks have involved transmission both to residents of the facilities and to staff. In each case, the source of the outbreak was a resident with pulmonary TB in whom the diagnosis was delayed by 2 to 12 months or was only made postmortem. In some instances, the outbreaks were discovered as a result of a routine TST screening program for staff or residents *(134,137,139)*; in other instances, the outbreaks were discovered in the course of conducting a contact investigation *(135,136,138)* (see also Chapter 98).

Dental Settings An outbreak of TB in dental patients following tooth extractions has been reported *(140)*. The source of the outbreak was a dentist with undiagnosed pulmonary TB. Of 15 secondary cases, 13 involved tuberculous lesions in the mouth with involvement of regional lymph nodes, one involved both the mouth and the lungs, and one involved a pleural effusion with associated erythema nodosum. The investigators postulated that the tooth sockets became infected at the time of extraction, presumably by mycobacteria on the dentist's fingers. In another outbreak, transmission occurred from one dental worker to another in an HIV patient dental clinic without evidence of transmission to dental patients *(94)*. The source of the index worker's infection was not determined. Both workers were HIV positive and the clinic had no routine screening program for employees. There are no reported episodes of *M. tuberculosis* transmission from a patient with TB to dental workers as a result of performing dental procedures.

One prospective study has been conducted on the TST conversion rates of dental healthcare workers in Texas counties along the Mexican border with a high prevalence rate of TB in the population. Although the study size was small (n = 240), the authors reported a 1.7% conversion rate after 12 months *(141a)*. Dental personnel should be familiar with specific recommendations for reducing risk of *M. tuberculosis* in dental settings (141b).

International Settings Tuberculosis is increasing in the developing world *(142)*. Since TB infection control programs in most low-income countries are nonexistent or ineffective, there is concern about the risk of *M. tuberculosis* transmission to healthcare workers in those settings. There are several reports suggesting that healthcare workers caring for infectious TB patients in low-income countries are at increased risk of *M. tuberculosis* infection and disease. During 1993 to 1994, a study of the incidence of TB disease in nurses working at a hospital in Malawi showed that 12/310 (4%) nurses had been diagnosed and treated

for TB *(143)*. The number of nurses acquiring TB while working on the medical and the TB wards was significantly higher (13%) than among nurses working in other areas of the hospital (3%). Rates of TB among the nurses working on medical or TB wards were five times higher than rates among nurses working in other hospital areas *(143)*.

In 1996, a TST cross-sectional evaluation of 512 healthcare workers working in a hospital in Abidjan, Ivory Coast, was conducted to assess the risk of TST positivity and to identify risk factors for occupational *M. tuberculosis* acquisition *(144)*. Seventy-nine percent of the healthcare workers had positive TST at the 10-mm cutoff. The duration of employment in areas where TB patients were admitted and the level of patient care influenced levels of positive TST reactions. Healthcare workers working ≥1 year in areas where TB patients were admitted and those involved in patient care (physicians, nurses, and midwives) had a significantly higher rate of TST positivity than those working in the same areas for <1 year or those who did not have patient contact. Five healthcare workers had radiographic abnormalities suggestive of TB. Two of those, both working in areas with high TB prevalence, were diagnosed with active TB.

In 1996, a similar TST survey was conducted among 911 healthcare workers in a hospital in Chiang Rai, Thailand *(145)*. Sixty-nine percent of healthcare workers had an initial positive TST at the 10-mm cutoff. Risk factors for TST positivity included working in the hospital 1 year and having contact with patients. Eleven healthcare workers had an abnormal chest radiograph compatible with TB; of these, seven (64%) were determined to have active TB.

The increased risk of active TB among healthcare workers is not limited to nations with high rates of HIV. For example, the rate of active TB among healthcare workers in Estonia was 1.5–3 times that of the general population from 1994 through 1998 *(146)*. Reported rates were 30–90 times higher among workers in a regional chest hospital. MDR-TB accounted for 38% of disease among healthcare workers, but was 10% to 14% of TB in the general population. A lack of infection control strategies for protecting workers from infectious patients was cited as the cause of the high rates of active disease.

An increased risk of healthcare-associated acquisition of *M. tuberculosis* infection also was shown among Brazilian healthcare workers *(147)*. In 1997, 542 healthcare workers in a large urban hospital in Belo Horizonte, Brazil, completed an exposure questionnaire and received a two-step TST. Of those, 48% had TST reactions ≥10 mm. Having a positive TST was associated with working in areas of the hospital where TB patients were admitted and with prolonged employment duration. A study in Rio de Janeiro, performed during 1994 to 1997, evaluated the risk of TST conversion among 351 healthcare workers in a large urban hospital (A. L. Kritski, personal communication). TST conversion was defined as an increase of ≥10 mm for BCG-negative healthcare workers and an increase of ≥15 mm for healthcare workers who had a previous history of BCG vaccination. TST conversion rates among healthcare workers were significantly higher than in the general population (8% vs. 1%). Also, TST conversion rates were significantly higher among medical, technical, and nursing personnel (14%, 13%, and 11%, respectively) compared to administrative and maintenance personnel (1%). An additional study in Rio de Janeiro evaluated the risk of TST conversion after 1 year among 414 junior and senior medical students with negative two-step TST in 1998. The 1-year TST conversion rate was 3.9%, and the degree of patient contact in the teaching hospital was independently associated with TST conversion (148a). Another longitudinal study of TST conversions after an initial two-step TST conducted at four Brazilian hospitals also documented increased risk of TST conversion of 10.7 per 1,000 person months and documented an increased healthcare worker TST conversion rate at hospitals without TB control measures (148b).

In 1997, teams from the CDC composed of industrial engineers and medical epidemiologists visited several healthcare facilities in five developing countries (Malawi, Brazil, Thailand, Ivory Coast, and Latvia) to develop simple, cost-effective, and feasible TB control interventions to be implemented in these settings. During these visits, a number of factors contributing to the spread of healthcare-associated *M. tuberculosis* were identified. The main factors contributing to the healthcare-associated spread of *M. tuberculosis* in low-income countries are delays in diagnosis, usually due to the lack of suspicion of TB by healthcare providers, slow laboratory turnaround of sputum AFB smears, and atypical clinical manifestations in HIV-infected patients. Inadequate isolation of infectious TB patients, underestimation of risk due to BCG coverage leading to a false sense of security, and the lack of personal protection during high-risk procedures (i.e., bronchoscopy, sputum induction, or autopsies) are additional factors contributing to the spread of healthcare-associated *M. tuberculosis* in low-income countries. TB control guidelines for hospitals in resource-limited countries have been published by the World Health Organization *(149)*.

Other Modes of Transmission

Although healthcare-associated transmission of *M. tuberculosis* nearly always occurs via the airborne route, there are occasional reports of transmission by other routes. Primary cutaneous inoculation TB has been reported in medical students, autopsy students, or laboratory workers as a result of accidental self-inoculation during postmortem examinations *(150,151)* and during injection of laboratory animals with *M. tuberculosis (152,153)*. A case of primary cutaneous inoculation TB was reported in a nurse who was lacerated with a needle that had been inserted in the port of a central line catheter of a patient who had disseminated TB with positive blood cultures for *M. tuberculosis (154)*.

Transmission of *M. tuberculosis* to patients via bronchoscopes that have been used on patients with TB have been reported *(93,155a,)*. In one case, the bronchoscope had been inadequately disinfected with a detergent soap solution, wiped with alcohol, and soaked for 30 minutes in a solution of povidone-iodine, ethanol, and sterile water *(155)* (see also Chapter 62). In another, an undetected leak in the distal end of a bronchoscope or a sheath used on a patient with cavitary TB created a reservoir for bacteria and apparently inoculated nine subsequent patients, two of whom developed active disease with the same strain as the index patient *(93)*. In another, a hole in the bronchoscope sheath led to inadequate disinfection and infection

in at least two patients *(93)*. In another outbreak, specimen contamination occurred after an inadequately disinfected bronchoscope (use on a patient with AFB smear positive TB) was used on two subsequent patients; no evidence of infection was documented *(155b)*.

Finally, transmission of *M. tuberculosis* via organ transplantation has been reported (*156a,156b*,156c). TB is a known infectious disease complication associated with organ transplantation; it occurs in an estimated 0.35% to 6.5% of organ recipients in the United States and Europe post-transplantation (156c). In one incident, active TB developed in two patients, each of whom received a kidney from the same cadaver donor, whose cerebrospinal fluid cultures grew *M. tuberculosis (156a)*. In another incident, active TB in a double lung transplant in the United States was traced to the donor from Guatemala; a previously undetected pulmonary opacity was identified in the transplanted lung and the genotype of the isolate was distinct from U.S., but similar to TB isolates from Guatemala *(156b)*. In 2007, a deceased donor of tissue was identified 3 weeks postmortem to have had TB (156c). Disseminated TB developed in two-third recipients of the tissue, one of whom died; genotypes of the donor and the recipient isolates were identical.

PREVENTION AND CONTROL OF HEALTHCARE-ASSOCIATED TRANSMISSION OF M. TUBERCULOSIS

Because *M. tuberculosis* is transmitted by the airborne route, its control is complex and requires multiple interventions. Therefore, prevention of healthcare-associated transmission of *M. tuberculosis* requires the complete implementation of an appropriately designed TB infection control program that ensures the early identification, isolation, and treatment of persons who have active TB (157). In each of the healthcare-associated TB outbreaks previously described, the CDC guidelines for preventing the transmission of *M. tuberculosis* were incompletely implemented *(79,82,84,86,97,101–103,112,124–126)*. Follow-up studies at several of these hospitals have documented termination of patient-to-patient and/or patient-to-healthcare worker *M. tuberculosis* transmission after implementation of the recommended guidelines (111,*112*,113,114).

The TB infection control program should be based on the hierarchy of control measures recommended to prevent healthcare-associated *M. tuberculosis* transmission. This hierarchy includes (a) administrative procedures to reduce the risk of exposure to persons with infectious TB, (b) engineering controls to reduce the concentration of infectious droplet nuclei and prevent their spread, and (c) a respiratory protection program to protect healthcare workers and other persons in settings where administrative and engineering controls alone may not provide adequate protection (e.g., airborne infection isolation [AII] rooms).

Specific measures to reduce the risk of healthcare-associated *M. tuberculosis* transmission (Table 38-6) include (a) clearly assigning to specific persons the responsibility for the TB infection control program; (b) conducting a risk assessment and developing a written program based on this assessment; (c) developing protocols to facilitate the early identification of persons who may have infectious TB, and promptly initiating and maintaining isolation for such persons; (d) using ventilation and other engineering controls to reduce the potential for airborne exposure to *M. tuberculosis*; (e) maintaining an appropriate healthcare worker respiratory protection program; (f) educating and training healthcare workers about TB; (g) maintaining a program for routine periodic counseling and screening of healthcare workers for LTBI and TB; (h) evaluating possible episodes of *M. tuberculosis* transmission in the facility; (i) coordinating activities with the appropriate public health department; and (j) periodically evaluating the effectiveness of the control program and modifying it, if necessary.

Administrative Controls

To ensure the appropriate design, implementation, and evaluation of the TB infection control program, one person should be assigned supervisory responsibility. This person should have expertise in infection control and occupational health and should work with a multidisciplinary team, including persons with experience in infection control, infectious diseases, pulmonary medicine, microbiology, occupational health, engineering, administration, and employee representation.

The first step in the development of the TB control program is to assess the risk of *M. tuberculosis* transmission in each area of the healthcare facility and in certain occupational groups (Table 38-7 and Fig. 38-2). The risk assessment should be based on the incidence of TB in the community, the number and location of TB patients in the facility, the likelihood of healthcare worker exposure to a patient with infectious TB, the incidence of healthcare worker TST conversions in each area and job category, and the evaluation of possible person-to-person transmission of *M. tuberculosis*. Based on the results of the risk assessment, a written TB infection control plan with explicit policies and procedures should be developed. Systematic, periodic reassessment of these data will allow estimation of the number of TB isolation rooms needed, facilitate identification of healthcare-associated *M. tuberculosis* transmission and outbreaks, allow estimation of the risk of occupational *M. tuberculosis* exposure, and suggest ways in which the infection control program can be made more effective and efficient.

Information on the incidence of TB in the community can be obtained from the public health department. To determine the hospital areas where TB exposures are most likely to occur, microbiology and infection control records should be reviewed to identify all TB patients seen in the facility and the locations in which they were evaluated or treated. These data should be examined to identify the degree of risk in various locations within the hospital. Examination of these data, including evaluation of drug-susceptibility test results, also may lead to recognition of possible healthcare-associated transmission from patient to patient and to recognition of the need to enhance the initial treatment regimen that is used empirically until drug-susceptibility results are available. These data should be collected prospectively and analyzed periodically to identify changes in the distribution of infectious TB patients by location,

TABLE 38-6

Characteristics of an Effective Tuberculosis (TB) Infection Control Program[a]

I. Assignment of responsibility
  A. Assign responsibility for the TB infection control program to qualified person(s).
  B. Ensure that persons with expertise in infection control, occupational health, and engineering are identified and included.
II. Risk assessment, TB infection control plan, and periodic reassessment
  A. Initial risk assessments
    1. Obtain information concerning TB in the community.
    2. Evaluate data concerning TB patients in the facility.
    3. Evaluate data concerning purified protein derivative (PPD) tuberculin skin test conversions among healthcare workers (HCWs) in the facility.
    4. Rule out evidence of person-to-person transmission.
  B. Written TB infection control program
    1. Select initial risk protocol(s).
    2. Develop written TB infection control protocols.
  C. Repeat risk assessment at appropriate intervals.
    1. Review current community and facility surveillance data and PPD-tuberculin skin test results.
    2. Review records of TB patients.
    3. Observe HCW infection-control practices.
    4. Evaluate maintenance of engineering controls.
III. Identification, evaluation, and treatment of patients who have TB
  A. Screen patients for signs and symptoms of active TB.
    1. On initial encounter in emergency department or ambulatory care setting.
    2. Before or at the time of admission.
  B. Perform radiologic and bacteriologic evaluation of patients who have signs and symptoms suggestive of TB.
  C. Promptly initiate treatment.
IV. Managing outpatients who have possible infectious TB
  A. Promptly initiate TB precautions.
  B. Place patients in separate waiting areas or TB isolation rooms.
  C. Give patients a surgical mask, a box of tissues, and instructions regarding the use of these items.
V. Managing inpatients who have possible infectious TB
  A. Promptly isolate patients who have suspected or known infectious TB.
  B. Monitor the response to treatment.
  C. Follow appropriate criteria for discontinuing isolation.
VI. Engineering recommendations
  A. Design local exhaust and general ventilation in collaboration with persons who have expertise in ventilation engineering.
  B. Use a single-pass air system or air recirculation after high-efficiency particulate air (HEPA) filtration in areas where infectious TB patients receive care.
  C. Use additional measures, if needed, in areas where TB patients may receive care.
  D. Design TB isolation rooms in healthcare facilities to achieve >6 air changes per hour (ACH) for existing facilities and >12 ACH for new or renovated facilities.
  E. Regularly monitor and maintain engineering controls.
  F. TB isolation rooms that are being used should be monitored daily to ensure they maintain negative pressure relative to the hallway and all surrounding areas.
  G. Exhaust TB isolation room air to outside or, if absolutely unavoidable, recirculate after HEPA filtration.
VII. Respiratory protection
  A. Respiratory protective devices should meet recommended performance criteria.
  B. Respiratory protection should be used by persons entering rooms in which patients with known or suspected infectious TB are being isolated, by HCWs when performing cough-inducing or aerosol-generating procedures on such patients, and by persons in other settings where administrative and engineering controls are not likely to protect them from inhaling infectious airborne droplet nuclei.
  C. A respiratory protection program is required at all facilities in which respiratory protection is used.
VIII. Cough-inducing procedures
  A. Do not perform such procedures on TB patients unless absolutely necessary.
  B. Perform such procedures in areas that have local exhaust ventilation devices (e.g., booths or special enclosures) or, if this is not feasible, in a room that meets the ventilation requirements for TB isolation.
  C. After completion of procedures, TB patients should remain in the booth or the special enclosure until their coughing subsides.

(*Continued*)

TABLE 38-6

Characteristics of an Effective Tuberculosis (TB) Infection Control Program[a] (*Continued*)

IX. HCW TB training and education
- A. All HCWs should receive periodic TB education appropriate for their work responsibilities and duties.
- B. Training should include the epidemiology of TB in the facility.
- C. TB education should emphasize concepts of the pathogenesis of and occupational risk for TB.
- D. Training should describe work practices that reduce the likelihood of transmitting *M. tuberculosis*.

X. HCW counseling and screening
- A. Counsel all HCWs regarding TB and TB infection.
- B. Counsel all HCWs about the increased risk to immunocompromised persons for developing active TB.
- C. Perform PPD skin tests on HCWs at the beginning of their employment, and repeat PPD tests at periodic intervals.
- D. Evaluate symptomatic HCWs for active TB.

XI. Evaluate HCW PPD test conversions and possible healthcare-associated transmission of *M. tuberculosis*.

XII. Coordinate efforts with public health department(s).

[a]A program such as this is appropriate for healthcare facilities in which there is a high risk for transmission of *Mycobacterium tuberculosis*. (From Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare facilities, 2005. *MMWR Recomm Rep* 2005;54:(RR-17):1–147.)

possible clusters of patient infection, and changes in *M. tuberculosis* antimicrobial resistance patterns by location.

To determine the risk of acquiring *M. tuberculosis* infection or active disease from occupational exposure and to assess the effectiveness of the infection control program, employee health records should be maintained to identify all healthcare workers who have developed active TB or those who have had TST conversions (or IGRA evidence of LTBI or disease) and to facilitate analysis of this information. At the time of hire, all healthcare workers should be screened for a history of TB or receipt of BCG and should receive either a TST using the two-step Mantoux method (if analysis of the data indicates a very low level of boosting, for example, <1%, two-step testing may not be needed) or be tested using a single IGRA.

If the TST is used, it should be applied and read by trained personnel responsible for maintaining healthcare worker TST records, not by the healthcare workers who are being tested. Individual results should be recorded in the employee's health record and a retrievable aggregate database. Persons with positive TSTs or TST conversions should be evaluated for preventive therapy. All TST-negative healthcare workers (paid and unpaid) with the potential for exposure to infectious TB patients or *M. tuberculosis*–contaminated air should be included in the facility's ongoing TST program. The frequency of repeat testing (TST or IGRA) should be based on the risk in each area or occupational group (157). Initial and then periodic review of these data will allow identification of areas where healthcare workers are at increased risk for *M. tuberculosis* infection or disease and permit classification of these areas by degree of risk. This permits focusing of infection control and educational efforts to areas where they are most needed.

Healthcare worker *M. tuberculosis* infection conversion rates (i.e., the number of healthcare workers who have converted to positive divided by the number of healthcare workers tested) should be calculated during the initial risk assessment and then periodically during reassessments for healthcare workers in each area of the hospital and for healthcare workers in job categories that involve work in multiple areas of the facility (e.g., respiratory therapists). Overall hospital conversion rates may dilute high rates in specific units or occupational categories and fail to detect problem areas; therefore, ward- or unit-specific rates should be calculated (113). If a cluster of *M. tuberculosis* infection conversions is identified (i.e., two or more TST conversions or positive IGRAs occurring within a 3-month period among healthcare workers in a specific area or occupational group, with epidemiologic evidence suggesting occupational [healthcare-associated] transmission), additional control measures should be immediately implemented and further evaluation conducted to identify factors that may be leading to transmission (Fig. 38-3).

The most important element of the TB control program is early identification, treatment, and triage of patients with suspected or confirmed infectious TB. To prevent healthcare-associated *M. tuberculosis* transmission, it is essential that all potentially infectious TB patients be rapidly identified on first contact with the healthcare facility. This requires that physicians, nurses, and other triage personnel who perform initial patient evaluations understand the signs and symptoms of TB, the populations at greatest risk of TB, and the appropriate approach to the evaluation and initial management of patients with TB. In addition, written protocols to facilitate the early identification of persons who have infectious TB should be developed. These protocols may vary in different facilities, depending on the incidence of TB in the area and the characteristics of the TB patients treated in the facility.

Previously, most healthcare-associated *M. tuberculosis* transmission was associated with exposure to an unknown or unsuspected TB patient *(158)*. Often, these patients were either unsuspected or unknown, were not receiving anti-TB therapy, or were receiving inadequate therapy. Clinicians should be alert to the possibility of concomitant infection with other pathogens. In particular, HIV-infected patients may be coinfected with *M. tuberculosis* and *Pneumocystis carinii* or *M. avium (67,159)*. For these reasons, HIV-infected patients with signs and symptoms of TB and AFB-positive sputum smears should be

TABLE 38-7

Elements of a Risk Assessment of Tuberculosis in Healthcare Facilities

1. Review the community TB profile (from public health department data).
2. Review the number of TB patients who were treated in each area of the facility (both inpatient and outpatient). (This information can be obtained by analyzing laboratory surveillance data and by reviewing discharge diagnoses or medical and infection control records.)
3. Review the drug-susceptibility patterns of TB isolates of patients who were treated at the facility.
4. Analyze purified protein derivative (PPD) tuberculin skin test results of healthcare workers (HCWs), by area or by occupational group for HCWs not assigned to a specific area (e.g., respiratory therapists).
5. To evaluate infection control parameters, review medical records of a sample of TB patients seen at the facility:

Calculate intervals from:

- Admission until TB suspected
- Admission until TB evaluation performed
- Admission until acid-fast bacilli (AFB) specimens ordered
- AFB specimens ordered until AFB specimens collected
- AFB specimens collected until AFB smears performed and reported
- AFB specimens collected until cultures performed and reported
- AFB specimens collected until species identification conducted and reported
- AFB specimens collected until drug-susceptibility tests performed and reported
- Admission until TB isolation initiated
- Admission until TB treatment initiated
- Duration of TB isolation

Obtain the following additional information:

- Were appropriate criteria used for discontinuing isolation?
- Did the patient have a history of prior admission to the facility?
- Was the TB treatment regimen adequate?
- Were follow-up sputum specimens collected properly?
- Was appropriate discharge planning conducted?

6. Perform an observational review of TB infection control practices.
7. Review the most recent environmental evaluation and maintenance procedures.

(From Centers for Disease Control and Prevention. Centers for Disease Control. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare facilities, 2005. *MMWR Recomm Rep* 2005;54(RR-17):1–147.)

assumed to have TB until proven otherwise. In MDR-TB outbreak settings, early identification, treatment, and triage of infectious TB patients significantly reduced or terminated patient-to-patient and patient-to-healthcare worker transmission (111,*112*,113).

Patients suspected of having TB should be immediately triaged to an appropriate isolation room. In the outpatient setting (e.g., emergency room or clinic), such patients should not be placed in common waiting rooms or in areas where air is recirculated to other patient areas without high-efficiency particulate air (HEPA) filtration. They should either be masked (surgical masks) or instructed to cover their mouth and nose with tissues when coughing or sneezing while they are waiting or being evaluated. Ambulatory care settings in which patients with TB are frequently examined or treated should have a room that is equipped for TB isolation.

Inpatients should be placed in AII rooms and promptly evaluated for TB by appropriate history, physical examination, TST or IGRA, and appropriate laboratory (smears and cultures) and radiologic tests. Healthcare facilities in which TB patients are evaluated should have the capability to provide AFB sputum smear results to clinicians within 24 hours. To reduce the time from specimen collection until smear, culture, and antimicrobial-susceptibility results are available, more rapid methods such as fluorescence staining of smears and use of radiometric culture and susceptibility testing and genetic probes are recommended *(160,161)*.

Prompt treatment with appropriate antimicrobial agents significantly reduces the period of infectiousness. Because of the relatively high proportion of adult patients with TB caused by microorganisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the 6-month regimen to be maximally effective *(162)*.

Patients in TB isolation should remain in their rooms with the door closed, unless a medically essential procedure is necessary and cannot be performed in the room. Persons entering AII rooms should wear appropriate respiratory protective devices (see below). Patients with suspected or confirmed TB should remain in isolation until the diagnosis of TB has been ruled out or until they are no longer infectious (i.e., they have clinical improvement *and* negative AFB sputum smears on three separate days). Patients with MDR-TB are at risk of relapse and thus should be considered for isolation during their entire hospitalization. When infectious TB patients are kept in appropriate isolation rooms, the risk of healthcare-associated *M. tuberculosis* transmission from patient to patient is significantly reduced (111,*112*,113,114,*115–123*). When TB patients are to be discharged, continuation of therapy should be ensured by coordinating with the public health department and local healthcare providers prior to the time of discharge. The patient's treatment strategy should always emphasize directly observed therapy.

The last element of administrative controls is providing healthcare workers with education and training about TB. All healthcare workers should be educated about the epidemiology and the pathogenesis of TB, the risk of occupational *M. tuberculosis* transmission, the infection control measures needed to reduce *M. tuberculosis* transmission, the increased risk of disease in immunocompromised healthcare workers, the importance of adhering to infection control recommendations, the importance of the healthcare worker *M. tuberculosis* infection detection (TST/IGRA) program, and the importance of prompt evaluation of healthcare workers with symptoms consistent with TB.

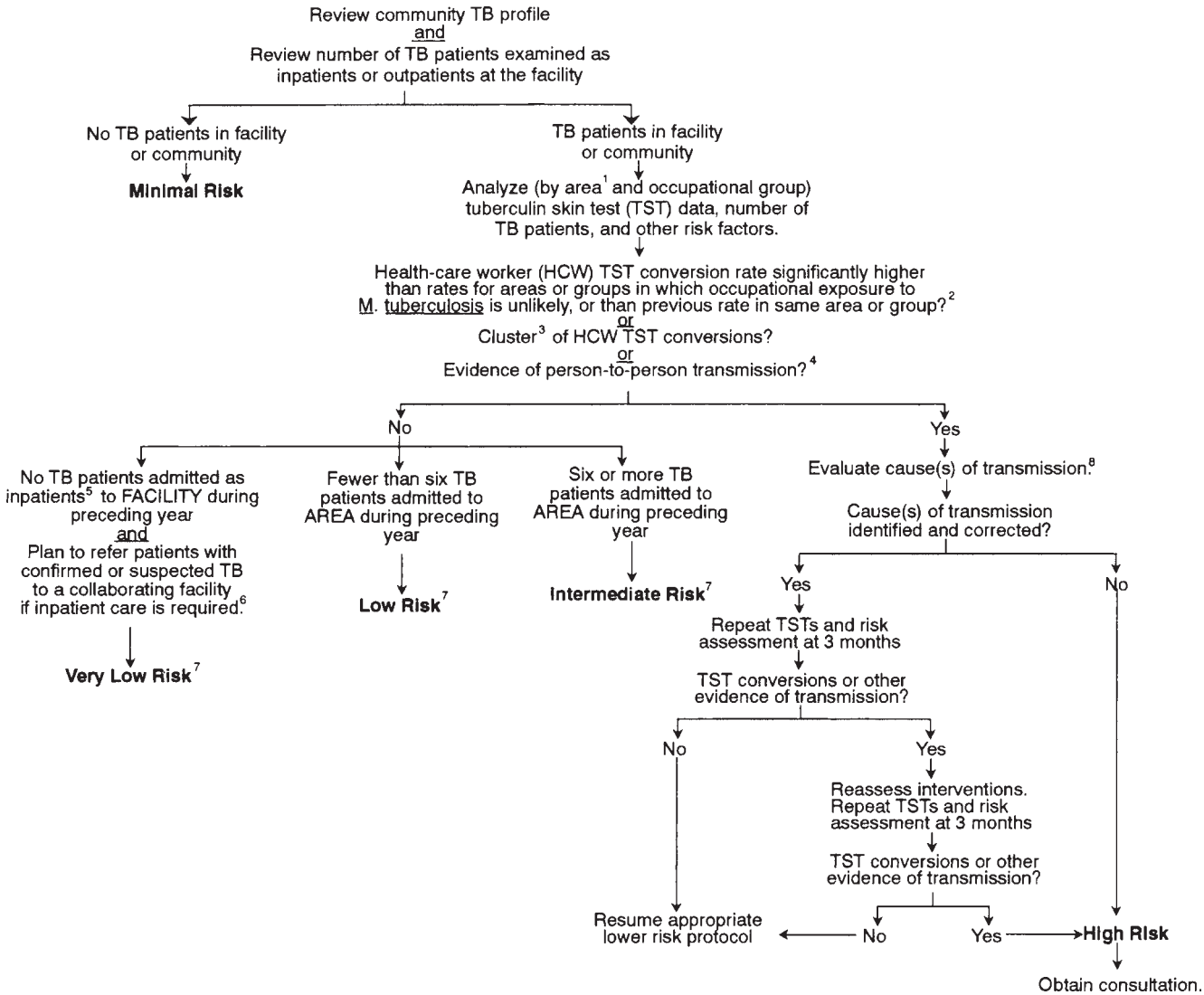

FIGURE 38-2 Example of an algorithm for conducting a tuberculosis risk assessment in a healthcare facility.

Environmental Controls

The most important environmental control measures include engineering controls via ventilation and the use of UVGI. There are a variety of methods that can be used to reduce the concentration of airborne droplet nuclei and achieve appropriate directional airflow (i.e., negative pressure) (Table 38-8). Ventilation controls can be divided into local exhaust, general exhaust, and air cleaning.

Local Exhaust Ventilation Local exhaust captures infectious droplet nuclei at the source and removes them before dispersion into the air. This is the safest and most efficient type of control, since it prevents infectious *M. tuberculosis* particles from ever getting into the air circulation system. This method is primarily used during medical procedures, such as sputum induction, bronchoscopy, or aerosolized pentamidine administration. Local exhaust hoods can be of the enclosing type, where the hood totally or partially encloses the source, or the exterior type, where the source is near but not inside the hood. The enclosing type of hood, booth, or tent is preferable *(163)*. Booths or other enclosing-type devices should have sufficient air flow capacity to remove nearly 100% of airborne particles between patient uses. The time required to remove airborne particles depends on the number of air changes per hour, the rate at which air enters the device, the location of the air inlet and outlet, and the rate of air exhaust. To minimize the possible escape of infectious *M. tuberculosis* droplet nuclei, the exhaust fan should be located on the discharge side of the filter at the booth discharge. For exterior devices, the patient should face directly into the opening and the air flow should be sufficient (200 ft/min) across the patient's breathing zone to prevent crosscurrents near the patient's face.

Air from booths, tents, and hoods may be discharged into the room in which the device is located or it may be exhausted to the outside. If the air is discharged into the

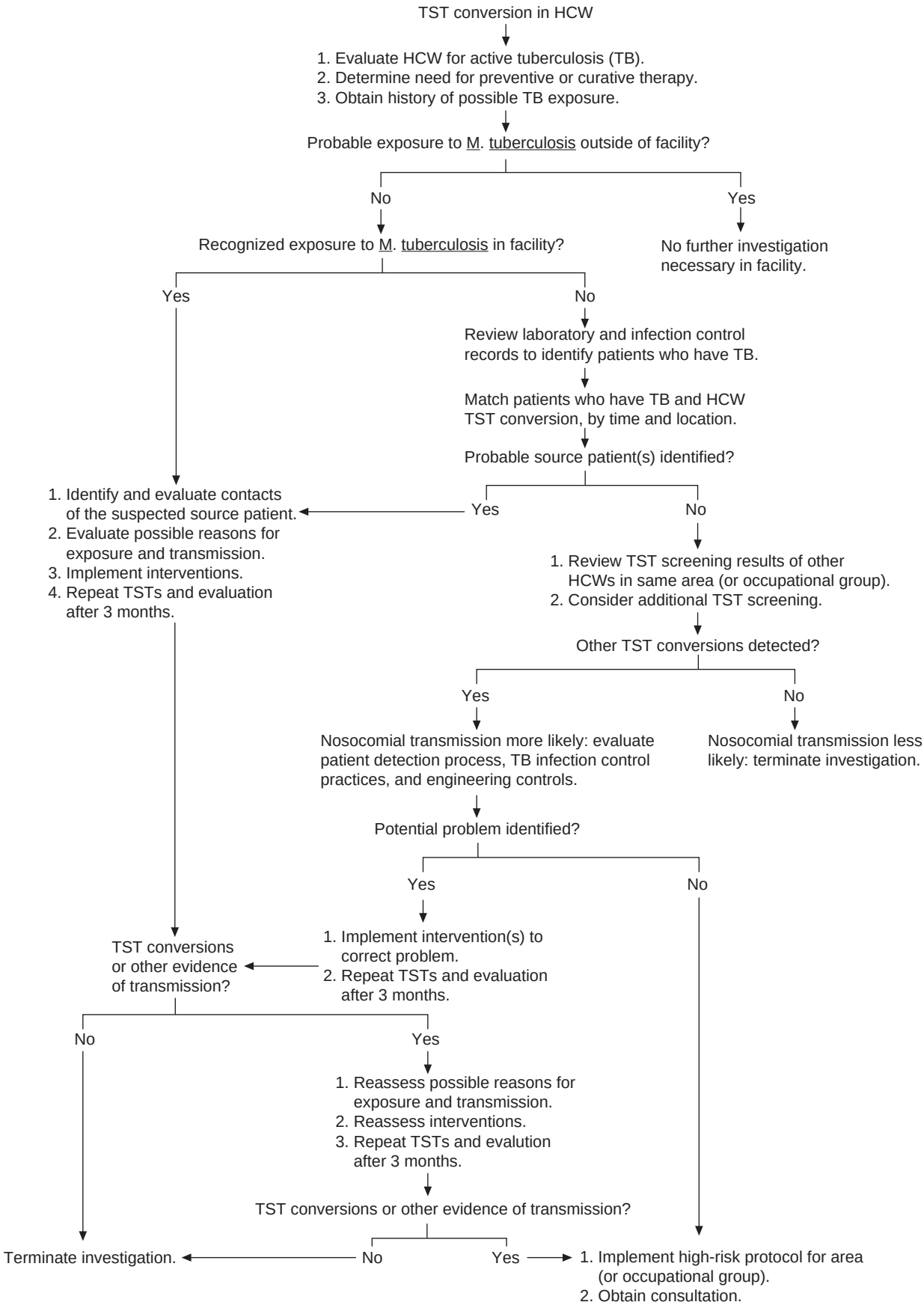

FIGURE 38-3 Example of an algorithm for investigating tuberculin skin test (TST) conversions in healthcare workers (HCWs).

room, a HEPA filter should be incorporated at the discharge duct or vent of the device. The exhaust fan should be located on the discharge side of the HEPA filter to ensure that the air pressure in the filter housing and booth is negative with respect to adjacent areas. If the device does not incorporate a HEPA filter, the air from the device should be exhausted directly to the outside.

General Exhaust Ventilation General ventilation reduces airborne contaminants by dilution and removal and can be achieved by either single-pass or recirculating systems. In single-pass systems, the supply air is either outside air or air from a central system that supplies a number of areas. After air passes through the room or the area, 100% of that air is exhausted directly to the outside. This type of ventilation system is preferred in areas where infectious airborne contaminants exist, since it prevents contaminated air from being recirculated to other areas of the facility. In recirculating systems, a small portion of the exhaust air is discharged to the outside and is replaced with fresh air, which mixes with the portion of exhaust air that was not discharged to the outside. The resulting mixture, which can contain a large proportion of contaminated air, then is recirculated to the areas serviced by the system. If the air mixture is recirculated into the general ventilation, airborne contaminants could be carried from contaminated to uncontaminated areas. Alternatively, the air mixture could be recirculated only within a specific room or area in which case other areas of the facility will not be affected.

Recommended general ventilation rates for healthcare facilities are based on comfort and odor control rather than infection control considerations. For facilities built or renovated before 2001, the American Society of Heating, Refrigerating, and Air Conditioning Engineers (ASHRAE) and the American Institute of Architects (AIA) recommend six air changes per hour for isolation and treatment rooms *(164,165)* to reduce the concentration of droplet nuclei. Where feasible, this airflow should be increased to 12 air changes per hour by adjusting or modifying the ventilation system or by using auxiliary means (e.g., recirculation of air through fixed HEPA filtration units or portable air cleaners or use of UVGI). Since 2001, the AIA has recommended 12 air changes per hour for renovated or newly constructed isolation and treatment rooms (166), a recommendation now endorsed by the CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC) *(167)*.

The number of air changes per hour is equal to the ratio of the volume of air entering the room per hour to the room volume and is equal to the exhaust flow divided by the room volume multiplied by 60. Because air mixing within a room usually is not perfect, this calculated ventilation rate should be multiplied by a mixing factor to estimate the effective ventilation rate (157). Although ventilation rates higher than six air changes per hour probably improve dilution and removal of airborne particles, few if any studies have been done assessing the efficacy of this or any other level of air flow in reducing transmission of *M. tuberculosis*. Airflow patterns should be from more clean to less clean areas. For example, in emergency departments or AII rooms, air should flow inward to prevent spread of airborne infectious droplet nuclei.

AII isolation rooms should be designed to have negative pressure with respect to the hallway or adjacent rooms. The airflow direction in AII rooms should be checked with smoke tubes on a periodic basis, preferably each day that an infectious TB patient is in the room. An anteroom outside the AII room is not essential, but may serve as an extra measure of protection to prevent the escape of droplet nuclei during opening and closing of the isolation room door.

Air from AII rooms and treatment rooms used for patients with TB should be exhausted directly to the outside of the building and away from air-intake vents, persons, and animals in accordance with applicable laws and regulations. If recirculation of air from such rooms into the general ventilation system is unavoidable, the air should be passed through a HEPA filter before recirculation.

TABLE 38-8

Hierarchy of Ventilation Methods for Tuberculosis Isolation Rooms and Treatment Rooms

Reducing concentration of airborne tubercle bacilli[a]
Facility heating, ventilation, and air-conditioning system
Fixed room-air high-efficiency particulate air (HEPA) recirculation system
Wall- or ceiling-mounted room-air HEPA recirculation system
Portable room-air HEPA recirculation unit[b]
Achieving directional airflow using negative pressure[c]
Facility HVAC system
Bleed air[d] from fixed room-air HEPA recirculation system
Bleed air from wall- or ceiling-mounted room-air HEPA recirculation system
Bleed air from portable room-air HEPA recirculation unit
Exhaust air from room through window-mounted fan[e]

[a]Ventilation methods are used to reduce the concentration of airborne tubercle bacilli. If the facility HVAC system cannot achieve the recommended ventilation rate, auxiliary room-air recirculation cleaning methods may be used. These methods are listed in order from the most desirable to the least desirable. Ultraviolet germicidal irradiation may be used as a supplement to any of the ventilation methods for air cleaning.

[b]The effectiveness of portable room-air HEPA recirculation units can vary depending on the room's configuration, the furniture and persons in the room, the placement of the unit, the supply and exhaust grilles, and the achievable ventilation rates and air mixing. Units should be designed and operated to ensure that persons in the room cannot interfere with or otherwise compromise the function of the unit. Fixed recirculating systems are preferred over portable units in TB isolation rooms of facilities in which services are provided regularly to TB patients.

[c]Directional airflow using negative pressure can be achieved with the facility HVAC system and/or the auxiliary air recirculation cleaning systems. These methods are listed in order from the most desirable to the least desirable.

[d]To remove the amount of return air necessary to achieve negative pressure.

[e]This method simply achieves negative pressure and should be used only as a temporary measure.

(From Centers for Disease Control and Prevention. Centers for Disease Control. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare facilities, 2005. *MMWR Recomm Rep* 2005;54(RR-17):1–147.)

Air Cleaning: High-Efficiency Particulate Air Filtration High-efficiency particulate air filtration can be used as a method of air cleaning to supplement other ventilation measures. HEPA filters can be used in a number of ways to reduce the concentration of infectious droplet nuclei in the air. These methods include placement of HEPA filters (a) in exhaust ducts to remove droplet nuclei from air being discharged from a room or a booth to the outside or into the general ventilation system; (b) in fixed room-air cleaners, which may be built into a room or may be mounted on the wall or ceiling; and (c) in portable room-air cleaners. With wall- or ceiling-mounted or portable HEPA filter units, the effectiveness of the unit is dependent on all the air in the room circulating through the HEPA filter, which can be difficult to achieve. The effectiveness also is dependent on the room configuration, unit placement, and location of furniture and people. Thus, the effectiveness of the unit may vary considerably in rooms with different configurations or in the same room if moved from one location to another within the room. Portable HEPA filtration units have been evaluated for their ability to remove aerosolized particles in the size range of *M. tuberculosis (168)*. Although this study indicates that portable filtration units reduce levels of airborne particles similar in size to infectious droplet nuclei, studies are needed to confirm that these units reduce *M. tuberculosis* exposure risk. If HEPA filtration units are used, they must be installed, maintained, and monitored properly.

Ultraviolet Germicidal Irradiation UVGI is effective in killing *M. tuberculosis* under experimental conditions *(169–172)*. UVGI is another method of air cleaning that can be used to supplement other TB control measures. UVGI can be installed in the ventilation duct, as was the case in the experiments of Riley et al. *(169–172)*, or can be placed in the upper part of the room. Duct UVGI, in which UV lamps are placed inside the ducts that remove air from the room, has two advantages: high levels of UV irradiation may be produced; and since the UVGI is inside the duct, the risk of human exposure is reduced or eliminated. Duct UVGI is dependent on adequate air flow from the room into the duct. Duct UVGI may be particularly useful in AII rooms and other patient areas, such as waiting rooms and emergency departments. Most of the experimental data on UVGI are derived from studies using duct irradiation.

In upper room air irradiation, UVGI lamps are suspended from the ceilings or mounted on walls. The lamp must be shielded so that radiation is directed upward rather than down toward patients or healthcare workers. The UVGI disinfects the upper air; thus, adequate air mixing in the room is essential. Contact time is very important; thus, increased ventilation rates actually may decrease the efficacy of UVGI. The effectiveness of upper room UVGI depends on the room configuration, lamp placement, air flow pattern and mixing, intensity of the UVGI, relative humidity, and contact time.

Appropriate installation, regular maintenance, and monitoring are essential if UVGI is used. Short-term exposure to UV irradiation can cause keratoconjunctivitis or erythema of the skin (173). UVC radiation is classified by the International Agency for Research on Cancer as "probably carcinogenic to humans" *(174)*. Recommended exposure limits for occupational exposure to UV radiation have been published (173). If UVGI is used, workers should be educated about how UVGI works and its limitations, the potentially hazardous effects of overexposure, the potential for photosensitivity, and the principles of maintenance of UVGI fixtures.

Respiratory Protection

The precise level of effectiveness of respiratory protective devices in protecting healthcare workers against inhaling *M. tuberculosis* is unknown. Numerous studies have been conducted on the efficacy of respiratory protection for other hazardous airborne materials, but not *M. tuberculosis*. Information concerning the transmission of *M. tuberculosis* is incomplete; for example, neither the smallest infectious dose of *M. tuberculosis* nor the highest level of exposure to *M. tuberculosis* at which transmission will not occur has been defined. The size distribution of droplet nuclei and the number or concentration of viable *M. tuberculosis* particles generated by infectious TB patients have not been adequately defined. Nevertheless, personal respiratory protection should be used by (a) persons entering rooms where patients with known or suspected TB are being isolated, (b) persons present when cough-inducing or aerosol-generating procedures are performed on such patients, and (c) persons in other settings where administrative and engineering controls are not likely to protect them from inhaling infectious airborne droplet nuclei. These other settings should be identified on the basis of the facility's risk assessment. Respiratory protective devices used in these settings should have characteristics that are suitable for the microorganism they are protecting against and the settings in which they are used.

In 1990, the CDC first recommended that particulate respirators be used by healthcare workers for protection against inhalation of *M. tuberculosis (175)*. In 1994, the CDC's TB guidelines enhanced its recommendations to include specific performance criteria (157). In 1995, the National Institute for Occupational Safety and Health (NIOSH) developed a new set of regulations, 42 CFR 84, for testing and certifying nonpowered, air-purifying, particulate-filter respirators *(176)*. The new regulation provides for nine classes of filters (three levels of filter efficiency, each with three categories of resistance to filter efficiency degradation). The three levels of filter efficiency are 95%, 99%, and 99.97% (referred to as 95, 99, 100). The three categories of resistance to filter efficiency degradation are as follows: not resistant to oil, resistant to oil, and oil proof (labeled as N, R, and P). For example, a filter labeled N95 would mean an N-series respirator (not resistant to oil) that is at least 95% efficient. All nine classes of nonpowered, air-purifying, particulate-filter respirators certified under 42 CFR 84 meet or exceed the CDC filtration efficiency performance criteria set forth in the 1994 CDC Guidelines. Current Occupational Safety and Health Administration (OSHA) policy permits the use of any 42 CFR 84 particulate filter for protection against TB *(177)*.

To understand the complex nature of arriving at an appropriate respirator recommendation for healthcare workers to prevent occupational acquisition of TB, it is important to understand the relationship between OSHA and NIOSH. OSHA requires that any respiratory protective device used to protect workers *must be* NIOSH-certified.

NIOSH certifies respirator filtration in two ways. N100, R100, and P100 particulate-filter respirators are challenged with the most penetrating aerosol size (~0.3 μm) particles; 99.97% of particles must be collected in a filter (i.e., the instantaneous penetration must be <0.03%). N99, R99, and P99 are challenged with the same-size aerosol, with 99% of the particles collected (<1% penetration). N95, R95, and P95 are challenged with the same-size aerosol, with 95% of the particles collected (<5% penetration). No certification test uses a biologic particle or a particle size similar to that of *M. tuberculosis*, nor is there evidence to indicate that a biologic particle acts any differently than a nonbiologic particle.

Based on all of the above considerations, the CDC recommends that respiratory protective devices used in healthcare settings for protection against inhaling *M. tuberculosis* should meet the following standard criteria: (a) the ability to filter particles 1 μm in size in the unloaded state with a filter efficiency of 95% at flow rates of up to 50 L/min; (b) the ability to be qualitatively or quantitatively fit-tested in a reliable way to obtain a face-seal leakage of ≤10%; (c) the ability to fit different facial sizes and characteristics of healthcare workers, which can usually be met by making the respirators available in at least three sizes; and (d) the ability to be checked for face-piece fit by healthcare workers each time they put on their respirator. The facility's risk assessment may identify a limited number of selected settings (e.g., bronchoscopy performed on patients suspected of having TB) where the estimated risk for transmission of *M. tuberculosis* may be such that a level of protection exceeding the standard criteria is appropriate. The N95 respirators meet the above criteria.

Follow-up data from several of the MDR-TB outbreak hospitals show that use of submicron surgical masks or dust-mist respirators that meet the CDC filtration criteria, when used with a fully implemented CDC TB control program, prevents patient-to-healthcare worker *M. tuberculosis* transmission (111,*112*,113). Furthermore, *in vitro* studies of particulate respirators show that some dust-mist or dust-fume-mist respirators filter >95% of particles with a mean size of 0.8 μm, smaller than the estimated size of droplet nuclei that contain *M. tuberculosis*.

Factors used to determine the efficacy of respirators include face seal and filter efficacy. Face-seal leakage may compromise the ability of particulate respirators to protect the healthcare worker from airborne droplet nuclei. Face-seal leakage may result from incorrect face-piece size or shape, defective face-piece or sealing lip, beard growth, moisture (i.e., perspiration, facial oils), failure to use the head straps properly, improper maintenance, or damage. Filter leakage through the respirator is dependent on filter filtration characteristics, size of the aerosol, velocity through the filter, filter loading, and electrostatic charge. All healthcare workers with potential exposure to infectious TB patients should be fit tested and trained in the proper use and maintenance of respirators and should fit check the respirator before each use in accordance with the OSHA regulations, which require that a respiratory protection program be in place whenever a respirator is used to prevent exposure of the healthcare worker, regardless of class of respirator. The OSHA-mandated program includes written standard operating procedures, selection of respirators based on the hazard, respirator use instruction and training, cleaning and disinfection of the respirators, storage of the respirators, inspection of the respirators, surveillance of work area conditions, evaluation of the respirator protection program, medical evaluation of the user's ability to wear a respirator, and the use of NIOSH-certified respirators.

BCG Vaccination

Because of the risk of occupational acquisition of TB, some have advocated the BCG vaccination of healthcare workers. Over the years, there has been considerable debate about the efficacy of BCG. A large number of studies of BCG vaccination of infants have been conducted. These studies provide widely disparate results, with vaccine efficacy ranging from 0% to 100% *(178)*. Differences in vaccine efficacy may be due to different BCG products used, different populations studied (e.g., rural vs. urban, high risk vs. low risk, geography), differences in the prevalence of TB and nontuberculous mycobacteria, or the intensity of follow-up. These studies suggest that when BCG is efficacious, it does not prevent infection but rather prevents disseminated disease or mortality, especially in infants and young children. Few data exist assessing the efficacy of BCG given for the first time in adulthood. This would be the situation with healthcare workers in most U.S. hospitals, since BCG is not given in infancy in the United States.

Potential advantages of using BCG are that it is inexpensive and that, even with 50% efficacy, it might reduce the risk of TB disease in some healthcare workers. The disadvantages are that, once given, it will hinder the interpretation of the TST (but perhaps not the IGRA) as a measure of *M. tuberculosis* infection, thus halting the use of preventive therapy, an intervention with a known and predictable effectiveness. TST studies among healthcare workers in the Ivory Coast, Thailand, and Brazil showed that having a BCG scar was associated with a positive TST when considering the 10-mm cutoff *(144,145,147)*. No association between having a BCG scar and a positive TST was seen when using the 15-mm cutoff. Furthermore, BCG is unlikely to be protective (and may even be harmful) in the highest risk healthcare worker group, those who are infected with HIV or are otherwise severely immunocompromised.

Transmission of *M. tuberculosis* in healthcare facilities poses a risk not only to healthcare workers, but also to patients, volunteers, and visitors. Therefore, BCG vaccination of healthcare workers cannot substitute for a comprehensive TB infection control program. In the United States, BCG vaccination of healthcare workers may be considered on an individual basis in high-risk settings where (a) a high proportion of *M. tuberculosis* isolates are resistant to both isoniazid and rifampin, (b) there is a strong likelihood of transmission and infection with such drug-resistant microorganisms, and (c) comprehensive TB infection control precautions have been implemented but have proved inadequate. BCG vaccination is not recommended for HIV-infected persons. BCG vaccination is not recommended for healthcare workers in settings in which there is a relatively high risk of *M. tuberculosis* transmission but most isolates are susceptible to isoniazid or rifampin, nor is it recommended in settings in which there is a low risk of transmission *(179)*.

Special Considerations in Pediatric Hospitals

It is a widely held belief that pediatric TB patients usually are not infectious. Unfortunately, this is the result of

historical belief rather than extensive published scientific data. Several factors are given for assuming that pediatric patients are less infectious. First, pediatric patients usually present with primary disease, whereas adults usually present with disease resulting from progression of LTBI. For this reason, it is believed that the bacterial burden is less in pediatric TB patients. Second, pediatric TB patients, particularly those <10 years of age, usually do not produce sputum with coughing. Most pediatric TB patients are diagnosed as a result of contact investigation of an adult, and <50% of pediatric patients with active disease have a positive culture. In contrast, adults often have cavitary, endobronchial, or laryngeal TB and cough and have AFB-positive sputum smears.

Despite these facts, there is no documentation that pediatric patients always are noninfectious, and markers to identify infectious pediatric TB patients have not been developed. In contact investigations, an adult with TB is usually present, and any secondarily infected patients are thought to have acquired the infection from the adult rather than the pediatric patient. Although one study reports TST conversion rates between 0.03% and 0.40% from 1986 to 1994 among workers in a pediatric hospital in Ohio with mandatory annual TST screening *(56)*, most children's hospitals have not maintained active healthcare worker TST programs (particularly including house staff or attending physicians), so that documentation of TST negativity after pediatric TB patient exposures is lacking. An observational study of adherence to TB control guidelines was conducted during 1996 to 1997 in two pediatric hospitals *(178)*. Investigators noted that despite frequent lapses in respiratory protection and isolation, neither institution had documented any healthcare worker TST conversions in the previous 2 years. These studies suggest that the risk to workers in pediatric hospitals is low, but no separate guidelines for pediatric hospitals exist. The TB infection control program in a pediatric hospital should be designed with consideration of the epidemiology of TB in its catchment area and with awareness that teenage patients with active TB may be as infectious as adults.

Because pediatric patients with suspected or confirmed TB may transmit *M. tuberculosis*, such patients should be evaluated for potential infectiousness using the same criteria as adults (i.e., on the basis of symptoms, radiologic findings, sputum AFB smears, treatment status, and performance of cough-inducing or aerosol-generating procedures). Children who may be infectious should be placed in AII until the diagnosis of TB is ruled out or they are determined to be noninfectious. Pediatric patients who may be infectious include those with laryngeal or extensive pulmonary involvement (especially with pulmonary cavitation), pronounced cough, or AFB-positive sputum smears, or those for whom cough-inducing procedures are being performed. Because the source of infection for a child with TB often is a member of the child's family, parents and other visitors of all pediatric TB patients should themselves be evaluated for TB as soon as possible *(96b)*.

Regulation of Tuberculosis Infection Control

The OSHA has been concerned about the safety of healthcare workers from the threat of occupationally acquired TB infection. In 1997, OSHA published a draft standard for the protection of healthcare workers from TB in hospitals, but to date no standard has been adopted *(179)*. Concern expressed from the medical community over the necessity and cost of such regulation and potential compromise of patient care has halted implementation of these proposed regulations indefinitely. Even without regulation, hospitals have improved their application of TB infection control guidelines (114,*180*), although institutions still exhibit problems with the inclusion of attending physicians and house officers in mandatory employee TB screening programs, consistent use of appropriate respiratory protection by healthcare workers, or testing of engineering controls in isolation rooms (114,*178,180,181*). Despite these lapses, these studies did not find evidence of ongoing transmission of *M. tuberculosis* to healthcare workers. In hospitals that apply the CDC guidelines, the risk of exposure to *M. tuberculosis* in the workplace can be minimized effectively in both low- and high-transmission areas *(56,59)*. In light of hospitals' continued improvement in the application of CDC guidelines, OSHA will continue to regulate TB infection control under its general duty clause for employee protection from hazards in the workplace, rather than under separate and specific TB infection control regulations.

The OSHA general duty clause states in section 5(a) *(1)* of the Occupational Safety and Health Act of 1970 that the employer "shall furnish.. a place of employment which is free from recognized hazards that are causing or are likely to cause death or serious harm to his employees." Every hospital that may treat a patient with active TB should maintain a TB protection program addressing five abatement methods outlined by OSHA's 1993 enforcement policy *(183)*: (a) a protocol for early identification of patients with active TB, (b) a program of medical surveillance of employees, (c) evaluation and management of employees with a positive TST or active TB, (d) isolation of persons with suspected or confirmed TB, and (e) appropriate training of employees. The implementation of these methods may be tailored to the specific needs of the institution; OSHA expects institutions to follow the CDC guidelines in selecting these methods (157). In the states and territories where OSHA has direct jurisdiction, citations for failure to protect healthcare workers may be issued only where exposure of workers to *M. tuberculosis* occurs and where every known feasible and useful method to correct the hazard has not been implemented. Hospitals are in compliance with OSHA as long as the methods they select for TB control ensure that no exposure occurs *(184,185)*.

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CHAPTER 39

Nontuberculous Mycobacteria

Barbara A. Brown-Elliott and Richard J. Wallace, Jr

Although the existence of nontuberculous mycobacteria (NTM) was recognized over a century ago, the microorganisms were originally thought to be contaminants or harmless colonizers. Increases in numbers of severely immunosuppressed patients, extensive utilization of invasive procedures, and more sensitive diagnostic tests have contributed to an increase in the isolation of the NTM from clinical samples (*1–6*,7). As a consequence, over the past four decades, the recognition and relative importance of NTM as a cause of human disease have increased dramatically. NTM are ubiquitous in nature, having been isolated from a variety of environmental sources, including dust, water, soil, domestic and wild animals, milk, and food *(5,8–18)*. More than 130 species are currently recognized. While many of these species are nonpathogenic, an increasing number, including *Mycobacterium avium* complex (MAC), *M. kansasii*, *M. chelonae*, *M. fortuitum*, *M. mageritense*, *M. xenopi*, *M. lentiflavum*, *M. marinum*, *M. simiae*, *M. haemophilum*, and *M. genavense*, have been associated with disease in normal and immunosuppressed hosts *(1,2,4,19–30)*. A select number of these species have also been linked to healthcare-associated disease, including the *M. fortuitum* group, the *M. chelonae/abscessus* group (including *M. immunogenum*, *M. chelonae*, and *M. abscessus* [recently reclassified as *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii (31)*, and collectively referred to hereafter as *M. abscessus* group]), *M. neoaurum, M. bacteremicum, M. kansasii,* MAC, and *M. xenopi*.

MICROBIOLOGY

The slowly growing NTM, including those species usually associated with healthcare-associated diseases, grow well on the same types of media used for cultivation of *M. tuberculosis* complex (MTBC). Optimal incubation temperatures vary from 28°C (for species typically associated with cutaneous infections such as *M. marinum, M. haemophilum*, and *M. chelonae*) to 35°C to 37°C for most of the slowly growing NTM.

M. xenopi grows optimally at 42°C to 43°C but, with prolonged incubation, will grow at 37°C. Most species produce visible colonies on solid agar within 7 to 14 days. More than 60 species of rapidly growing mycobacteria (RGM) are recognized, with this number increasing rapidly with the primary use and availability of 16S ribosomal RNA (rRNA) gene sequencing for identification. The RGM are susceptible to the NaOH decontamination process performed on sputum to facilitate isolation of MTBC. They are nonfastidious microorganisms that produce mature, visible colonies on solid agar in 3 to 7 days. The microorganisms grow well at 30°C to 37°C on standard bacterial media, including 5% sheep's blood and chocolate agar, and on media specifically formulated for mycobacterial species. Isolation of *M. chelonae* is optimal at an incubation temperature of 28°C to 32°C.

IDENTIFICATION

The reemergence of tuberculosis including multidrug-resistant strains (MDR and XDR) as well as the heightened awareness of NTM as human pathogens has fueled an intense effort to develop rapid and accurate methods of identifying mycobacteria at the species level. Traditional identification schemes for slowly growing species utilize growth rates, pigment production, and biochemicals such as niacin production, urease, and catalase. Biochemical tests traditionally used in identifying the pathogenic RGM include the rapid (3-day) arylsulfatase reaction, iron uptake, nitrate reduction, and the ability to utilize mannitol, inositol, and/or citrate as carbon sources *(32)*. Although these biochemical methods (utilized throughout the 1980s) have been replaced by molecular methods and high-performance liquid chromatography (HPLC), some laboratories report the NTM only to a group or complex level.

The decade of the 1990s saw identification of NTM by HPLC *(33,34)*, while the last 10 years have seen a revolution of molecular-based tests, including commercial DNA probes, polymerase chain reaction (PCR) amplification followed by PCR restriction-enzyme analysis (PRA), 16S rRNA *rpoB*, *hsp65*, and other gene sequencing *(35–40)*. HPLC methods for separation of mycolic acids have allowed the identification of some slowly growing mycobacterial species and some RGM groups or complexes, with a greater specificity and speed than traditional biochemical methods *(33,34)*. Nonradioactive commercial probes are available (Accu-Probe, Gen-Probe) and are routinely utilized for identifying isolates of MTBC, MAC, *M. kansasii,* and *M. gordonae*. These probes offer excellent sensitivity and specificity, and because they can be used directly on broth

cultures (usually the first medium to show growth), they have significantly reduced the time for final reporting of results *(41,42)*. Currently, no commercial probes are available for identification of the RGM. Newest among the modern identification methods are adaptations of PCR technology for detection and identification of mycobacteria in clinical samples *(43)*. Two different nucleic acid amplification techniques for assaying directly from sputum are now commercially available (Amplicor, Roche; and MTD test, Gen-Probe) and are approved for detection of *M. tuberculosis*. Currently, no systems are commercially available for direct detection of NTM from clinical specimens or for species identification of pure cultures, although several novel approaches have been published. One approach utilizes PCR to amplify the gene encoding the 16S rRNA. The amplified fragment is then analyzed by species-specific probes or partial nucleotide sequencing *(39)* for speciation. A second approach capitalizes on species-specific restriction fragment length polymorphisms (RFLPs) in a PCR-amplified segment of the 65 kDa heat shock protein gene *(44–46)*.

TYPING SYSTEMS

Typing systems for RGM have utilized a number of phenotypic and genotypic methods, including detailed species identification, heavy metal and antimicrobial susceptibility patterns, plasmid profiles, multilocus enzyme electrophoresis (MEE), pulsed-field gel electrophoresis (PFGE), and, more recently, random amplified polymorphic DNA (RAPD) PCR (*47*,48,49,*50–52*). PFGE has proven to be a highly useful tool for strain typing of RGM. This method utilizes restriction endonucleases with rare recognition sites such as *Xba*I, *Dra*I, and *Asn*I to generate a small series of large genomic restriction fragments (LRFs), the pattern of which is strain specific. Wallace et al. (48) described the use of PFGE to type *M. chelonae* and the *M. abscessus* group with three reference strains, 28 sporadic isolates, and 62 healthcare-associated isolates from 10 healthcare-associated outbreaks. LRF patterns satisfactory for comparison were achieved in 54% of the *M. abscessus* group and 90% of *M. chelonae* isolates by using the restriction endonucleases *Dra*I, *Asn*I, *Xba*I, and *Spe*I. The sporadic isolates were all highly variable. Isolates from 5 of 10 outbreaks that gave satisfactory LRF patterns were identical. Strains that had been repetitively isolated from patients over periods of time ranging from 2 to 11 years demonstrated that LRF patterns were highly stable. Previous studies with *M. fortuitum* with this technique showed similar results, except that satisfactory LRF patterns were obtained with all strains studied (49,*53*). Environmental water isolates were identical (clonal) to some outbreak strains, indicating that water was the likely source of these past outbreaks. No human carrier or environmental nonwater sources have been identified as an outbreak source by this technique. PFGE is currently the most definitive epidemiologic tool available for comparing suspected outbreak strains of most isolates and species of RGM.

More recently, methods have been introduced for DNA stabilization, which prevent the DNA denaturation seen with PFGE with select strains of bacterial species. Application of one of these methods, the use of hydroxyurea in the running buffer, allows for quality PFGE patterns with the approximate 50% of the *M. abscessus* strains that produced broken DNA *(50)*.

Another nucleic acid amplification technique, RAPD-PCR or arbitrary primer -PCR, has also been applied to the investigation of outbreaks of the *M. abscessus* group *(50–52)*. This technique offers the advantage of being simpler and unaffected by spontaneous lysis of the DNA sample during preparation for PFGE, as occurred previously with 50% of isolates of *M. abscessus* (48). Its major disadvantage is that fewer patterns are produced with each primer; hence, at least three primers that produce quality patterns are needed—a finding that likely reflects the closely related character of these strains *(50,52)*.

PFGE has also been used to study clustering or pseudo-outbreaks of slowly growing mycobacteria, including MTBC, *M. xenopi (53,54)*, *M. kansasii (55,56)*, *M. simiae*, *(57–59),* and MAC *(60–62)*. Other fingerprint techniques used for slowly growing species include MEE with *M. fortuitum (47)*, the *M. abscessus* group *(63)*, *M. simiae (64)*, and the use of hybridization with repetitive insertional elements for *M. xenopi (53)*, *M. kansasii (55)*, and *M. avium (60)*. Previously, serotyping of MAC was used for strain typing *(62)* but currently has been replaced by molecular strain typing.

Recently, a commercial system from DiversiLab system (BioMerieux, Durham, NC), using repetitive elements interspersed throughout the genome, was introduced for strain typing of microorganisms including mycobacteria. The method was reported to be more rapid, required less sample size, and provided equivalent or better than standard RFLP for some species of mycobacteria *(65)*.

Another method that has been evaluated recently with isolates of *M. fortuitum* and the *M. abscessus/chelonae* group is the enterobacterial repetitive intergenic consensus (ERIC) PCR. In an outbreak of the *M. abscessus* subsp. *bolletii* in Brazil recently, the ERIC PCR showed higher discrimination than PFGE for the *M. abscessus* group but less discriminatory power among isolates of *M. fortuitum (66–68)*.

Finally, multigene sequencing has recently been used to characterize isolates of *Mycobacterium* in hemodialysis water and may provide a reliable method of DNA strain typing *(69)*.

EPIDEMIOLOGY

NTM are not reportable by law in most states, and thus, precise estimates of their incidence and prevalence are not available. Most NTM species, with the exception of MAC, are found in specific geographic areas. Overall, MAC is the most common NTM species recovered in the United States, followed by *M. kansasii* and the *M. abscessus* group *(1)*. Although less frequently recovered in the United States, *M. xenopi* is the second most commonly isolated NTM species in England and Canada *(70)*. In some areas of northern Europe, *M. malmoense* is second only to MAC (7). Although this species is rare in the United States, *M. simiae* is second to MAC in some cities in the southwestern United States *(57,58,71,72)*. Tap water and biofilms in the pipes appear to be the major reservoirs for *M. kansasii, M. xenopi*, and *M. simiae*, and a reservoir for *M. avium* and *M. intracellulare* (73).

In contrast to surveys done in the late 1970s and early 1980s *(1,70,74)*, more recent studies show that there

are now more laboratory isolates of NTM in developed countries, especially MAC, than isolates of *M. tuberculosis*. The epidemiology of disease due to NTM has changed because of the improvement in laboratory recovery and identification of these species and the increased awareness of the clinician of these species as potential pathogens. The emergence of better antiretroviral therapies for human immunodeficiency virus (HIV) infection (acquired immunodeficiency syndrome [AIDS]) has resulted in a dramatic decline in the incidence of NTM disease in patients with far advanced disease. Among AIDS patients, MAC had been a common mycobacterial cause of opportunistic infection and a frequent cause of disseminated disease.

The RGM are the most commonly described and the most significant NTM for healthcare-associated epidemiology (75). Of the human diseases attributable to this group of microorganisms, over 90% are due to *M. fortuitum*, the *M. abscessus* group, and *M. chelonae* (*2*,*13*,*21*,75). These species readily survive nutritional deprivation and extremes of temperature. For example, most pathogenic species have been shown to grow and survive in distilled water, and they have been identified from soil, dust, domestic animals, and marine life (*3*,*5*,73,*76*,*77*). Multiple water sources have been identified, including tap water, municipal water, and aquariums (*2*,*3*,*5*,*10*). Mycobacteria have also been found in high numbers in biofilms on water-delivery devices, such as dental hand pieces *(78)*. Similar biofilms may exist within bronchoscope channels, endoscope washers, ice machines, and water tanks, explaining the tendency of these devices to become colonized with mycobacteria. Biofilms are important not only because they enable bacteria to adhere and persist on artificial surfaces but also because they provide protection from the action of disinfectants *(79–82)*.

PATHOGENESIS AND CLINICAL MANIFESTATIONS

The pathology of NTM infection can be identical to that of *M. tuberculosis*. Chronic inflammation, acute suppuration, nonnecrotic epithelioid tubercles, and caseation are all seen on histopathology. The coexistence of granulomatous and acute inflammation (so-called dimorphic inflammatory response) is not seen with tuberculosis but is commonly seen in cervical lymph nodes *(83)* and cutaneous disease *(2,21,84)* due to the NTM. Animal models to study the pathology of NTM have been difficult to develop, even when the animals are immunosuppressed *(85,86)*.

Isolation of NTM in the laboratory may represent an environmental or laboratory contaminant, transient patient colonization, or true disease. In the absence of known environmental contamination, isolation of any NTM from a normally sterile site should be considered significant. Contamination of a skin wound with these microorganisms is rare, and even a single positive culture from this site generally indicates disease. Similarly, recovery of these microorganisms from cultures of lymph node specimens or blood is sufficient for establishing the diagnosis of nontuberculous lymphadenitis or disseminated disease, respectively.

In contrast, isolation of NTM from pulmonary specimens can be particularly difficult to evaluate. The American Thoracic Society last published criteria for the diagnosis of NTM pulmonary disease in 2007 (7). According to these criteria, a definitive diagnosis requires compatible clinical symptoms along with characteristic radiographic abnormalities, which are not attributable to any other cause. Multiple cultures of respiratory specimens are required to demonstrate persistent culture positivity. The microorganism must be grown from two acid-fast bacilli (AFB) specimens of sputum or from at least one specimen obtained from a normally sterile site such as a bronchial wash or bronchopulmonary tissue. The clinical syndromes most commonly associated with NTM infections and the microorganisms usually responsible are summarized in Table 39-1. The major risk factor for pulmonary NTM disease appears to be underlying bronchiectasis.

TABLE 39-1

Clinical Presentations of Nontuberculous Mycobacterial Species

Clinical Syndrome	*Common Causes*	*Less Common Causes*
Bronchopulmonary infection	*M. avium* complex *M. kansasii* *M. abscessus* group	*M. xenopi* *M. fortuitum* group *M. chelonae* *M. malmoense* *M. immunogenum* *M. szulgai* *M. simiae* *M. asiaticum*
Lymphadenitis	*M. avium* complex	*M. malmoense* *M. abscessus* group *M. fortuitum* group
Disseminated disease	*M. avium* complex *M. chelonae*	*M. abscessus* group *M. fortuitum* group *M. haemophilum* *M. genavense* *M. kansasii*
Skeletal and joint infection	*M. marinum* *M. avium* complex *M. fortuitum* group *M. abscessus* group	*M. kansasii* *M. chelonae* *M. haemophilum* *M. goodii*
Skin and soft tissue infection	*M. marinum* *M. fortuitum* group *M. chelonae* *M. abscessus* group *M. ulcerans*	*M. haemophilum* *M. smegmatis* group *(M. goodii, M. wolinskyi)* *M. mageritense*

Note: *M. abscessus* group includes isolates now reclassified as *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *bolletii*.

DESCRIPTION OF COMMUNITY-ACQUIRED INFECTIONS

Rapidly Growing Mycobacteria

Cutaneous Disease RGM most commonly cause post-traumatic and postsurgical skin and soft tissue infections but can also cause lymphadenitis, keratitis, suppurative arthritis, osteomyelitis, endocarditis, peritonitis, bacteremia, and disseminated disease (*21*,*51*,*87–90*,91,*92–98*). In a review of 125 cases of infection due to RGM (*2*), 60% presented with cutaneous manifestations, half of which were due to penetrating trauma. The usual pathogens in this setting are *M. fortuitum*, the *M. abscessus* group, and the former *M. fortuitum* third biovariant complex *(2,99)*. (The major species within the *M. fortuitum* third biovariant complex include *M. porcinum*, *M. houstonense*, *M. senegalense*, and less commonly, *M. boenickei*, *M. brisbanense*, and *M. neworleansense*.) Patients with the *M. fortuitum* group and the *M. abscessus* group are generally healthy, and drug-induced immune suppression is not considered a risk factor in contrast to those patients with *M. chelonae* in which corticosteroid usage is a major risk factor.

Infections are typically chronic and may heal spontaneously or after surgical debridement. Even without medical intervention, the lesions usually remain well localized. Infections typically present as cellulitis with acute and chronic inflammation, which may form ulcers or sinus tracts with serous, watery drainage *(2,51,84,100,101)*.

Disseminated Disease Disseminated disease due to RGM is typically related to immunosuppression, particularly corticosteroid therapy (91,*92*,*93*). Dissemination primarily occurs in patients with *M. chelonae* and, to a lesser degree, with *M. abscessus*. These patients typically have no history of trauma but present with multiple draining skin lesions. Infections with *M. chelonae* and the *M. abscessus* group have been described in solid organ transplant patients, including renal, heart, and lung transplant patients as well as patients with rheumatoid arthritis or other autoimmune disorders on long-term, low-dose corticosteroids *(2,21,93,102)*. In one series of renal transplant patients, 10 patients with *M. chelonae* infections (including both *M. chelonae* and the *M. abscessus* group) were identified over a 6-year period from four hospitals *(103)*.

Pulmonary Disease Chronic pulmonary disease may occur with RGM, especially in older women with bronchiectasis. The *M. abscessus* group accounts for >80% of these cases. Pulmonary infection is usually chronic, insidious, and slowly progressive. Lung infection may also be associated with MAC, and similarities between patients with MAC and those with the *M. abscessus* group suggest a common pathogenicity or host susceptibility defect (7). Patients may have minimal symptoms of cough or fatigue for many years, and subtle changes on high-resolution computed tomography scanning or subtle deterioration in pulmonary function may be the only markers of disease progression. Clinically, these patients are older and typically present with bilateral nodular interstitial disease associated with cylindrical bronchiectasis *(2,21,*75,*104)*. Their presentation appears identical to that in women with MAC lung disease.

Patients with cystic fibrosis may also be involved with increasing frequency, and *M. abscessus* appears to be more frequent than MAC in this setting. Primary risk factors for susceptibility to NTM lung infection include bronchiectasis and chronic recurrent airway and parenchymal infections with other microorganisms (7).

Other RGM including *M. chelonae*, the *M. smegmatis* group, and *M. fortuitum* infrequently may be associated with pulmonary disease in such underlying disorders as achalasia or lipoid pneumonia (7).

Hypersensitivity pneumonitis has been observed among factory workers working with metalworking fluids contaminated with a newly described species, *M. immunogenum (105)*, and among users of poorly maintained indoor hot tubs in association with MAC *(106,107)*.

Bone and Joint Infection

Osteomyelitis may follow open bone fractures, puncture wounds, and hematogenous dissemination. The most frequent pathogens in this setting are members of the *M. fortuitum* group, although two newly described species in the *M. smegmatis* group—*M. goodii* and *M. wolinskyi*—may also be involved (7,*108*).

Slowly Growing Nontuberculous Mycobacteria

Among the slowly growing NTM, *M. malmoense*, *M. kansasii*, MAC, *M. xenopi*, and *M. simiae* can all occasionally cause community-acquired pulmonary or extrapulmonary disease in HIV-negative patients (*4*,7). MAC, *M. kansasii*, *M. haemophilum,* and *M. genavense* are the usual causes of infections including disseminated disease in HIV-infected persons. However, the slowly growing species are less frequent causes of healthcare-associated disease than the RGM (*4*,7). Detailed descriptions of the clinical disease associated with these microorganisms are reported elsewhere (*4*,7,*13*).

Previous studies in different sections of one hospital in Madrid, Spain, have shown identical strains of MAC in clinical samples—21/23 (91%) of urine isolates and 5/19 (26%) of respiratory isolates by PFGE and other typing methods such as hybridization with IS1245 *(109)*. The investigation hypothesized that contamination of clinical samples with an environmental strain was the most likely cause since none of the patients with this strain had disease *(109)*. A similar study in California examined potable water as a possible source of MAC infection in both AIDS and non-AIDS patients. The investigation revealed that the MAC isolates from potable water in three homes, two commercial buildings, one reservoir, and eight hospitals had varying degrees of genetic relatedness to 19 clinical isolates from 17 patients. Hospitals had the highest incidence (93%) of MAC isolates. Aronson et al. stated that the large number of isolates found in hospital water with a close genetic relationship to patient isolates suggested the possibility of a healthcare-associated spread of MAC to immunocompromised patients, especially AIDS patients, although a prospective epidemiologic study was not performed *(110)*.

DESCRIPTION OF HEALTHCARE-ASSOCIATED INFECTIONS

Healthcare-associated mycobacterial infections (almost exclusively due to RGM) have been recognized for more than 25 years and remain relatively common. They have been most often recognized primarily as causes of surgical site infections and postinjection abscesses; however, they have also been reported to cause catheter-related infections, dialysis-related infections, bronchoscope and endoscope contamination, and most recently, infections resulting from cosmetic procedures including plastic surgery, liposuction, and a healthcare-related practice involving subcutaneous injections of minute quantities of various drugs called mesotherapy (*47*,48,111,*112*,113,*114*,*115*). For outbreaks and sporadic reports of infections due to RGM, there is a strong geographic relationship to the Gulf Coast and southeastern states in the United States. Figure 39-1 demonstrates the focal geography of some of the early outbreaks reported in the United States. Recently, several outbreaks of NTM have occurred in South and Central America (*66*,*116*,117,*118–121*).

Surgical Site Infections

Outbreaks of mycobacterial surgical site infections were first recognized in 1975 to 1976 with the report of four such outbreaks *(122–124)*. These reports were followed in the 1980s by at least 14 additional outbreaks *(125–130)*. Outbreaks have been described involving cardiothoracic surgery, plastic surgery, augmentation mammaplasty, and arthroplasty *(122–130)*. A summary of the major healthcare-associated outbreaks due to RGM is given in Table 39-2. Following recognition of epidemic surgical site infections, it became apparent that most surgical site infections due to RGM are sporadic *(21,47,125,131–143)*. Such infections with RGM have been described following vascular surgery, oophorectomy, neurosurgery, corneal surgery, the insertion of middle ear tubes, biopsy procedures, and plastic surgery, including procedures such as face-lifts and liposuction *(94*,*96*,*136*,*137*,*140*,*143–150*). It is unclear whether there is a predisposition for certain types of surgery; however, more than 60% of surgical site infections due to RGM reported in the 1980s were reported after cardiac surgery *(122,126,129,134)* or augmentation mammaplasty *(125,137,145)*. In the past 10 years, however, these latter surgeries have been replaced in incidence by cosmetic surgical procedures (111,*116*,117,*118*,*120*,151).

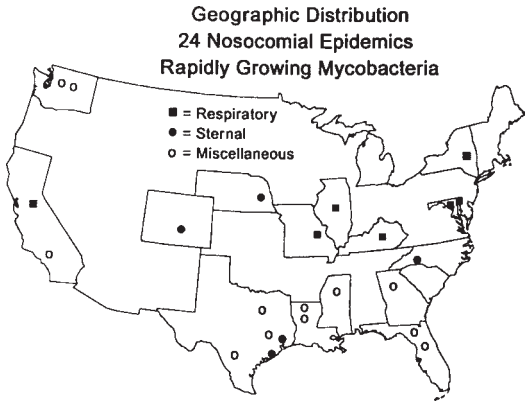

FIGURE 39-1 The geographic focality of healthcare-associated outbreaks due to rapidly growing mycobacteria.

Cardiothoracic Surgery

A review of RGM isolates associated with cardiac surgery was published in 1989 *(47)*. This study evaluated isolates from eight cardiac surgery outbreaks, as well as 45 sporadic isolates. Disease isolates were recovered from sternal wounds, donor vein graft sites, blood, and artificial valves. The isolates included *M. fortuitum*, the *M. abscessus* group, and the *M. smegmatis* group *(47)*. Several years later, the development of DNA fingerprinting for *M. fortuitum* and the *M. abscessus* group permitted better evaluation of these outbreaks (48,49,*50–52*). The first reported cardiac surgery–associated outbreak occurred in 1976 in North Carolina. Nineteen cases of disease due to *M. abscessus* occurred over a 10-week period, but no source was identified. Five (26%) patients died of their disease. In a second similar outbreak in Colorado, 10 of 75 cardiac surgery patients developed infections with *M. fortuitum*. *M. fortuitum* was recovered from a settling plate in the operating room *(122)*, but subsequent molecular studies using PFGE showed that the environmental strain differed from the disease strain *(53a)*.

The best clue to the potential reservoir for these outbreaks was provided in a later outbreak from Texas involving both *M. fortuitum* and the *M. abscessus* group. An isolate of *M. fortuitum* with a DNA fingerprint identical to that of the outbreak strain was isolated from the tap water in the operating room, ice water used to cool the cardioplegia solution, ice machines, and municipal water coming into the hospital. An identical strain was recovered from patients with several types of noncardiac surgical site infections. In this same outbreak, RAPD-PCR showed *M. abscessus* isolated from hospital ice water used to cool the cardioplegia solution and a pair of surgical scissors was identical to some disease isolates *(47,52,53a,126)*. This investigation was the first major study to identify water (in this case as ice used for surgical purposes) as the major reservoir for the microorganism. Another unreported outbreak in Texas also helped to clarify the role of water as a reservoir for RGM. In this outbreak, PFGE demonstrated the clonality of tap water and case isolates (Fig. 39-2). Several cases of perivalvular infection occurred following contamination of commercial porcine valves with *M. chelonae* *(152,153)*.

Outbreaks of sternal wound disease have not been limited to the United States. An outbreak of sternal infections due to *M. abscessus* following cardiac surgery in Budapest was described in 1976, but the source was not identified *(124)*. An outbreak of sternal surgical site infections caused by *M. fortuitum* and *M. peregrinum* occurred in Hong Kong among patients who had undergone cardiothoracic surgery at a single hospital during 1987 to 1989 *(130)*. Investigators used rRNA gene RFLP to determine that, in most cases, the microorganism belonged to one of two groups. The source of contamination could not be identified and was presumed to be environmental in origin. No additional outbreaks have been reported since 1989, presumably because of avoidance of contaminated tap water and ice in the operating room.

TABLE 39-2

Outbreaks Due to Rapidly Growing Mycobacteria

Source of Infection	*Year of Outbreak*	*Location*	*Microorganism*
Types of Surgery			
Cardiac surgery	1977	Hungary	*M. abscessus* group
	1987–1989	Hong Kong	*M. fortuitum* and *M. peregrinum*
	1987	Texas	*M. abscessus* group
	1976	N. Carolina	*M. abscessus* group
	1976	Colorado	*M. fortuitum*
	1976	Multistate	*M. abscessus* group
	1981	Nebraska	*M. fortuitum*
	1981	Texas	*M. fortuitum* and *M. abscessus* group
Laparoscopic surgery	1986	Mississippi	*M. abscessus* group
	2002–2004	Brazil	*M. fortuitum* group
Arthroscopic surgery	2005–2007	Brazil	*M. abscessus* subsp. *bolletii* (formerly *M. massiliense, M. bolletii*)
Prosthetic endocarditis	1999–2008	Brazil	*M. chelonae*
Herniotomy/orchiopexy	1998	India	*M. abscessus* group
Plastic surgery	2002–2003	Bangalore, India	*M. chelonae*
Augmentation mammaplasty	1985	Florida	*M. abscessus* group
	2002–2004	Brazil	*M. fortuitum group*
Vascular (vein stripping)	1974	Spain	*M. abscessus* group
Nasal surgery	1987–1988	Mexico	*M. abscessus* group?[a]
Liposuction /liposculpture	1996–1997	California	*M. chelonae*
	1996–1998	Venezuela	*M. fortuitum/M. abscessus* group
Abdominoplasty	2003–2004	Dominican Republic	*M. abscessus* group
Ocular surgery (LASIK)	1991	Taiwan	*M. fortuitum* and *M. chelonae*
	1998–2000	Brazil	*M. chelonae*
	2003	Brazil	*M. immunogenum*
Injection abscesses	1961	Belgium	*M. fortuitum?*[a]
	1962	Congo	*M. fortuitum?*[a]
	1963	Texas	*M. fortuitum?*[a]
	1966–1968	England	*M. chelonae*
	1969	Netherlands	*M. chelonae*
	1977	Texas	*M. abscessus* group
	1989	Georgia	*M. chelonae*
	1993	Colombia, SA	*M. abscessus* group
	1995–1996	Multistate	*M. abscessus* group
	1997–1998	China	*M. abscessus* group
	1999	Texas	*M. abscessus* group
	2005	Korea	*M. abscessus* subsp. *bolletii* (formerly *M. massiliense, M. bolletii)*
Injection abscesses (mesotherapy)	2000	Brazil	*M. chelonae*
	2006–2007	Argentina	*M. immunogenum*
	2006–2007	France	*M. chelonae, M. frederiksbergense*
	2004–2009	Brazil	*M. abscessus* subsp. *bolletii*
EMG needles	1985	Washington	*M. fortuitum*
Podiatry jet injector	1988	Florida	*M. abscessus* group
Dialysis-related	1982	Louisiana	*M. abscessus* group
	1987	California	*M. abscessus* group
	1987	Washington	*M. mucogenicum*[b]
Bronchoscopy/endoscopy	1981	Illinois	*M. chelonae*?[a]
	1989	Missouri	*M. immunogenum*
	1989	England	*M. immunogenum*
	1989	Switzerland	*M. immunogenum*

(*Continued*)

TABLE 39-2

Outbreaks Due to Rapidly Growing Mycobacteria (*Continued*)

Source of Infection	*Year of Outbreak*	*Location*	*Microorganism*
	1991	Missouri	*M. immunogenum*
	1991–1992	England	*M. fortuitum* and *M. chelonae*
	1992	Maryland	*M. immunogenum*
	1992	Ireland	*M. chelonae*
	1992	Australia	*M. chelonae*
	1992	Kentucky	*M. immunogenum*
	1992	Taiwan	*M. chelonae*
	1993	Florida	*M. chelonae*
	1999	Scotland	*M. chelonae*
Catheter-associated bacteremia	2006	Texas	*M. mucogenicum, M. porcinum*
Respiratory	1985	New York	*M. peregrinum*
	1988–1989	California	*M. fortuitum*
	1989–1990	Washington, DC	*M. fortuitum*
Other			
Bone marrow biopsy	1987	Texas	*M. fortuitum*
Middle ear irrigation	1988	Louisiana	*M. abscessus* group
Acupuncture	2001	Korea	*M. abscessus* group
Tattoos	2007–2008	Minnesota	*M. chelonae*
	2005	France	*M. chelonae*
Furunculosis (nail salons)	2000	California	*M. fortuitum*
	2002–2003	Georgia	*M. mageritense*
Cutaneous (wading pool) "hand and foot disease"	2003	Alberta, Canada	*M. abscessus* group

Note: *M. abscessus* group designation includes the new taxonomic reclassification of *M. abscessus* subsp. *abscessus* (formerly *M. abscessus*) and *M. abscessus* subsp. *bolletii* (formerly *M. massiliense* and *M. bolletii*) unless specifically stated as *M. abscessus* subsp. *bolletii*. (Outbreaks occurred prior to reclassification.)
[a]Species of the microorganism by current taxonomy has not been confirmed.
[b]Formerly known as *M. chelonae-like organism* or MCLO.
SA, South America; EMG, electromyography.

In addition to these outbreaks, numerous sporadic infections due to RGM have been reported following cardiac surgery *(2,134,139,154–157)*, including a case of subacute bacterial endocarditis for which a source was never documented. When 89 isolates from cardiac surgical site infections were analyzed, 45 were sporadic; these were more likely to be due to *M. fortuitum* or the *M. smegmatis* group. Eighty percent were from southern coastal states (48). Sporadic cases of disease continue to be seen.

Cardiac surgery patients with surgical site infections due to RGM have presented with failure of surgical site healing or breakdown of healed surgical sites with drainage of serous fluid. Endocarditis patients presented with fever and cutaneous and embolic phenomena, along with positive blood cultures 4 to 12 weeks after surgery *(2,158)*. In the outbreak related to contaminated porcine valves, patients presented with pericardial effusions and aortic abscesses.

Plastic Surgery/Augmentation Mammaplasty

Infections due to RGM following plastic surgery for breast augmentation have been well described *(125,127,135, 137,142,145)* and, along with cardiac surgery infections, were the most common surgical site infections due to these microorganisms. However, with the exception of one outbreak, the pathogenesis of these infections has yet to be defined *(125,127,159)*. The one outbreak in which a well-defined source was identified included infections following both augmentation mammaplasty and blepharoplasty *(127)*. During April to October 1985, an outbreak of *M. abscessus* was identified affecting eight patients. *M. abscessus* was recovered from the gentian violet in the office and the stock solution in the pharmacy, which had been using distilled water to reconstitute the gentian violet crystals instead of 10% alcohol, thus allowing *M. abscessus* to replicate. Previous studies have shown that isolates of the *M. abscessus* group grow well in potable and distilled water *(8,76,126)*. No source has been identified for any of the cases of sporadic mammaplasty wound infections, although the tendency for more than one case to occur in a plastic surgeon's practice makes environmental sources highly likely *(125,142,159)*. Almost 90% of sporadic cases of surgical wound infections following augmentation mammaplasty have been reported from three states—Texas, North Carolina, and Florida *(125,142)*. Sporadic surgical wound infections after other types of breast surgery

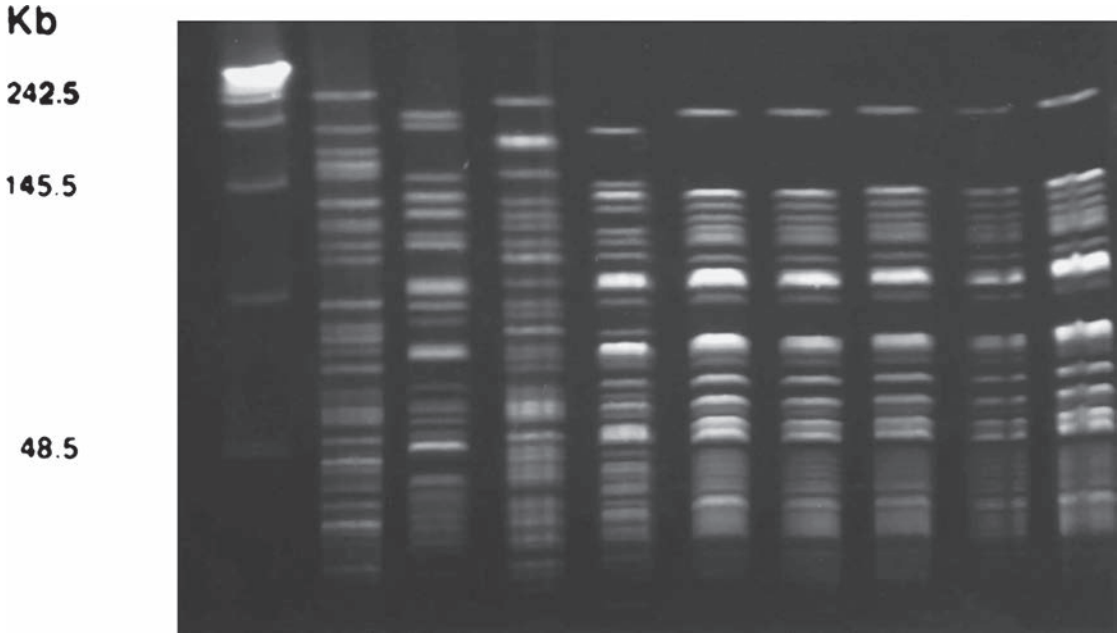

FIGURE 39-2 Pulsed field gel electrophoresis of *M. abscessus* from a surgical site outbreak in Texas using xba.1. Lanes 1–5 are genomic DNA and control strains. Lanes 6 and 10 are isolates obtained from tap water, and lanes 7–9 are case isolates from infected patients.

as well as spontaneous breast infections have also been reported *(142)*.

Outbreaks and/or sporadic wound infections have been described after other types of plastic surgery procedures, including face-lifts *(141)*, blepharoplasty *(136)*, and liposuction (111). In a liposuction-associated outbreak reported in 2001 involving an outpatient clinic, tap water was used for flushing and rinsing suction tubing, and inadequate sterilization procedures were in place. *M. chelonae* isolates recovered from patient wounds and the tap water system were clonal when studied by PFGE (111).

Although reports of NTM outbreaks following cardiac surgery or augmentation mammaplasty have declined in the United States recently, a cluster of cases of postaugmentation mammaplasty surgical site infections occurred between 2002 and 2004 in southern Brazil. RGM were isolated from samples from 12 patients. Eleven isolates of *M. fortuitum* and one of *M. porcinum* were identified by molecular studies *(66)*. A total of 492 patients in 12 hospitals were evaluated. Fourteen cases were confirmed. Fourteen were possible and one was a probable case using clinical criteria. Molecular strain typing revealed that the outbreak was caused by polyclonal strains at different institutions, and in one hospital, a unique genotype was responsible for the majority of cases *(160)*.

Outbreaks of NTM infections also have recently been associated with laparoscopic and cosmetic procedures in Brazil, the Dominican Republic, and Venezuela (*116*,117,*118*,*121*,151).

Miscellaneous Surgery

Although outbreaks of surgical site infections were first reported after cardiac surgery and augmentation mammaplasty, outbreaks have been described after general surgical procedures as well. In one outbreak, a cluster of the *M. abscessus* group in surgical site infections occurred in a Mississippi hospital in 1985 in women who had undergone laparoscopy. In this outbreak, four cases confirmed by culture and 12 probable cases were identified. An isolate of *M. abscessus* with the same antimicrobial susceptibility profile as the patient isolates was identified from the mineral oil used to lubricate the laparoscope and from multiple specimens of tap water throughout the hospital. The outbreak stopped when a sterile aqueous-based solution was substituted for mineral oil as a lubricant and when laparoscopes received high level disinfection without exposure to tap water (CDC investigation no. 91-01).

Similar outbreaks of laparoscopic port sites have also occurred in 2002 to 2003 in Bangalore, India. The presence of biofilms on the surgical instruments and improper rinsing was hypothesized but not confirmed as the source of the outbreak *(161)*.

One of the largest recent postsurgical outbreaks has involved the recently reclassified species, *M. abscessus* subsp. *bolletii* (formerly identified as two separate species, *M. massiliense* and *M. bolletii*), in 63 hospitals in the state of Rio de Janeiro, Brazil, between August 2006 and July 2007. One hundred and ninety-seven cases were confirmed from 38 hospitals. A total of 148 isolates were recovered from 146 patients. DNA strain typing by PFGE revealed a single clone with the same PFGE pattern that was previously observed in other regions of Brazil (*116*,117).

Previous reports of outbreaks associated with *M. abscessus* subsp. *bolletii* (formerly *M. massiliense*) in Brazil described post–video-assisted surgical infections that began in 2004 (151,*162*) in the northern and central regions of Brazil. No infections following video-assisted medical procedures had been reported prior to 2004 in Brazil although video-assisted technology was available since 1990 *(116)*.

The first outbreak related to this series occurred in 2004 to 2005 in the northern region of Brazil. Fifty-eight

of the 67 isolates studied were from patients who had undergone laparoscopic surgeries (151). A second cluster occurred between 2005 and 2007 in the central region of Brazil and involved laparoscopic and arthroscopic surgeries on 18 patients from seven private hospitals. Again, in both of these outbreaks, the confirmed cases belonged to a single clone *(162)*.

A postsurgical outbreak of herniotomy and orchiopexy in 45 patients in a pediatric unit in New Delhi, India, was associated with the *M. abscessus* group. The outbreak ceased when the source of the outbreak—a leaking vacuum pump and faulty pressure gauge in the autoclave used to sterilize the gauge and boiled tap water—was repaired *(163)*.

Postsurgical wound infections with NTM usually manifest several weeks to months following the surgical procedure *(162)*. Clinical evidence of disseminated infection is uncommon in patients who are immunocompetent.

Postinjection Abscesses

The first description of *M. fortuitum* as a pathogen in 1936 involved an abscess that resulted from a vitamin injection *(164)*. Since that time, a number of sporadic cases as well as outbreaks of localized cutaneous abscesses have been reported involving injections with needles *(51,84,165–174)*. Unlike other healthcare-associated infections, outbreaks of postinjection abscesses are most often due to *M. chelonae*, although outbreaks involving *M. fortuitum* and *M. abscessus* have also been reported. Some outbreaks, especially those before the 1980s, relate to reused or inadequate sterilization of needles *(165,172)*. Other outbreaks appear to relate to contaminated biologics, especially the use of multidose vials or materials. An outbreak among student nurses occurred when a single liter bottle of saline was used repetitively to practice injection techniques *(166)*. An outbreak of *M. abscessus* (identified then as *M. chelonae* subspecies *abscessus*) was identified from a podiatry practice in which jet injectors were placed in distilled water for rinsing between patients. *M. abscessus* was identified in the container of distilled water. A similar outbreak of *M. fortuitum* infections occurred in patients who had undergone electromyography. This office was using reusable needle electrodes that were disinfected with 2% glutaraldehyde and then rinsed with tap water. The outbreak stopped when the needles were routinely autoclaved between patients. Tap water was considered the likely source of infection, but no environmental cultures were positive *(173)*.

An outbreak of *M. abscessus* following penicillin injections in 86 patients in a factory hospital was recently reported in the People's Republic of China from 1997 to 1998. During the investigation of the outbreak, seven lids from bottles of penicillin from the same lot number that was used and stored in the outpatient department of the hospital along with 1 out of 25 soil samples from the floor were revealed to be similar to 50 clinical strains using sodium dodecyl sulfate -polyacrylamide gel electrophoresis of whole cell proteins and plasmids *(175)*. An additional epidemic of *M. abscessus* subsp. *bolletii* (formerly *M. massiliense*) associated with intramuscular injection of an antimicrobial was reported in 2005 in South Korea *(176)*. This procedure, known as mesotherapy, was originally indicated for cases of medical trauma but has gained universal popularity for various cosmetic and noncosmetic reasons including fat reduction, body contouring, reduction of rheumatism pain, or treatment of psychoneurological disorders (113). Most of the recent NTM outbreaks have been associated with aesthetic fat reduction.

Outbreaks of mesotherapy-associated subcutaneous infections derived from the inappropriate cleaning of the automatic repetitive device used for the injections have also been described in France from 2006 to 2007. Cultures grew *M. chelonae* and *M. frederiksbergense*. PFGE patterns of *M. chelonae* from 11 patients who had undergone mesotherapy and that obtained from tap water in the examination room were identical (113).

Even though these infections have been described for more than four decades, they continue to occur. From 1995 to 1996, an outbreak of abscesses occurred in 87 patients throughout the United States (177). All had received intramuscular injections of a preparation alleged to be adrenal cortex extract provided by a single physician as part of a weight-loss regimen. The extract, which had not been approved by the U.S. Food and Drug Administration (FDA), was found to be contaminated with *M. abscessus*. The largest single outbreak of postinjection abscesses due to RGM occurred in Colombia, South America *(51,84,170)*. Of 2,000 patients treated by a single physician from November 1992 to April 1993, 350 developed skin abscesses due to the *M. abscessus* group. Five representative isolates from the epidemic were identical by RAPD-PCR *(51)*. The outbreak was associated with local injections of lidocaine administered by the physician, and the microorganism was recovered from one of the reusable multidose vials *(170)*. The most recent reported outbreak of postinjection abscesses occurred in 1999 and involved the use of contaminated benzalkonium chloride used for skin disinfection. Clinical and environmental isolates of the *M. abscessus* group were indistinguishable by RAPD-PCR (178).

Single sporadic cases of postinjection abscesses likely occur in the same way as epidemic disease *(174)*. Focal abscesses, especially of the arm or hip, should therefore be investigated for any relationship to injections, and if a relationship is identified, infection control policies and procedures should be reviewed to prevent recurrences and outbreaks.

Dialysis Related

Hemodialysis The risk of infection due to RGM in patients undergoing hemodialysis was first reported in 1982, when 27 cases of NTM infection were identified in a group of patients from two Louisiana hemodialysis centers. *M. abscessus* was identified in 24 patients, and *M. mucogenicum* was cultured from one patient sample. The attack rate in one dialysis unit was 19%. Bacteremia occurred in 18 patients, and four had localized infections. There were 13 deaths, for an overall mortality rate of 48%. NTM were identified throughout the water system in two dialysis centers. *M. abscessus* (later shown by PFGE to be identical to disease isolates) (48) was identified in the water of the reverse osmosis room, the reverse osmosis tank, and the formaldehyde used to reprocess dialyzers, and from the blood compartment side of 5 of 31 dialyzers. The outbreak stopped when the reuse of dialyzers was discontinued *(179)*.

A number of important lessons were learned from this outbreak. Tap water is not sterile and allows the growth of RGM. These microorganisms are relatively resistant

to chlorine and glutaraldehyde, and decontamination of dialyzers and dialysis machines may be difficult. Protocols for disinfection and reprocessing of dialyzers must therefore be rigorously followed. Finally, cultures of dialysis patients should be held for a minimum of 14 days to facilitate identification of fastidious or unusual water microorganisms *(179,180)*.

From 1987 to 1988, another outbreak of *M. abscessus* disease occurred; this one involved a hemodialysis unit in California. Infection occurred in five patients; four of five had arteriovenous graft infections and two died. *M. abscessus* was subsequently identified from municipal water and the hose of the water spray device used for reprocessing the high-flux but not the regular dialyzers. High-flux dialysis had been instituted in this center in 1986, and in 1987, renalin (hydrogen peroxide/peracetic acid–based disinfectant) was substituted for 4% formaldehyde to reprocess dialyzers. A number of infection control issues were identified that may have contributed to the outbreak *(180–183)*. These types of infections may increase with widespread use of high-flux dialysis, reprocessed dialyzers, and increasing use of renalin. The effectiveness of dialyzer disinfection is critical to providing patients with safe dialysis *(180,183)*.

No major outbreak of mycobacterial infection involving hemodialysis has been reported since 1987, although a recently described species, *M. llatzerense*, has been identified from a pure-water distribution unit and hemodialysis water in a single hospital in Spain *(184)*.

Peritoneal Dialysis Peritonitis is a common complication of chronic ambulatory peritoneal dialysis (CAPD). After beginning peritoneal dialysis, 60% of patients develop peritonitis in the first year and 80% develop peritonitis within 2 years. Most episodes are due to staphylococci (40–70%) and aerobic gram-negative bacilli (15–30%). Culture-negative peritonitis represents 8% to 27% of reported episodes of CAPD-related peritonitis. Mycobacteria account for <3% of cases but may be more common and simply underrecognized. Hakim et al. *(185)* reviewed 31 cases of peritonitis in CAPD patients due to NTM. Most of the cases reported in the literature have been due to RGM (86%), mostly *M. fortuitum*, although other mycobacteria have also been implicated *(95,186–190)*. In one outbreak involving 17 cases due to RGM *(191)*, most patients presented with fever, abdominal pain, and cloudy dialysis fluid. Catheter dysfunction, vomiting, diarrhea, and weight loss were also described. However, the illness may be more insidious in onset, signaled only by increases in cell counts in the dialysis fluid, particularly with polymorphonuclear leukocytes. Diagnosis is usually made by culture, since AFB smears are generally negative. The unexpected staining and growth characteristics of the RGM may result in misidentification as diphtheroids or debris due to fragmentation and beading on the Gram stain. When gram-positive rods resembling corynebacteria are isolated from peritoneal fluid, a smear stained for AFB should be examined *(191–195)*. Peritoneal biopsies may be helpful in some cases, particularly if they show mixed acute and chronic granulomatous inflammation with pyogenic abscesses or sinus tracts *(2)*. Management consists of catheter removal along with multidrug chemotherapy, based on *in vitro* susceptibility (7,*95*,*196*). Catheter removal improves the success rate *(197)*. Treatment in the past has consisted of aminoglycosides, although the fluoroquinolones, clarithromycin, and imipenem have also shown potential utility *(95,191,197,198)*.

Catheter-Related Infections

Catheter-related infections are currently the most frequently encountered healthcare-associated infection due to RGM. They are well-described complications of central intravenous catheters, arteriovenous catheters, peritoneal dialysis catheters, and even lacrimal duct catheters. Exit-site infections, tunnel infections, and bacteremias have all been reported *(2,94,199–206)*. One of the largest single series of infections was reported by Raad et al. *(201)*, who described intravenous catheter-related infections due to rapid growers in 15 cancer patients over 12 years duration at M. D. Anderson Hospital (Texas). These authors also reviewed the literature through 1991 and described an additional 14 cases. Among the M. D. Anderson cases, 60% had cancer as an underlying disease. There were 11 bacteremias and four catheter-site infections with nine due to *M. fortuitum* and six due to the *M. chelonae/abscessus* group (the authors did not discriminate between *M. chelonae* and *M. abscessus*). All the patients who had their catheter removed recovered. Treatment failed in seven bacteremic patients who had their central line left in place. After catheter removal, six of the seven infections subsequently responded. Foreign bodies and devices appear to play a significant role in facilitating and perpetuating such infections *(131,142,153,202,203,205)*. An unusual syndrome of cholestatic hepatitis associated with fever, right upper quadrant pain, and marked elevation of alkaline phosphatase has been observed in some patients with central venous catheter sepsis due to mycobacteria. The patients have granulomas with positive cultures on liver biopsies. The syndrome presumably results from seeding of the liver at the time of bacteremia *(207)*. An additional syndrome is the development of multiple pulmonary nodules, which presumably relates to seeding of the lung from the central catheter.

Recently, an outbreak of a newly described RGM species, *M. phocaicum,* and *M. mucogenicum* was reported in five patients with central venous catheters in an oncology unit in a Texas hospital (208). This was the first report of clinical isolates of *M. phocaicum* in a hospital in the United States. Rare reports of catheter sepsis have falsely incriminated slowly growing mycobacteria *(209–212)* due to undetected mycobacteria (RGM), failure to use appropriate culture media, and/or too short an incubation time. The most common species associated with central line infections is *M. fortuitum*. Other associated species include the *M. abscessus* group, *M. chelonae*, *M. mucogenicum*, and two pigmented species—*M. neoaurum* and the newly described *M. bacteremicum (206)*.

Infectious Keratitis Following LASIK

Laser in situ keratomileusis (LASIK) has recently been involved in outbreaks of NTM including *M. chelonae*, *M. szulgai*, and *M. immunogenum (119,213–215)*. Importantly, NTM keratitis is characterized by an indolent course and poor response to antimicrobial therapy *(119)*. One major outbreak occurred in a Texas medical center and

was traced to ice used to cool the interface lavage syringe from an ice machine contaminated with *M. szulgai (213)*. Freitas et al. summarized three published cases of NTM clusters of infectious keratitis following LASIK including the publication by Holmes et al. The other two clusters involved *M. chelonae* but no source of the outbreaks was identified *(119,216)*.

Infections Related to Foreign Bodies/ Prosthetic Devices

Healthcare-associated infections due to RGM have been described after the insertion of a variety of prosthetic devices other than catheters and silicone breast implants, including prosthetic hips, prosthetic knees, pacemakers, defibrillators, and myringotomy tubes. Although most cases have been sporadic, disease outbreaks have been reported. Seventeen cases of otitis media due to *M. abscessus* (identified then as *M. chelonae*, subsp. *abscessus*) identified in Louisiana in 1987 were related to an outbreak in an ear, nose, and throat (ENT) practice *(217)*. All of the patients involved in the outbreak had myringotomy tubes and developed chronic otorrhea. The most important risk factors for infection were presence of a perforation or myringotomy tube, suctioning of the ears, and an increasing number of ear examinations. Pathology showed abundant granulation tissue and multiple granulomas with positive AFB smears. In outbreak cases, the suction catheters used to wash out patients' ears had been rinsed with tap water. Instruments were not disinfected or sterilized properly. Ear specula were never sterilized. *M. abscessus* was identified in the water supply *(217)*. However, the epidemic isolate seen in 13 of 14 cases had high-level aminoglycoside resistance (including amikacin), subsequently shown to result from an acquired point mutation in the 16S rRNA gene *(218)* that occurs only with prior aminoglycoside therapy *(94,218–220)*. This finding suggests that the epidemic strain originated from an infected patient rather than the tap water in the physician's office and spread because of improper sterilization of instruments between patients.

Subsequently, 21 sporadic cases of chronic otitis media due to RGM were reported. All the patients with available histories had prior myringotomy tubes, and more than 90% of cases were due to the *M. abscessus* group *(94)*. In a survey of infection control practices in ENT offices, 70% of ENT physicians were using tap water on their instruments, and 52% used tap water to rinse suction catheter tips between patients. Eighty-six percent reported performing high-level disinfection on their instruments between patients, but only 67% used adequate time to actually achieve high-level disinfection (30 minutes in a 2% glutaraldehyde solution, boiling for 5 minutes, and autoclaving for 20 minutes) *(217)*. Epidemic disease potentially could occur with high-level tap water colonization or spread from an already infected patient. In addition to these infections due to RGM, foreign body–associated healthcare-associated infections with other NTM have been reported sporadically *(209,210)*. These have included meningitis in a baby with a ventriculoperitoneal shunt *(211)*, peritonitis in patients undergoing peritoneal dialysis *(189,190,212)*, and endocarditis in a patient with a prosthetic aortic valve *(221)*.

A recent study identified the occurrence of *M. chelonae* valve endocarditis from a cardiac bioprosthesis in a Brazilian hospital. Investigators showed that the microorganisms were present in the prosthesis received from the manufacturer. Five of the 15 AFB-positive paraffin-embedded samples generated 100% similarity by DNA sequencing of the 16-23S internal transcribed sequence region (*222*). A previous probable manufacturer with mycobacterial contamination was reported in 1978 *(223)*. Other cases of cardiac NTM infection have been pacemaker related *(224)*.

Miscellaneous

Additional outbreaks of NTM infections have been associated with receiving acupuncture treatments and tattoos *(225,226)*.

Forty patients who received acupuncture in a single Korean medicine clinic had genetically identical isolates of *M. abscessus*. The source of the outbreak was not determined, although the majority of the patients with infections received deep insertions on the back and knee joint area. Investigators hypothesize that the *M. abscessus* may have been introduced via contaminated towels or hot pack covers to the site, but this was never proven *(225)*.

Reports of 20 men with skin infections with *M. chelonae* in France may be the first NTM outbreak associated with tattoos *(226)*. Subsequent NTM outbreaks in France and, most recently, the United States have occurred *(227,228)*. Interestingly, the infections have involved the gray parts of the tattoo. The gray wash is traditionally prepared by diluting black pigment with tap water, which may have been the source of the outbreaks *(226,227)*. The true incidence of tattoo-associated NTM infections is unknown *(226)*.

A large outbreak of lower extremity furunculosis was caused by *M. fortuitum* in more than 100 patrons of a northern California nail salon as a result of exposure to improperly cleaned whirlpool footbaths (229). The microorganism was cultured from contaminated footbaths and from the inlet suction screens containing hair and other debris. Shaving the legs with a razor prior to the footbath and pedicure was a major risk factor, although some patients who did not shave were also infected (229,*230–232*).

A survey of 18 nail salons (30 foot spas) from five California counties recovered 10 species of NTM from whirlpool footbaths including *M. fortuitum, M. mucogenicum, M. smegmatis* group, *M. mageritense, M. neoaurum*-like RGM, a nonidentified pigmented RGM, MAC, *M. simiae*, *M. gordonae*, and *M. lentiflavum. M. fortuitum* was most commonly recovered and found in 47% of the 30 foot spas cultured. The RGM were the more frequently encountered NTM and were found in 23 (76%) of the foot spas. Investigators hypothesized that the NTM were likely introduced via the municipal water supply where they colonized parts of the spas and plumbing to the spas *(230)*.

One limitation of the survey was the inability to quantify the risk for infection despite the recovery of the NTM. The investigators stated that the findings in the 18 nail salons may not be representative of other nail salons, although the presence of potentially pathogenic NTM is of public health concern *(230)*.

Another smaller outbreak of two patients occurred in a nail salon in Georgia. PCR restriction enzyme analysis using a 439-bp segment of the 65 kDa heat shock protein gene and

HPLC identified the isolates as *M. mageritense*. Subsequent cultures from three of the seven foot spas yielded *M. mageritense*, and PFGE patterns for the patient and environmental isolates appeared to be closely related (233).

An outbreak of cutaneous infections involving the hands and feet in "*M. abscessus* hand-and-foot disease" of 41 children and one adult is the first documented *M. abscessus* outbreak associated with wading pool exposure. The rubber mat in the implicated pool was the suspected reservoir, and installation of a smooth nonabsorbent surface was recommended to prevent future outbreaks *(234)*.

PSEUDOINFECTIONS AND PSEUDO-OUTBREAKS

Generally, an increase in frequency of NTM isolates recovered from patients without disease should alert healthcare personnel to the possibility of a pseudo-outbreak. Often, the recovered species is subsequently isolated from one or more environmental sources. Unless pseudo-outbreaks are recognized, patients may receive unnecessary therapy.

Equipment Related

Bronchoscopes Since the early 1980s, mycobacteria have been the major pathogens transmitted via the bronchoscope, resulting in both pseudoinfections and true infections. Mycobacterial contamination of bronchoscopes and other endoscopes has previously been reported most commonly with *M. abscessus* and *M. chelonae*. A subsequent study has shown, however, that the isolates of *M. chelonae/abscessus* recovered in this setting were actually a related species called *M. immunogenum* (235). Contamination has also occurred with *M. xenopi* and MAC (236,*237–240*,241,*242–248*) and has been linked to suction valves, suction channels, and biopsy forceps. Further contamination has been linked to automated endoscope washers, use of tap water to rinse endoscopes after manual disinfection, and failure to disinfect endoscopes adequately between patients (*58*,236,*238*,241,*245*,*256*). Bronchoscopes and other endoscopes as well as automated washers are difficult to disinfect, in part due to the propensity for formation of biofilms, which are resistant to chemical disinfectants (249). Colonization of some automated endoscope disinfection machines with NTM has been associated with contamination of bronchoscopic and other endoscopic equipment due to problems with product design that facilitated the formation of biofilms in the automated washers (236,*237*,241,*244*,*246*). One such outbreak occurred in St. Louis, Missouri, from December 1989 to September 1990, when 14 patients were identified with *M. abscessus* (later identified as *M. immunogenum*) in their bronchoscopic washings in a hospital using an automated disinfection machine to reprocess bronchoscopes. All specimens were smear negative and no patients developed disease. The patient isolates had the same DNA fingerprint pattern by PFGE (236). This same isolate (with the same fingerprint pattern) was identified from the rinse water in the endoscope-disinfecting machine. The PFGE patterns from this outbreak are shown in Figure 39-3. To determine the mechanism of bronchoscope contamination, experiments were performed to evaluate the mycobactericidal activity of the glutaraldehyde solution being used to disinfect the bronchoscopes. The microorganisms were susceptible to glutaraldehyde. However, a 2% concentration of glutaraldehyde <14 days old was required to kill *M. chelonae* (236).

Outbreaks of endoscope contamination have been described with the Olympus EW 10 and EW 20 and the Keymed auto disinfector II. In 1990, because of these reports,

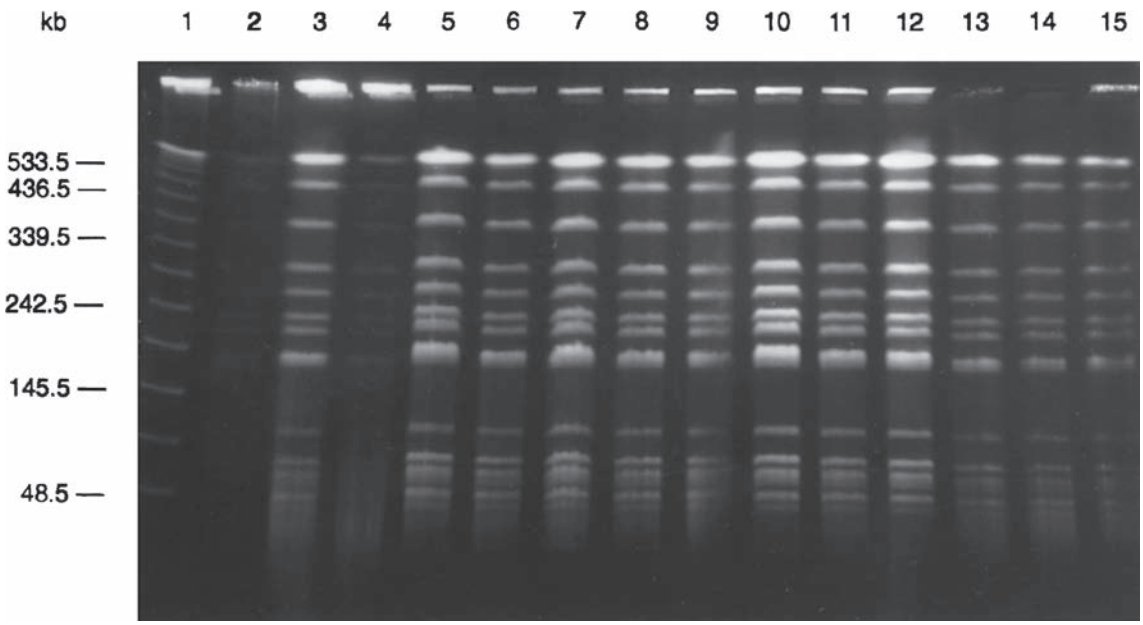

FIGURE 39-3 Pulsed field gel electrophoresis of *M. immunogenum* (originally identified as *M. abscessus)* associated with bronchoscope contamination from St. Louis, Missouri. Lane 1 is genomic DNA, lane 6 is an isolate from the rinse water, and lane 7 is the isolate identified from the endoscope washing machine. All other lanes are patient isolates of *M. immunogenum* obtained from bronchoalveolar lavage.

the FDA issued a class II recall prohibiting further sale of the Olympus EW 10 and EW 20 washers in the United States. The manufacturer was also required to modify the machines in use in US hospitals to try to eliminate the problem. A product alert was also issued, recommending that all users institute a terminal rinse of endoscopes or bronchoscopes with 70% alcohol after disinfection in one of these automated washers.

However, pseudoinfection and contamination of endoscopes have been reported from automated washers that have undergone modifications (241). Maloney et al. (241) reported 15 patients with *M. abscessus* (later identified as *M. immunogenum*) (235) pseudoinfection due to bronchoscopes contaminated by an automated endoscope washer. *M. immunogenum* positive cultures were more likely to have been obtained from bronchoscopes than from gastroscopes ($p = .002$) and from bronchoscopes that had been processed by an automated washer rather than manual disinfection ($p = .001$). *M. immunogenum* was cultured from the inlet water, a flexible bronchoscope, and the automated washer. Environmental and case isolates had identical large restriction fragment patterns of genomic DNA separated by PFGE (241).

Several similar outbreaks have been reported from outside the United States *(243–247)*. In another pseudo-outbreak from England, bronchoscopes became contaminated with RGM when the endoscopes were rinsed with tap water after they had undergone manual high-level disinfection with glutaraldehyde. *M. chelonae* (details were not provided as to whether the causative agent was *M. immunogenum*) was identified from the detergent dispensers and the water in the room used to reprocess the bronchoscopes. The contamination was impossible to eradicate until the bronchoscopes were sterilized with ethylene oxide and the use of tap water for rinsing was discontinued *(243)*.

Although this issue has been reported numerous times, the problem is probably still underrecognized. RGM survive well in adverse conditions and are resistant to antibiotics and disinfectants. Since they are present in tap water, the use of tap water has been associated with contamination of instruments and specimens. *M. fortuitum* and *M. abscessus* can also multiply to levels of 10^4 to 10^6 in commercially distilled water and retain viability with only a slight decline in 1 year *(76)*. Tap water should not be used to rinse bronchoscopes or critical or semicritical instruments. If tap water must be used, it should be followed by a 70% alcohol rinse (236,241,*243*,*246*,*251*). (For additional information on cleaning and disinfection of endoscopes, see Chapter 62.)

Ice Machines Hospital ice contaminated with NTM has been associated with several healthcare-associated outbreaks due to RGM. These outbreaks have included cardiac surgery infections *(126)* and a pseudo-outbreak involving bone marrow aspirates *(252)*. Another pseudo-outbreak involving 14 respiratory and one stool specimen from 10 patients admitted to the same tertiary care medical center *(253)* was related to contaminated ice. It has not always been determined whether the machine was contaminated or the contaminated ice reflected contamination of the hospital water supply. In one outbreak, a single ice machine was at fault. This outbreak occurred in 1987 when 30 patients in a New York hospital became colonized with *M. peregrinum* (identified at the time as *M. fortuitum* biovariant *peregrinum*). *M. peregrinum* was identified in a single ice machine and in the ice produced by the machine. Contamination of sputum samples in these patients was associated with consumption of tap water, melted ice, and ice chips, as well as showering and bathing immediately before obtaining the sputum samples *(128)*. Pseudoinfections due to contamination of bone marrow specimens were reported from a Texas hospital where *M. fortuitum* was cultured from bone marrow aspirates in four patients. Only syringes chilled with ice from contaminated ice machines were involved. Both the ice and the ice machine were found to be contaminated *(252)*.

From June 1980 to 1981, the Delaware State Laboratory noticed an increased number of positive cultures for *M. gordonae*. Extensive hospital cultures of water, ice, and ice water from contaminated ice machines was found to be the source of this pseudoepidemic. The number of isolates sharply decreased following cleaning of the ice machines *(254)*.

Outbreaks and Pseudo-Outbreaks Directly Related to Contaminated Hospital Water Supplies

The prior sections discussed contaminated equipment, but these pseudo-outbreaks were almost certainly associated with the hospital and/or municipal water supply being contaminated with the same microorganism that contaminated the equipment. Direct contamination of culture specimens or colonization or transient contamination of the respiratory tract with NTM has been a major healthcare-associated problem related to contaminated hospital water systems. Healthcare-associated respiratory tract infections due to these microorganisms have been rare and have been limited to occasional single cases. This, presumably, reflects the fact that, despite frequent exposure from the environment, the lungs are relatively resistant to infection.

M. gordonae, MAC, *M. scrofulaceum*, *M. fortuitum*, the *M. abscessus* group, *M. chelonae*, *M. mucogenicum*, *M. immunogenum*, *M. terrae* complex, *M. kansasii*, *M. simiae*, *M. xenopi*, and a newly described species, *M. paraffinicum* have all been identified from hospital water systems (*49*,*54*,*61*,250,*253*,*255–259*). Some of these microorganisms have been associated with hospital outbreaks/pseudo-outbreaks and, thus, are of significance for the healthcare epidemiologist and infection preventionist (IP).

M. xenopi has been associated with four healthcare-associated outbreaks/pseudo-outbreaks in the United States. The first of these occurred in a Los Angeles hospital in 1983; *M. xenopi* was identified in 43 specimens from 34 patients. Fewer than five colonies were recovered from cultures in 70% of these cases. None of the patients had a clinical picture compatible with mycobacterial disease, except a 76-year-old woman whose isolate was obtained from a lung biopsy that showed caseating granulomas with AFB, from which *M. xenopi* was identified on culture. Cultures yielded *M. xenopi* throughout the hospital water system. Case control studies suggested that patients acquired *M. xenopi* from exposure to hospital water in various ways, including showering (CDC investigation 84-78-1).

A second outbreak/pseudo-outbreak occurred in a Connecticut hospital where 608 patients over a 7-year

period had positive respiratory cultures for *M. xenopi* due to heavy contamination of the hospital water supply. The water was maintained at 110°F, and *M. xenopi* grows in water at temperatures as high as 115°F. By 1981, 19 patients had developed healthcare-associated pulmonary disease *(260,261)* (CDC investigation 92-01).

The third outbreak/pseudo-outbreak occurred over a 3-year period from 1988 to 1991 in a Michigan hospital *(54)*. Seventeen isolates of *M. xenopi* were identified, of which 13 were bronchoscopy specimens. *M. xenopi* was isolated from warm tap water samples taken from various parts of the hospital, including the bronchoscopy unit. Tap water had been used to rinse the bronchoscopes following disinfection.

A fourth outbreak was identified in 1993 when CDC investigated a hospital that had recovered 13 of the 20 isolates of *M. xenopi* isolated in Indiana (250). All the specimens were smear negative and yielded rare or few colonies on culture. Only one isolate was identified from each of 13 patients. None of the patients met American Thoracic Society criteria for pulmonary disease; however, 38% of the patients were treated with antituberculous therapy for a mean of 3 months. The investigation found frequent use of tap water throughout the hospital, including use of tap water to rinse bronchoscopes and bedpans as well as use of tap water gargles before sputum induction. *M. xenopi* was isolated from 17 of 19 (89%) water samples in patient care areas, and heavy growth of *M. xenopi* was observed on cultures from the hospital water mixing tank. This pseudo-outbreak was terminated by improving culture techniques and by eliminating the use of tap water to rinse bronchoscopes (250).

Although *M. xenopi* has been found in hot water taps in hospitals (250,*255*), it has generally not been identified in city water. The microorganism can replicate between 43°C and 45°C; thus, small numbers of microorganisms may enter hospital water tanks and multiply, resulting in colonization of the water systems. The pseudo-outbreak in the Indiana hospital was thought to have occurred after the hospital decreased its baseline water temperature in the tanks from 54°C to 49°C. Overgrowth or contamination may be eradicated from hospital water systems by mechanically cleaning the holding tanks, increasing the water temperature to 82°C for 1 hour, flushing the system, and then increasing the baseline hot water temperature to 54°C. Routine surveillance cultures may be indicated in certain areas to detect overgrowth (*54*,250,*255*,256,*261*). In another similar outbreak, *M. terrae* was identified from 163 patients in a hospital that had recently renovated one wing *(257)*. The source of contamination was the new water system. No *M. terrae* was cultured from patients after the water system was flushed and hyperchlorinated.

M. simiae has been a problem in several hospitals in the southwestern United States *(57–59)*. A New Mexico hospital reported an outbreak of *M. simiae* involving 56 patients over a 3-year period. *M. simiae* was identified from sputum, stool, and gastric biopsy specimens. None of the patients had clinical disease due to *M. simiae*. Although environmental cultures have been negative to date, MEE was performed on 23 isolates and demonstrated three electrophoretic types. Eighteen (78%) were type 1, four were type 2, and there was a single isolate of a third type, implying a likely common environmental source *(64)*. (For more information on pseudo-outbreaks, see Chapter 9). A similar cluster of 33 isolates, identified over 12 months, was reported from a single clinical laboratory in Tucson, Arizona. It was the third most common NTM to be recovered during this time period. Isolates studied by PFGE were either the same or highly related (clonal), suggesting a common source *(57)*. It is unclear whether these represented hospital pseudo-outbreaks or if most samples were contaminated from another source.

Recently, two pseudo-outbreaks involving *M. simiae* have been reported from Texas, with identical strains recovered from the hospital water systems. El Sahly et al. reported recovery of 65 isolates of *M. simiae* from 62 patients in a single hospital in Houston *(58)*. This represented 90% of *M. simiae* isolates recovered in the city. *M. simiae* was recovered from multiple sites in the hospital water system, with identical or highly related genomic DNA restriction patterns by PFGE. Conger et al. *(59)* reported recovery of seven patient isolates over a 5-month period from a single hospital in San Antonio, with identical DNA patterns by PFGE that also matched the pattern of microorganisms from the hospital water supply. The latter two pseudo-outbreaks represent the first recovery of *M. simiae* from the environment.

Another pseudo-outbreak involving an unusual species of slowly growing NTM occurred from 1999 to 2000 in the Veterans Affairs Medical Center (VAMC) in Houston, Texas. During that period, 37 strains of *M. szulgai* were isolated from patients at the VAMC. The previous base rate for the past 10 years had been <1 isolation of this species annually. The phenotypic properties and genetic relatedness of these strains (31 of which were nonpigmented) suggested a common source for this strain of *M. szulgai*. A single clinical strain isolated in 1996 was the only pigmented strain and the only strain associated with disease. Investigation found no common reagents, specimen-processing patient locations, or procedures linking the pseudoepidemic strains. However, a pigmented strain by gene sequence and DNA strain typing was identical to a strain recovered from a hospital water storage tank. The conclusion was that this latter strain was transiently inoculated into the patients, and although no disease was associated with this cluster, the pseudo-outbreak caused unnecessary expense and concern because most of the patients were immunocompromised and were candidates for opportunistic infections *(262)*.

Contaminated Biologics

There have been numerous reports of pseudoinfections with NTM due to contaminated biologics. In one hospital, pseudoinfection of the urinary tract with *M. avium-intracellulare* was related to contamination of urine specimens by contaminated phenol red *(62)*. In another report, a cluster of *M. gordonae* was identified in bronchoscopy specimens due to a contaminated dye used in the topical anesthetic *(263)*. Multiple pseudo-outbreaks due to RGM and slowly growing species have been linked to the BACTEC blood culture system. In one report, pseudoinfection with *M. gordonae* was traced to the BACTEC antimicrobial solution and enrichment broth added by the user to the BACTEC vials *(264,265)*. Pseudoinfection with *M. gordonae* has also been described in association with the BACTEC TB system and a contaminated antimicrobial additive. In this pseudo-outbreak, *M. gordonae* was recovered from 46 specimens

submitted for culture for mycobacteria over 8 weeks in a single northeastern laboratory. Two lots of BACTEC PANTA Plus shipped to 173 laboratories were found to be contaminated with *M. gordonae*. The contamination was due to failure to sterilize the water used in processing. This was the first report of mycobacterial pseudoinfection due to a commercially distributed product. Twenty other laboratories also reported contamination *(263)*. In a more recent report, 23 blood cultures from HIV-positive patients grew *M. abscessus*, which was ultimately traced to a multidose supplement vial used with the BBL Septi-check AFB culturing system *(63)*. Additionally, a series of 18 out of 21 samples of MGIT liquid medium tubes (Becton Dickinson, Sparks, NJ) in a hospital laboratory in Spain were positive for *M. gordonae*. The source of the epidemic strain was not confirmed, although RAPD analysis showed the profiles of the outbreak strains were identical but different from nonoutbreak isolates *(266)*.

Laboratory Cross-Contamination

A number of pseudo-outbreaks have resulted from laboratory cross-contamination involving the BACTEC system or related to specimen contamination at the time of digestion or processing. In one case, *M. chelonae* was identified due to contamination of the BACTEC system during automated reading *(264)*. Similar pseudo-outbreaks, attributed to inadequate heating of the needle probe of the BACTEC system, have been reported more recently *(267,268)*. Given the large numbers of specimens processed in many laboratories and the close proximity of the specimens, it is not surprising that cross-contamination occurs. In another case, a 6-year long laboratory pseudo-outbreak of *M. abscessus* used DNA strain typing to identify a strain of *M. abscessus* from an in-house distilled water source (269). As molecular typing techniques become more widely available, more precise confirmation will be possible. Laboratories should be aware of this potential problem and take steps to limit the possibility of cross-contamination.

Other Pseudo-Outbreaks with a Nonspecific Source of Contamination

Pseudo-outbreaks of mycobacteria may be difficult to recognize due to the extended time required to culture some species of NTM. A 2006 report from a clinical laboratory revealed a slowly growing NTM species, *M. terrae,* was cultured from 12 patients at two hospitals over a 6-day interval. However, the isolates were originally misidentified as *M. fortuitum*. Subsequent investigation by PFGE at the Centers for Disease Control and Prevention (CDC) determined that the isolates were an identical strain of *M. terrae* from 22 samples of 20 patients, thus confirming the pseudo-outbreak. Since the outbreak, the number of cultures of *M. terrae* has returned to baseline without any specific intervention *(259)*.

PREVENTION AND CONTROL OF DISEASE DUE TO NONTUBERCULOUS MYCOBACTERIA

Surveillance plays an important role in early recognition and identification of outbreaks and pseudo-outbreaks due to NTM. Surveillance should identify and facilitate investigation of any increase in isolation of NTM above thresholds. In addition, given the strong association with healthcare-associated disease, IPs should evaluate every patient with an NTM infection, particularly NTM isolated from surgical patients, dialysis patients, bronchoscopy specimens, or sterile sites. Active surveillance should facilitate early identification of healthcare-associated infections or pseudoinfections and, thereby, limit the extent of the problem. In addition, personnel in areas in which immunosuppressed, high-risk patients are hospitalized or where diagnostic or therapeutic procedures that require high-level disinfection of instruments are performed should receive intensive education about healthcare-associated pathogens and the relationship between NTM and tap water.

Education regarding the appropriate disinfection procedures for critical and semicritical instruments may help prevent healthcare-associated infections and pseudoinfections. Special attention must be given to meticulous cleaning and disinfection of items that are particularly difficult to disinfect, including bronchoscopes and other endoscopes. Personnel should be reminded that tap water should not be used to rinse instruments or for preparing specimens for culture, including tap water rinses for sputum expectoration. Use of ethylene oxide to sterilize endoscopes or other instruments between patients can eliminate contamination due to NTM, but processing with ethylene oxide is expensive and requires extended periods of time for sterilization and aeration following sterilization. Glutaraldehyde disinfection using an automated system has been shown to be effective, provided appropriate safeguards are taken to guard against contamination *(270)*. Some strains of NTM with increased resistance to glutaraldehydes have been noted *(116)*.

Some problems with instrument disinfection have been associated with slowly progressive dilution of glutaraldehyde during multiple uses, and RGM have been demonstrated to survive in 2% glutaraldehyde (236,*271*). Personnel using glutaraldehyde must be aware of the necessity for monitoring its concentration, the duration of its activity after activation, and the immersion time required for high-level disinfection *(251,272)*. Other than glutaraldehyde, mycobactericidal disinfectants include peracetic acid, iodophors, ethyl and isopropyl alcohol, chlorine compounds (minimum/1,000 ppm free chlorine), formaldehyde, and hydrogen peroxide *(273)* (see also Chapter 80).

Active surveillance, periodic review of cleaning and disinfection procedures for equipment, and the use of sterile water to rinse critical and semicritical items after disinfection are strongly recommended as infection control measures to prevent both true outbreaks and pseudo-outbreaks due to NTM *(274)*. A recent study has shown that disinfecting bronchoscopes with 70% alcohol prior to the use of automated washers, increasing the glutaraldehyde concentration to 3%, and recirculating used disinfectant were effective in the elimination of established contamination. The use of in-line filters may help reduce water contamination. Ice should be considered potentially contaminated, and its use should be limited in operating rooms. Dialysis units should be aware that water may be a source of NTM. Dialysis units need to be meticulous when they disinfect and reuse dialyzers, and they must perform careful

surveillance for infections. Tap water cultures are routinely performed as a quality assurance measure in many dialysis units; these data should be evaluated to determine whether excessive contamination or colonization is developing. Elimination of colonization above established thresholds before any patients develop infections should be the goal of performing such cultures. In addition, renalin may be a less effective disinfectant than formaldehyde or glutaraldehyde, and so, its use must be monitored closely. Dialysis centers that reuse dialyzers or perform high-flux dialysis should be particularly meticulous in their disinfection practices and their surveillance.

If increases in the isolation of NTM are detected, a chart review should be performed to determine whether patients are infected and to obtain demographic information, medical history, information on inpatient or outpatient procedures, and other possible risk factors. A case definition should be developed and microbiology and pathology records reviewed to find additional cases. The laboratory should be notified to save all isolates so that case and environmental isolates may be typed. Investigations should focus on the key issues described above, including the relationship of NTM to tap and distilled water, ice, ice machines, and improperly or inadequately sterilized instruments. Policies and procedures for obtaining and processing specimens and for disinfecting equipment should be reviewed. Frequently, direct observation of the process is often more enlightening than reviewing the written procedure. The written policy and procedure may be technically correct, but direct observation of the performance of the procedure may provide evidence to suggest the route of contamination. Selected environmental cultures may be useful to identify the source of the contamination. Patients who have been exposed to contaminated bronchoscopes or other critical or semicritical instruments should be followed closely for the development of disease.

Increasing recognition of the role of NTM in healthcare-associated pseudoinfections and infections should facilitate early identification of clusters and outbreaks. Prevention and control of these infections relies on active surveillance and rigorous attention to aseptic technique, appropriate disinfection and sterilization of instruments, and awareness that water is frequently contaminated with NTM. Recent improvements in culture, species identification, and application of molecular typing methods will also facilitate more prompt identification of the source of the problem so that prevention and control measures can be instituted.

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PART C. Fungal Infections

CHAPTER 40

Candida

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Medical and surgical advances in the areas of chemotherapeutics, cancer therapy, biological therapy, and organ transplantation have markedly altered the hospitalized patient population. Widespread use of these advances has considerably lessened the morbidity and mortality associated with a wide spectrum of severe life-threatening medical and surgical conditions and enabled the survival of a greater number of hospitalized patients who are severely ill. Frequently, these patients are in medical and surgical intensive care units (ICUs) that care for neonatal, pediatric, and adult patients. These patients are at increased risk for infections with opportunistic fungal infections caused by *Candida* species. Increasingly, healthcare-associated *Candida* species infections have been recognized to cause serious morbidity and mortality, in particular in immunocompromised hospitalized patients, and they have caused several well-documented healthcare-associated infection (HAI) outbreaks.

This chapter reviews current knowledge of the epidemiology of healthcare-associated *Candida* species infections, placing special emphasis on recent changes in the epidemiology associated with *Candida* species among hospitalized adult and pediatric patients, pathogenesis of these infections, newer laboratory methods for their diagnosis, risk factors for the development of healthcare-associated *Candida* infections, application of molecular typing techniques for *Candida* microorganisms, and current strategies and control measures for preventing both superficial and invasive infections.

ETIOLOGY

Among the many different *Candida* species described in the literature, relatively few are common human pathogens and isolated from clinical specimens. In humans, *Candida albicans* has been recognized as the most common *Candida* species causing both colonization and infection. In general, the spectrums of disease caused by *C. albicans* and by non–*C. albicans* species have been similar. However, notable differences exist between *C. albicans* and pathogenic non–*C. albicans* species with respect to some important healthcare-associated epidemiologic associations, their prevalence in surveillance cultures, virulence potential, and innate resistance to antifungal drugs.

The only major natural reservoirs for *Candida* species microorganisms are humans and animals. Although there have been reports of healthcare-associated *Candida* species outbreaks in which the microorganism was isolated from hospital environmental sources, these are usually not implicated as causes of *Candida* species outbreaks. *C. albicans* is the most common *Candida* species to be implicated in healthcare-associated fungal infections. Other medically important *Candida* species include *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, *C. krusei*, *C. lusitaniae*, *C. guillermondii*, and *C. dubliniensis*. Since the 1980s, there has been a marked increase in bloodstream infections (BSIs) due to non–*C. albicans Candida* species, especially *C. glabrata* in the United States and *C. parapsilosis* and *C. tropicalis* in Europe, Canada, and Latin America coincident with the widespread implementation of azole drug prophylaxis and therapy. Because of the emergence of pathogenic non–*C. albicans* species that have variable resistance to antifungal drugs and their widely variable interinstitutional occurrence, the accurate identification of bloodstream and other invasive *Candida* isolates to species level has become an infection control priority. In addition, surveillance of antifungal susceptibility patterns for *Candida* species may be important as a component in an institution's infection control program for these healthcare-associated fungal infections.

Candida albicans

C. albicans is generally the most frequently identified *Candida* species in the clinical laboratory and is one of the major pathogenic *Candida* species of humans. *C. albicans* is a part of the normal microbial flora of the human respiratory, enteric, and female genital tracts. Acquisition in most persons probably results soon after birth, presumably from the maternal vaginal flora; thereafter, carriage of this species in normal healthy persons, particularly in the gastrointestinal tract, is extremely common. Superficial *C. albicans* infections often affect the oropharynx (oral

thrush), esophagus, skin, nails, and vagina. Oral thrush especially occurs in neonates. However, adult patients may also be affected, especially denture wearers, diabetics, women taking oral contraceptives, pregnant women in the third trimester, patients taking inhaled or systemic steroids, and HIV-infected patients. These superficial infections are usually self-limited except in rare, often immunocompromised, individuals who may develop chronic mucosal involvement.

Importantly, *C. albicans* may exploit any deficiency in the host's cell-mediated immune defenses. This is evidenced by the development of unusually severe, chronic, and intractable *Candida* infection of cutaneous and mucosal sites in HIV-infected patients and patients who develop chronic mucocutaneous candidiasis. The most common AIDS-related *Candida* species infections are chronic or recurrent oral candidiasis, candidal esophagitis, and vulvovaginitis. Patients with chronic mucocutaneous candidiasis have a rare genetic condition that results from a specific alteration in cell-mediated immunity to *Candida*. Despite chronic and occasionally dramatic clinical involvement of mucosal and superficial sites with *Candida* species, candidemia and invasive candidiasis is a relatively rare complication in these patients and in HIV-infected patients; in the latter, it has usually been associated with the presence of other risk factors such as intravenous catheters.

Severely immunocompromised, usually granulocytopenic patients and patients on multiple immunosuppressive agents, are the major populations at high risk for the development of invasive *C. albicans* infection, and infection in these patients may involve multiple deep organ systems. Invasive infections caused by *C. albicans* may include fungemia, meningitis, brain abscess, ocular infection, pneumonia, endocarditis, peritonitis, enteritis, pyelonephritis, cystitis, arthritis, and osteomyelitis. Important additional factors that may affect the normal host defenses and predispose patients to invasive candidiasis include prematurity, surgery (especially gastrointestinal), parenteral drug abuse, the administration of broad-spectrum antimicrobial agents and total parenteral nutrition, and the use of indwelling central venous catheters (CVCs).

Candida glabrata

C. glabrata is also a common commensal in healthy individuals. It has been shown to become more common with increasing age. Over the last two decades, *C. glabrata* has been documented as an important emerging healthcare-associated pathogen. Compared to other *Candida* species, especially *C. albicans*, *C. glabrata* isolates tend to be associated with acquired *in vitro* resistance particularly to fluconazole. Thus, the selection of *C. glabrata* has been documented in patients treated with fluconazole for prolonged periods including AIDS patients with oropharyngeal/esophageal candidiasis, women with complicated vaginitis, and compromised hospitalized patients with fungemia. Cancer centers in particular have reported a shift away from *C. albicans* toward *C. glabrata* as a cause of fungemia. This is presumed to be related to increased utilization of fluconazole for prophylaxis in these high-risk patient populations *(1)*. Among cancer patients, *C. glabrata* fungemia has emerged most prominently in those with hematologic malignancies and hematopoietic stem cell transplants (HSCTs), compared with those with solid tumors. *C. glabrata* fungemia is seen more often in older adults (who also appear to have increased risk of death from the infection) and is uncommonly found in neonates and young children. Management of patients infected with *C. glabrata* and *C. krusei*, a species associated with inherent reduced susceptibility to azole drugs, is difficult.

Candida parapsilosis

C. parapsilosis is a component of the normal human skin flora and has been found particularly in cultures of the healthy subungual space. Rarely, this species causes onychomycosis. *C. parapsilosis* has also rarely been found colonizing the human gastrointestinal tract and female genital mucosal surfaces and may be an infrequent cause of vulvovaginitis or oral candidiasis. Additional specific sites of isolation of *C. parapsilosis* may include the oropharynx of healthy neonates and asymptomatic diabetics and the feces of malnourished patients. *C. parapsilosis* is most often isolated from the bloodstream, in particular from hospitalized patients. It is also known to be common among neonatal and infant patients. However, studies reporting the prevalence of *C. parapsilosis* BSIs have shown that this varies among institutions; in a review of reported series of *C. parapsilosis* fungemia from large hospitals, Weems *(2)* found that the prevalence of this infection ranged between 3% and 27%.

In contrast with fungemia caused by *C. albicans* and *C. tropicalis*, *C. parapsilosis* may more often be an important hospital environmental contaminant and gain access to the bloodstream from environmental sources. Although most *Candida* species have demonstrated the ability to form biofilms, this has become recognized as one of the characteristics of infections with this pathogen *(3,4)*. Healthcare-associated *C. parapsilosis* infections have been associated with both implanted prosthetic devices and invasive procedures. Several reports of healthcare-associated outbreaks of *C. parapsilosis* fungemia and endophthalmitis have implicated contaminated hyperalimentation solutions, intravascular pressure-monitoring devices, and ophthalmic irrigating solutions, respectively (Table 40-1) (*5–13)*. Transmission on healthcare workers' hands has recently been confirmed by molecular subtyping in an outbreak of prosthetic valve endocarditis *(14)* and candidemia in a neonatal intensive care unit (NICU) *(15)*.

Extravascular involvement caused by *C. parapsilosis* is relatively uncommon. Endophthalmitis is the most important ocular infection and usually arises following cataract extraction and intraocular lens implantation procedures. Rarely, this infection also occurs in patients as a complication of primary fungemia. *C. parapsilosis* may also cause arthritis and has a predilection for involvement of the large joints. In such patients, development of the infection often is preceded by prior joint surgery (e.g., placement of a joint prosthesis, intra-articular injection, or arthrocentesis). Peritonitis caused by *C. parapsilosis* has been reported among patients undergoing long-term ambulatory peritoneal dialysis or patients who have undergone abdominal surgery for intestinal perforation or other procedures involving peritoneal lavage. These patients may have a history of intraperitoneal and systemic antimicrobial therapy for bacterial peritonitis.

TABLE 40-1

Healthcare-Associated *Candida* species Outbreaks Investigated by the Centers for Disease Control and Prevention 1981–2009

Year (Reference)	*Fungi*	*Infection*	*No. of Patients*	*Unit/Service*	*Source*	*Control Measures*
1981 *(5)*	*C. parapsilosis*	Fungemia	5	Medical and Surgical	Contaminated PN	Discontinue use of pharmacy PN pump
1983 *(6)*	*C. parapsilosis*	Fungemia	8	NICU	Contaminated PN	General infection control
1984 *(7)*	*C. parapsilosis*	Endophthalmitis	13	Ophthalmic Surgery	Contaminated solution[a]	Discontinue product
1985 *(8)*	*C. parapsilosis*	Fungemia	12	ICU	Contaminated PN	General infection control
1988 *(9)*	*Candida* spp.	Fungemia	24	Hematology–oncology	Endogenous	General infection control
1989 *(10)*	*C. albicans*	Sternal wound infection	15	Cardiac surgery	OR scrub nurse carrier	Removal from or of implicated personnel
1990 *(11)*	*C. albicans*	Fungemia and endophthalmitis	4	Ophthalmic surgery and general surgery	Contaminated IV anesthetic agent[b]	Discontinue use of product, general infection control
1991 *(12)*	*C. parapsilosis*	Fungemia	5	NICU	Contaminated liquid glycerin[c]	Discontinue product and general infection control
1997 (CDC)	*C. parapsilosis*	Fungemia	5	NICU	Unknown	General infection control
1998 (CDC)	*C. parapsilosis and C. albicans*	Fungemia	4	NICU	Possibly personnel hand carriage	General infection control
1999 (CDC)	*C. parapsilosis*	Fungemia	5	Outpatients on home hyper-alimentation	General Infection Control	General infection control
2002 (CDC) *(13)*	*C. parapsilosis*	Fungemia	22	ICU	Personnel hand carriage	General infection control
2002 (CDC)	*C. parapsilosis*	Fungemia	9	ICU	Possibly personnel hand carriage	General infection control
2002 (CDC)	*C. parapsilosis*	Fungemia	8	NICU	Possibly personnel hand carriage	General infection control

[a]Intrinsic contamination.
[b]Extrinsic contamination.
[c]Unpublished data.
NICU, neonatal intensive care unit; ICU, intensive care unit; PN, parenteral nutrition fluid; OR operating room.

Recent reports of high MIC to therapeutic ratio in *C. parapsilosis* to echinocandins have been suggested as a cause of the recent increases in this pathogen as a cause of C*andida* infections *(16)*.

Candida tropicalis

C. tropicalis has been identified much less commonly than *C. albicans* or *C. glabrata* as a commensal fungal microorganism and has been an infrequent isolate from cultures of the urine, oropharynx, and stools of hospitalized patients. *C. tropicalis* is an important opportunistic *Candida* species that has been implicated in invasive candidiasis, in particular in acute leukemia patients. No specific risk factors for invasive *C. tropicalis* infections have been identified that differ from those for invasive *C. albicans*. However, a clinical triad of fever, rash, and myalgias has been suggested as characteristic of the clinical presentation of *C. tropicalis* infection *(17)*.

Other *Candida* Species (*C. krusei, C. lusitaniae, C. guillermondii, C. dubliniensis*)

C. krusei has been identified as a colonizing yeast in the gastrointestinal, respiratory, and urinary tracts of severely granulocytopenic patients, particularly patients with underlying hematologic malignancies, and has been associated with invasive opportunistic infections in these patients. Local gastrointestinal mucosal deterioration secondary to cytotoxic chemotherapy or radiation has been suggested as a risk factor for *C. krusei* fungemia *(18)*. In granulocytopenic patients, *C. krusei* fungemia is associated

with a high mortality. A shift to non–*C. albicans* species, predominantly *C. krusei* and *C. glabrata*, has been well documented in bone marrow transplant patients exposed to fluconazole prophylaxis.

C. lusitaniae is an unusual *Candida* species that has been recognized as a healthcare-associated pathogen. In the laboratory, *C. lusitaniae* may be misidentified as *C. parapsilosis* (both are germ tube negative and form blastoconidia and pseudohyphae on corn meal agar) *(19)*. Rarely, *C. lusitaniae* colonizes the gastrointestinal, respiratory, and urinary tracts of hospitalized patients. In addition, *C. lusitaniae* has caused invasive infections similar to *C. albicans* infections in immunocompromised patients. There have also been reports that clinical *C. lusitaniae* isolates may possess natural and sometimes acquired resistance to amphotericin B, a finding that may complicate the outcome of infected patients.

C. guillermondii is a rare, potentially pathogenic yeast that may colonize skin and has been described to cause invasive candidiasis in intravenous drug abusers (endocarditis), postsurgical patients, and severely immunocompromised patients. A pseudo-outbreak in a NICU has also been reported *(20)*.

C. dubliniensis is a species that shares many phenotypic characteristics with *C. albicans*, including the ability to form germ tubes and chlamydospores. Isolates have been recovered mainly from HIV-infected patients' oropharyngeal cultures, most often patients with recurrent oropharyngeal candidiasis following antifungal treatment. This species has been associated with invasive disease *(21)*. Although preliminary studies indicate that most strains of *C. dubliniensis* are susceptible to antifungal agents, fluconazole resistant strains have been detected. It has been suggested that *C. dubliniensis* may develop azole resistance faster than other *Candida* species *(22)*. The clinical importance and role of drug resistance in its epidemiology have yet to be determined *(22)*.

PATHOGENESIS

Candida species have been identified as saprophytes in the human respiratory tract, gastrointestinal tract, and vagina. Therefore, in the clinical laboratory, isolation of these microorganisms from specimens from these sites and the skin may be considered a normal finding. In addition, epidemiologic evidence suggests that in severely immunocompromised hospitalized patients, commensal yeast microorganisms are the major source of subsequent invasive infections. The pathogenesis of *Candida* species infections is multifactorial. Invasion by these colonizing *Candida* strains may be facilitated when there is disruption of local barriers, interference with the cellular host defenses, or both.

C. albicans appears to possess a number of virulence determinants, including proteases, adhesins, surface integrins, and switching, that may aid colonization at multiple sites and enable tissue invasion. Biofilm formation is a potential virulence factor that has been studied *in vitro* on catheter materials *(23)*. It provides a protective niche from antifungal treatment for these microorganisms and thus may be the source of persistent infection *(4)*. Relative to noninvasive *Candida* strains and species, invasive ones appear to be superior at forming biofilms, and unique biofilm morphology of *C. albicans* has been demonstrated compared to *C. parapsilosis*.

The intact skin is an effective barrier to invasion by *Candida* species. However, local disruption resulting from wounds (including intravascular catheters, burns, and ulceration) may permit skin penetration by these yeast microorganisms. Excessive moisture, as occurs in the perineum (in diapered infants), and hands and intertriginous regions (in workers whose hands are frequently immersed in water), may be another important local factor in determining sites of cutaneous or mucosal involvement.

Similarly, the intact gastrointestinal mucosa serves as a mechanical barrier preventing bloodstream invasion by *Candida* species. The passage of some *Candida* species microorganisms across the gastrointestinal tract wall may occur normally. However, disruption of this barrier, as occurs in patients with severe burns or those receiving cytotoxic chemotherapeutic drugs, may lead to *Candida* colonization and invasive infection.

Another locally protective mechanism in the gastrointestinal tract is the normal bacterial gut flora, which competes with colonizing *Candida* species microorganisms and prevents their overgrowth and subsequent bloodstream invasion. Antimicrobial agents that eliminate the gastrointestinal tract bacterial microflora and permit selective overgrowth of yeasts may be another cause of invasive disease in hospitalized patients.

The spectrum of host defenses against tissue invasion by *Candida* species include cell-mediated immunity that comprises cytokine release by lymphocytes and activation of natural killer cells and lymphocytes by interleukins. An increasing body of evidence also supports a role for specific antibody in protection against invasive *Candida* infection, which may have implications for potential vaccine development *(24)*. Clinical observations indicate that mucocutaneous *Candida* infections are commonly associated with defective cell-mediated immune responses. Innate immunity is the dominant protective mechanism against disseminated candidiasis. Recognition of *C. albicans* by Toll-like receptors (TLRs) (mainly TLR2 and TLR4), on phagocytic cells activates intracellular signaling pathways that trigger production of proinflammatory cytokines that are critical for innate host defense and orchestrate the adaptive response *(25)*. T helper (Th) cell reactivity plays a central role in regulating immune responses to *C. albicans*. Fungal infectivity is controlled by this proinflammatory (Th1) host response and optimized further through activation of Th2 and regulatory (Treg) cells. Recently, a new subset of Th cells, Th17, has been shown to play an important role in antifungal immunity *(25)*. A mutation in the beta-glucan receptor dectin-1 important for development of Th-17 cells and related stimulation of cytokine production has also been found in women with recurrent vulvovaginal candidiasis or onychomycosis *(26)*. Quantitative and qualitative abnormalities of neutrophils and monocytes are associated with invasive candidiasis.

The results of pathogenicity studies have suggested that *C. parapsilosis* and *C. krusei* isolates may be less virulent than those of other *Candida* species (*C. albicans* or *C. tropicalis*) *(2,4,27,28)*. Other potentially important findings are the enhanced growth of *C. parapsilosis* isolates in solutions with high glucose concentration and an apparent selective growth advantage of the yeast in hyperalimentation solutions.

TYPES OF HEALTHCARE-ASSOCIATED INFECTIONS CAUSED BY *CANDIDA* SPECIES

Invasive Infections

Of the HAIs caused by *Candida* species, BSI has been reported most frequently. As previously mentioned, *C. parapsilosis* candidemia has commonly been associated with the use of contaminated intravascular catheters or pressure-monitoring devices. An outbreak of *C. albicans* candidemias in postsurgical patients was also traced to use of a contaminated intravenously administered anesthetic agent *(11)*. Clusters of healthcare-associated *C. albicans* and *C. tropicalis* sternal surgical site infections have also been reported *(10,29)*.

Mucocutaneous Infections

Outbreaks of *Candida* species infections affecting mucocutaneous sites have rarely been described. However, one outbreak of oral thrush has been reported in the NICU of a hospital in the United Kingdom *(30)*. The source of these infections was traced to a bowl contaminated with *C. albicans*, *C. glabrata*, and *C. tropicalis* that was used for soaking rubber teats from infants' feeding bottles. In addition, investigation of an outbreak of superficial groin candidiasis in a team of college athletes identified use of a communal ointment container *(31)*.

CLINICAL MANIFESTATIONS

In severely immunocompromised patients, *Candida* infections usually have no specific symptoms and signs, and the only indication of underlying fungal infection may be fever that is unresponsive to antibacterial therapy. Nonetheless, clinical suspicion for the infection should be high in the management of predisposed severely ill patients. For patients predisposed to the infection, a careful search should be instituted for evidence of candidemia. For infected patients, establishing the diagnosis rapidly avoids an excessive and potentially life-threatening delay in instituting specific antifungal treatment.

The clinical presentation associated with candidemia may be variable. Some patients may have an acute onset of sepsis accompanied by high fever, chills, tachycardia, tachypnea, and hypotension with rapid progression to septic shock; alternatively, a chronic low-grade febrile illness may develop without any specific clinical findings. Development of septic shock in nonimmunocompromised patients with candidemia is rare, more often occurs in patients who have demonstrable renal failure, and is associated with a very high mortality *(32)*. Importantly, patients with candidemia may progress to develop disseminated disease with eventual widespread involvement of multiple organs.

Cutaneous lesions may develop in patients with candidemia, especially those with acute leukemia. Although these lesions may be extremely variable in number and appearance, they are usually described as firm, erythematous, raised nodules. A definitive diagnosis is provided only by histopathologic examination of a skin biopsy specimen that demonstrates the presence of *Candida* species microorganisms in the dermis. Distinctive skin lesions also occur in premature neonates with congenital cutaneous candidiasis. This rare disorder results from prenatally acquired *Candida* species infection and is often associated with the presence of an intrauterine foreign body. The spectrum of involvement in these neonates ranges from diffuse skin eruption (macules, papules, and/or pustules that may evolve into vesicles and bullae) in the absence of systemic infection, which usually affects infants weighing more than 1,000 g, to widespread desquamating and/or erosive dermatitis predominately, which affects infants who weigh under 1,000 g and is associated with frequent development of invasive candidiasis and high mortality *(33)*. In addition, candidemic patients frequently have evidence of muscle tenderness, particularly of the lower extremities. This may be the only clinical indication that the patient has an associated *Candida* myositis, and the diagnosis requires a muscle biopsy that shows histopathologic evidence of invasion of muscle tissue by *Candida* species.

Ocular candidiasis is common in patients with other clinical evidence of candidemia or invasive candidiasis. Ocular infection with *Candida* species is usually unilateral and often is asymptomatic. Patients with *Candida* species infection and ocular involvement demonstrate visual impairment, which may range from scotomata to complete blindness. Two prospective studies reported 9% and 26% candidemic patients, respectively, developed ocular candidiasis and emphasized the funduscopic finding of chorioretinitis (a focal white chorioretinal lesion with or without overlying vitreal haze) and less frequently the classic white fluffy mass with extension from the retina to the vitreous or a vitreal abscess (endophthalmitis) *(34,35)*. It has been proposed that the less common occurrence of endophthalmitis in candidemic patients may result from more of these patients receiving prophylactic antifungal therapy. In a postmortem study by Edwards et al. *(36)*, 22 of 26 patients (85%) had tissue candidiasis if hematogenous ocular candidiasis was present. Between 10% and 15% of surgical patients who were prospectively studied and received parenteral nutrition were found to demonstrate these same lesions *(37)*. The diagnosis of *Candida* endophthalmitis usually relies on characteristic intraocular findings in a patient with risk factors for invasive candidiasis along with positive blood or vitreous fluid cultures *(34)*. Krishna et al. *(35)* have recommended ophthalmologic follow-up for development of ocular candidiasis be done in patients for at least 2 weeks after an initial negative eye examination. The treatment of choice for this infection is usually systemic and intraocular amphotericin B therapy with or without flucytosine in conjunction with appropriate surgical management for advancing lesions or lesions threatening the macular (38); however, fluconazole is considered an acceptable alternative for less severe endophthalmitis (38). Among newer antifungal agents, voriconazole shows most promise, achieves high local and therapeutic concentrations in the vitreous against most *Candida* spp., when administered orally, and alternatively may be given as an intravitreal injection for sight-threatening macular involvement and vitritis. This agent may be useful for fluconazole-resistant, voriconazole-susceptible *Candida* strains *(39)*. However, serum levels should be monitored because of high variability among patients *(39)*. Posaconazole and the three echinocandins do not achieve adequate therapeutic levels in the vitreous *(40)*. Removal of a lens implant, if present in the infected eye, is considered critical for the resolution of the infection *(41)*. The outlook regarding the patient's vision is usually guarded.

Dissemination of *Candida* infection to the central nervous system (CNS) as a result of hematogenous spread has been increasingly recognized and may often be accompanied by invasive *Candida* species infection at other sites. Characteristic involvement of the CNS by candidiasis may include meningitis, diffuse cerebritis with microabscesses, mycotic aneurysms, fungus ball formation, and parenchymal hemorrhage. In infected patients, the diagnostic usefulness of cerebrospinal fluid (CSF) examination may vary; involvement of specific anatomic CNS sites determines whether fungal microorganisms are in the CSF and the nature of the cellular content. Meningitis caused by *Candida* species has been most frequently reported to affect newborns *(42)*. Intravenous amphotericin B with or without flucytosine is usually effective and intrathecal amphotericin B may be added to this regimen in some patients. Fluconazole is not recommended as primary therapy unless treatment with amphotericin B is contraindicated (38). Although the length of primary therapy has not been defined, several weeks of therapy are recommended before transition to treatment with an azole and only after the patient has demonstrated clinical and CSF improvement (38). Voriconazole may be appropriate therapy for *C. glabrata* or *C. krusei* meningitis after initial treatment with amphotericin B and flucytosine. Echinocandins are not recommended for CNS candidiasis. Removal of an infected ventricular device is recommended with systemic or systemic and intraventricular injection of amphotericin B into the device before its removal (38).

Chronic disseminated candidiasis (also called "hepatosplenic candidiasis") is a form of localized invasive candidiasis that, as the name implies, most commonly involves the liver and/or spleen. As with other forms of invasive candidiasis, blood cultures are frequently negative in these patients, and the diagnosis may not be made until postmortem examination. The most common histopathologic findings are hepatic granulomas and microabscesses. This form of the disease predominantly affects severely granulocytopenic patients, in particular patients receiving chemotherapy with cytosine arabinoside for underlying acute myeloblastic leukemia. The disease usually coincides with recovery of the patient's granulocyte count following a course of ablative chemotherapy. In these patients, gastrointestinal tract ulceration complicates receipt of this and other chemotherapeutic agents and allows gut-colonizing *Candida* species to gain direct access to the portal venous system. It has been suggested that this diagnosis should be suspected in any immunocompromised patient with unexplained fever with or without elevation of serum alkaline phosphatase or bilirubin. Magnetic resonance imaging is a technique that has also been shown to have high diagnostic accuracy for the acute, subacute-treated, and chronic-healed lesions of hepatosplenic fungal disease *(43)*. Optimal antifungal therapy for the infection is considered to be amphotericin B for the acutely ill patient or when there is refractory disease (38). Fluconazole is recommended in clinically stable patients or step-down therapy following initial therapy with amphotericin B. Recently, however, the disease incidence has decreased dramatically at large leukemia and bone marrow transplant centers where fluconazole prophylaxis has been extensively used.

Endocarditis caused by *Candida* species often has been associated with disseminated infection in patients with malignancies. It can originate from intravenous catheters and affect high-risk infants, patients receiving parenteral nutrition, parenteral drug abusers, and cardiac surgical patients, particularly as a complication of prosthetic heart valve implantation *(44)*. This infection may be an uncommon cause of persistent candidemia. However, only 50% of patients diagnosed postmortem with *Candida* endocarditis have positive premortem blood cultures for *Candida* species. Natural heart valves appear to be rarely affected; the infection usually is associated with implanted prosthetic heart valves. In their review of the Cleveland Clinic experience, Nasser et al. *(45)* found that patients with prosthetic heart valves who develop healthcare-associated candidemia are at significant risk of having or developing *Candida* prosthetic valve endocarditis even months or years later. These investigators also suggested that late-onset candidemia and lack of an identifiable portal of entry should heighten concern about *Candida* prosthetic valve endocarditis in such patients. Of 10 of their 11 patients with *Candida* prosthetic valve endocarditis treated with amphotericin B and valve replacement, 2 patients had a total of three documented relapses. Endocarditis may also occur as a secondary complication of an indwelling transvenous pacemaker, and surgical removal of the infected device and prolonged systemic antifungal therapy are required *(46)*.

Suppurative peripheral thrombophlebitis caused by *Candida* species has been reported to be a distinct clinical entity that may uncommonly cause persistent candidemia. Walsh et al. *(47)* reported seven patients with this infection over a 15-month period. Factors implicated by these authors as important in the occurrence of these infections were catheter insertion techniques and suboptimal care of the catheter insertion site. Therapy usually comprises removal of the catheter, surgical intervention, and a short course of systemic antifungal therapy (38). Rarely, *Candida* species may infect arteriovenous dialysis fistulas, and effective treatment in these patients includes removal of the fistula and systemic antifungal therapy *(48)*.

Peritonitis caused by *Candida* species has been reported as a complication in patients receiving long-term ambulatory peritoneal dialysis. Also, *Candida* species peritonitis may occur secondary to a perforated ulcer or postoperative anastomotic leakage following colonic surgery (as part of a polymicrobial infection) and may be complicated by the formation of intraperitoneal abscesses or subsequent candidemia. In patients with *Candida* species peritonitis, both an early diagnosis of the infection and prompt institution of specific systemic antifungal therapy are essential. In addition, appropriate surgical intervention in these patients to repair an underlying bowel perforation or to drain peritoneal abscesses may also be required.

Invasive renal candidiasis is most frequently the result of hematogenous dissemination and complicates candidemia or disseminated candidiasis. The kidney is the most commonly involved organ in invasive candidiasis (90%) *(49)*. Rarely, usually only when there is coexistent obstruction, renal parenchymal infection and pyelonephritis are the result of retrograde renal tract infection.

DIAGNOSIS

Diagnosis of mucocutaneous *Candida* species infections usually depends on examination and identification

of typical morphologic forms in a potassium hydroxide–stained smear preparation. Detection of budding yeasts and pseudohyphae is characteristic of *Candida* species. This same morphologic appearance on direct microscopic examination of other clinical specimens may also be important for the rapid presumptive diagnosis of invasive *Candida* species infection. The yield from direct microscopic examination of these specimens may be significantly improved by use of calcofluor white stain and subsequent examination by fluorescence microscopy. Use of commercial agar with chromogenic substrates may aid in rapid presumptive identification of *C. albicans*, *C. tropicalis*, and *C. krusei* in cultures; some reports have suggested modifications to this medium to allow for differentiation of *C. glabrata* and the incorporation of fluconazole to not only identify the *Candida* species present but to also identify antifungal drug resistant isolates during initial isolation *(50)*. A molecular-based method, the *C. albicans* peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH AdvanDx) test uses a fluorescein-labeled probe that is added to smears made directly from blood culture bottles that test positive and in which yeasts were observed by Gram staining, which are then examined under fluorescence microscopy. The test is unaffected by the type of blood culture system or broth formulation (e.g., lytic or other medium) used, it may provide a time savings in the laboratory of 24 to 48 hours compared with conventional laboratory identification methods, and single-center and multicenter studies have demonstrated its sensitivity (99–100%) and specificity (100%) in direct identification of *C. albicans* from blood cultures (51). FDA has approved several commercially available PNA-FISH kits (AdvanDx) for identification of yeasts (*C. albicans*, *C. parapsilosis*, *C. tropicalis*, *and C. dublinensis*) in a single assay directly from blood cultures. The test can rapidly (1.5 hours) indicate whether *C. albicans* is present or not and can thus help indicate whether a non–*C. albicans* yeast is present. With this test, laboratories can report whether a positive blood culture with yeast contains *C. albicans* within a few hours after the culture becomes positive *(52,53)*.

In patients with invasive candidiasis, the diagnosis can be difficult to establish because of the suboptimal sensitivity of blood cultures. Frequently, a high index of clinical suspicion, the use of blood cultures and diagnostic imaging techniques (computed tomography and magnetic resonance imaging), and invasive biopsy procedures are required. The combination of histopathologic demonstration of morphologically compatible yeasts and hyphal forms if present (*C. glabrata* does not form pseudohyphae/hypha) together with a positive culture is considered to be the gold standard for diagnosing invasive *Candida* species infection.

The sensitivity of routine blood culture methods has improved but is still not ideal (50–70%) (54); in granulocytopenic patients, this may be further exaggerated (<20%) (51). Advances reported to improve the recovery of *Candida* species from the bloodstream of infected patients include the lysis centrifugation system (Isolator, Wampole Laboratories, United States). and automated, continuous-monitoring, broth-based systems. Automated broth-based systems, for example, Bactec (Becton Dickinson) and BacT/Alert (bioMerieux), have equal sensitivity for detecting *Candida* species to the more labor-intensive lysis-centrifugation method (51). However, despite these advances in blood culture technology, recovery of *Candida* species from blood still does not identify many patients with invasive infections. In patients with postmortem-confirmed candidiasis, Berenguer et al. *(55)* found a direct relationship between the number of visceral organs involved and the frequency with which lysis centrifugation blood cultures detected *Candida* species. Using this modern method, only 28% patients with single visceral organ involvement (excluding gastrointestinal tract) and only 58% of patients with involvement of two or more visceral organs were fungemic.

False-positive *Candida* species blood cultures (positive culture in the absence of candidemia or invasive infection in the patient) may occur; this most often occurs when blood for culture is drawn via an intravascular catheter that itself has become colonized with *Candida* species. Another important mechanism of contamination of blood culture specimens is inoculation with extrinsic yeasts from sources such as the skin of the patient or personnel. This can occur because of improper techniques of specimen collection and handling or laboratory manipulation.

A single positive blood culture growing *Candida* species should be considered a clinical infection unless evidence suggests otherwise. From an infection control standpoint, *Candida* species is considered a recognized pathogen and fulfills the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Networks (NHSNs) surveillance definition of a central line–associated bloodstream infection (CLABSI) if the patient has a central line in place, the infection is not incubating or present on admission, and there is no infection at another site *(56)*. Further clinical evaluation of the patient is indicated to confirm whether it represents invasive infection, colonization of the central line it was drawn out of, or contamination of the blood culture during the culturing process. The finding of a single blood culture positive for *Candida* species, even when possibly caused by an indwelling intravascular line, should prompt empiric treatment and further clinical evaluation of the patient for evidence of invasive infection *(57)*.

Intravascular catheters may not only serve as the portal of entry for *Candida* species and be an important primary source of candidemia but also provide a secondary site of attachment for *Candida* species that invade the bloodstream from other sites, most frequently the gastrointestinal tract. A semiquantitative method developed principally for detecting catheter-associated bacteremia also is applicable to the evaluation of catheter-associated candidemia. Following removal from the patient, the distal (5-cm) intravascular segment of the catheter is rolled four times across the surface of a sheep's blood agar plate and immediately afterward is placed into a tube of broth medium for additional culturing. Growth of 15 or more colony-forming units (CFU) on the solid medium has been used to identify bacteria as the cause of catheter-associated bacteremia *(58)*. However, it has been suggested that the recovery of *Candida* species in any amount from either the solid or liquid media cultures of a vascular catheter tip should prompt a thorough clinical reevaluation of the patient for invasive candidiasis *(58)*.

Candida species in urine is an abnormal finding in clean-voided specimens or specimens obtained by suprapubic aspiration from normal individuals. However, the incidence of candiduria is high in ICU patients and often coexists with candidal colonization at other anatomical sites *(59)*. The

most commonly identified risk factor for the development of candiduria is an indwelling Foley catheter. Additional important factors that may coexist with an indwelling urinary catheter in seriously ill patients include diabetes mellitus, administration of antimicrobial agents, urinary tract instrumentation, and prior bacteriuria.

The presence of candiduria in an ICU patient may indicate extrinsic contamination of the urine specimen, innocuous lower urinary tract colonization from an indwelling Foley catheter, or, most importantly, invasive upper or lower urinary tract infection. Quantitative urine yeast colony counts are an unreliable method both for distinguishing active infection due to *Candida* species from colonization and for localizing the source of candiduria; although a level of $<10^4$ CFU/mL argues against renal candidiasis *(60)*, levels above 10^5 CFU/mL may be associated with a colonized indwelling Foley catheter. Microscopic examination of a Gram-stained urine specimen may not be helpful; however, the presence of hyaline renal tubular casts containing *Candida* species, particularly with pseudohyphae, may correlate with renal infection.

In patients following neurosurgery, the clinical significance of a single CSF sample culture positive for *Candida* species when obtained via an indwelling device (shunt) is difficult to assess, and a definitive diagnosis may require repeated cultures of CSF samples obtained by lumbar puncture *(61)*.

Conventional serologic techniques for detecting serum anti-*Candida* antibodies have not been useful for diagnosing invasive candidiasis, because most normal individuals have circulating antibodies to this microorganism and, in immunocompromised patients, antibody production is variable.

Several prototype antigen/metabolite tests (secreted aspartyl proteinases, D-arabinitol [Roche Diagnostic Systems], and Platelia Candida Ag test [Bio-Rad]) have been described and appear promising as methods for the diagnosis of invasive candidiasis, and these have been recently reviewed (54). Detection of β-1,3-glucan (BG) found in the cell wall of common pathogenic yeasts and other fungal pathogens is detected by two commercial kits, the Glucatell (Associates of Cape Cod) and the Fungitec-G (Seikagaku Corp.). The qualitative detection of BG in the serum of patients does not identify the infecting fungus, but these tests may be used as a rapid screening assay (results within 2 hours) permitting earlier initiation of antifungal therapy in patients with symptoms of or medical conditions predisposing to invasive fungal infections. A single positive test result provides generally good sensitivity and specificity *(62)*; however, repeat testing improves the specificity (repeat positive tests) and negative predictive value (repeat negative tests) *(62,63)*. Of note, BG is ubiquitous in the environment and false-positive results may be caused by hemodialysis using certain cellulose membranes, exposure to certain types of gauze, and recent receipt of albumin or immunoglobulin *(64)*. New approaches to shorten the time required to identify *Candida* species from blood (currently more than 24 hours using automated blood culture systems) include a rapid immunomagnetic separation system for *Candida* species from blood that will recover yeast directly from the specimen so they can be inoculated onto growth media *(65)* and real-time polymerase chain reaction (PCR) methods. Although real-time PCR has the ability to detect candidemia much earlier than conventional blood culture, it does not always detect all cases of invasive infection with all species *(66–68)*. Bennett has recently reviewed use of this technique that is likely to be used alongside blood culture protocols while it is developed further *(69)*.

EPIDEMIOLOGY

Descriptive Epidemiology

Candida species commonly cause healthcare-associated BSIs among patients in ICUs. Data from the CDC's National Nosocomial Infections Surveillance (NNIS) system during 1990 to 1999 have shown that risk-adjusted HAI rates decreased for all three body sites (i.e., respiratory tract, urinary tract, and bloodstream) monitored in ICUs *(70)*. In particular, rates for healthcare-associated BSIs decreased markedly in medical (nonsurgical) ICUs (44%), coronary ICUs (43%), pediatric ICUs (32%), and surgical ICUs (31%) *(70)*. However, coincident with this significant decrease in the incidence of *C. albicans* BSIs was a significant increase in the incidence of *C. glabrata* BSIs *(71)*. It has been postulated that these trends likely occurred in association with a national increase in fluconazole use, which received U.S. Food and Drug Administration (FDA) approval in 1990.

A review of NNIS system data from NICUs during 1995 through 2004 found a significant decrease in the incidence of candidemia among very low birthweight (<1,000 g) infants (3.51 per 1,000 patient days in 1995–1999 to 2.68 per 1,000 patient days in 2000–2004) but a stable rate among heavier birthweight infants (72). This decrease was also found for both the number of candidemias per 100 patients (attack rate) and the risk-adjusted CVC-associated BSI rate. In order of frequency, the *Candida* species causing primary BSIs in this high-risk population was *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. lusitaniae*, *C. glabrata*, and *C. krusei*. In addition, no increase in infections by *Candida* species that tend to demonstrate resistance to fluconazole (*C. glabrata* or *C. krusei*) was observed.

In 2005, CDC's NHSN, which replaced the NNIS system and adds surveillance of selected HAI data at locations other than ICUs in hospitals and other types of healthcare facilities, began collecting data. The first NHSN report from January 2006 to October 2007 identified *Candida* species as the fourth commonest pathogen group associated with HAIs overall and the second commonest species causing catheter-associated urinary tract infection, third commonest species causing CLABSI, seventh commonest species causing ventilator-associated pneumonia, and eighth commonest species causing surgical site infection (73). *C. albicans* was the predominant species identified in each of these categories with the exception of CLABSI where the proportion identified as *C. albicans* was not different from that of other *Candida* species/not otherwise specified.

Hospital Discharge Data National surveillance of healthcare-associated BSIs conducted prospectively in 49 hospitals in the United States by the SCOPE group (Surveillance and Control of Pathogens of Epidemiologic Importance) between 1995 and 1998 found *Candida* was the fourth leading cause of healthcare-associated BSIs,

accounting for 7.6% of all infections *(74)*. Of 934 episodes of candidemia, 46.8% were due to the non–*C. albicans* species identified as *C. glabrata* (42.3%), *C. tropicalis* (26.1%), *C. parapsilosis* (21.1%), *C. krusei* (3%), and other *Candida* species (2%) *(74)*. The proportion of non–*C. albicans* species isolates varied with geographic region and ranged from 30.2% in the Southwest to 54.5% in the Northeast *(74)*. A suggested important factor responsible for this increased trend in fungemias caused by non–*C. albicans* species is widespread use of fluconazole for prophylaxis and therapy. A follow-up report from this group on 22,631 episodes of BSIs during 1995 through 2001 observed that despite *Candida* species accounting for 9% and 8% of isolates recovered from all neutropenic and nonneutropenic patients with BSIs, respectively, *Candida* species was notably isolated latest during the patient's hospital stay (mean, 18 days) and monomicrobial *Candida* species BSIs were associated with the worst outcome (crude mortality rate, 45%), and this did not differ according to the patient's neutropenic status *(75)*.

The National Epidemiology of Mycoses Survey (NEMIS) prospectively identified *Candida* species isolated from blood and other normally sterile sites during 1993 to 1995 from patients hospitalized in surgical and NICUs of six academic medical centers located in Oregon, Iowa, California, Texas, Georgia, and New York *(76,77)*. The incidence reported for healthcare-associated BSIs due to *Candida* species was 0.99/1,000 patient days for surgical ICU patients and 0.64/1,000 patient days for NICU patients. Of the patients surveyed (4,276 surgical ICU patients and 2,847 babies), 30% to 50% developed incidental stool colonization, 23% of surgical ICU patients developed incidental urine colonization, and one-third of surgical ICU healthcare workers' hands were positive for *Candida* species. In addition to a marked interinstitutional variation in rates of BSIs due to *Candida* species, there was variation found in antifungal susceptibility to fluconazole *(77)*. Analysis of patient isolates using a DNA subtyping method enabled investigators to identify 13 clusters of suggested cross-infection occurring in five of the study centers. Nine (69%) of these clusters involved non–*C. albicans* species. The conclusions from this analysis were that the possible mechanisms of *Candida* species transmission that occurred were from patient to patient (*C. albicans*, *C. glabrata*, *C. tropicalis*, and *C. parapsilosis*) and from healthcare worker to patient (*C. albicans*, *C. parapsilosis*, and *C. krusei*) *(76)*. A comprehensive molecular subtyping study of *C. albicans* isolates from patients with BSIs and surgical ICU and NICU healthcare workers from four hospitals participating in the NEMIS study demonstrated that for the majority of patients (90%), isolates collected from commensal sites before and after collection of a BSI isolate were highly similar or identical to the BSI isolate *(78)*. The study also suggested that multiple endemic strains rather than a single, dominant endemic strain were more often responsible for healthcare-associated BSIs in surgical ICUs and NICUs and that cross-contamination occurs between patients and healthcare workers and between healthcare workers in the same ICU and in different ICUs *(78)*.

The SENTRY Antifungal Surveillance Program has been operational since 1997 and prospectively collects healthcare-associated bloodstream isolates from 72 participating hospitals in the United States, Canada, Latin America, and Europe *(79)*. Eighty percent of BSIs reported to this system were healthcare-associated (vs. community-acquired) and 50% occurred in patients in an ICU. In addition, this system has noted differences in species distribution, with US medical centers having higher rates of BSIs due to *Candida* species, such as *C. glabrata* and *C. krusei*, which are less susceptible to the triazoles compared with Canada and South America *(79)*. Data from this system have also demonstrated differences in antifungal resistance among isolates from pediatric and adult patients, which likely reflect differences in the distributions of infecting *Candida* species between these age groups (i.e., predominance of *C. albicans* and *C. parapsilosis* in age groups ≤1 year and 2–15 years of age and fewer *C. albicans* and significantly more *C. glabrata* infections in persons ≥65 years) *(80)*. A further report from this system has shown variation in antifungal susceptibility to fluconazole among *C. glabrata* bloodstream isolates according to geographic location and age group (i.e., lowest in Pacific [44%] and East South Central [47%] regions and highest in West South Central region [82%], and isolates from pediatric patients were virtually all susceptible to fluconazole, whereas the highest frequency of resistance was observed in isolates from patients 16–64 years of age) *(81)*. The SENTRY system in 2008 to 2009 has also reported that *C. glabrata* bloodstream isolates may show lower susceptibility rates to both azoles and echinocandins with the highest rates of resistance detected in 20- to 59-year-old patients *(82)*.

Reports of surveillance for candidemia conducted in other countries have increased understanding of the epidemiology of the condition. In a study of French hospitals in 1995, Richet et al. *(83)* reported an overall incidence rate of 0.29 per 1,000 admissions, ranging from 0.71 per 1,000 admissions in cancer referral centers to 0.17 per 1,000 admissions in general hospitals. In this study, *C. albicans* (53%) was the predominant species isolated, a CVC (26%) was the most common portal of entry, and 50% of the candidemic patients had a neoplasm. Bougnoux et al. *(84)* conducted a 1-year prospective observational study in 24 adult ICUs in France and identified mean incidence of 6.7 and 27.4/1,000 admissions for healthcare-associated candidemia and candiduria, respectively. Using multilocus sequence typing (MLST), these investigators found 8% of the candiduric patients developed candidemia with the same species, both types of infections were acquired late (i.e., 19 and 17 days after their ICU admission) and with high crude mortality (62% and 31%, respectively). Prospective candidemia surveillance conducted in 1992 to 1994 in 14 Canadian medical centers found a 4:1 adult to child ratio, more frequent occurrence of *C. parapsilosis* (second only to *C. albicans* and associated with lower mortality), and age >60 and stay in an ICU as the two most significant risk factors for overall mortality *(85)*. Five-year population surveillance in the Calgary Health Region during 1999 through 2004 found the annual incidence for invasive *Candida* species infections was 2.9 per 100,000. The highest risk was in patients with comorbidities and those at the extremes of age and 30% isolates showed reduced susceptibility to fluconazole *(86)*. In a retrospective review of *Candida* species BSIs in nine Australian tertiary referral hospitals during 1995 to 1998, Slavin's group *(87)* reported a rate for

candidemia of 0.1 to 0.27 per 1,000 discharges and demonstrated a decreasing trend in the proportion of *C. albicans* to non–*C. albicans* species. In a follow-up study, these investigators reported that hospitalizations with a diagnosis of disseminated, invasive, and noninvasive candidiasis added 31, 17, and 12 days to patients' length of stay, and costs of AU $33,274, AU $12,954, and AU $7,694 with the associated mortality being 26%, 9%, and 8%, respectively *(88)*. A retrospective analysis of candidemia episodes in an ICU in the United Kingdom found the attributable mortality for candidemia varied between 21.5% and 34.7% and infected patients spent on average more than 5.6 days in ICU than matched control patients and generated mean additional costs of at least £8,252 per patient, £16,595 in adults only *(89)*. By comparison, the estimated costs attributable to an episode of invasive candidiasis in the United States have been estimated to be US $28,000 to US $48,000 for pediatric and adult patients *(90,91)*. In a review of candidemia from Finland, Poikonen et al. *(92)* found the annual incidence increased from 1.7 per 100,000 population in 1995 to 2.2 per 100,000 in 1999; however, the proportion of non–*C. albicans* species cases (30%) did not increase during the study period. In addition, the highest annual incidence (24.4/100,000 population) occurred in 1999 in infants <1 year of age, which was primarily caused by *C. albicans*. A 1-year (November 2001–October 2002) surveillance program in Japan identified a similar species distribution of *Candida* bloodstream isolates and fluconazole resistance rate to those reported in North America and Europe *(93)*. A study of all Icelandic *Candida* spp. bloodstream isolates from 1991 to 2000 (n = 219 isolates) detected an increased incidence from 3.7 per 100,000 during 1991–1994 to 5.8 per 100,000 during 2003–2006 *(94)*. Using PCR fingerprinting, these authors found that between 19% and 40% of their isolates were from small unrecognized healthcare-associated clusters (average of only 2 patients), which significantly affected patients in adult and NICUs.

The Transplant-Associated Infection Surveillance Network (TRANSNET) is a consortium of 23 US transplant centers established in 2001 to perform prospective surveillance for invasive fungal infections among organ transplant recipients. Data from this network through 2006 for HSCT recipients found that invasive candidiasis represented only a minority (28%) of invasive fungal infections in this group, which compares to higher rates among this patient population during the 1980s and 1990s (95). Non–*albicans Candida* species accounted for almost 70% of these infections. Widespread use of azole prophylaxis likely influenced the decreased incidence and shift in epidemiology in the HSCT setting although other factors may be important. These are very similar findings to those described from another multicenter observational registry of United States and Canadian medical centers included in the Prospective Antifungal Therapy Alliance (PATH Alliance), which also monitors trends in the epidemiology, diagnosis, treatment, and outcomes of solid organ transplant recipients *(96)*.

Data from the TRANSNET through 2006 for solid organ transplant recipients, identified invasive candidiasis as the most common invasive fungal infection in each organ transplant type, except among lung transplant recipients, the median time to onset of candidiasis was 103 days, and the associated overall mortality was high (66% 12-month survival) *(97)*. The overall mortality was similar to that seen in recent treatment trials of candidemia and other forms of invasive candidiasis. The network has also found the distribution of *Candida* species to be similar to that reported in recent national surveys among hospitalized patients (*C. albicans* and *C. glabrata* were the predominant species). These are very similar findings to those described from the PATH Alliance *(98)*.

Population-Based Data National incidence rates for invasive candidiasis estimated using data from the National Hospital Discharge Survey (NHDS), which samples nonfederal short-stay hospitals, found an annual incidence of 22 to 24 infections per 100,000 population per year (19–20 per 10,000 hospital discharges) from 1996 through 2002, with an increase to 29 infections per 100,000 (24 per 10,000 discharges) in 2003 (51). This extrapolated to a national burden of approximately 63,000 infections in the United States per year. This estimate was similar to a high but stable population-based surveillance estimate for the Baltimore MD metropolitan area (24 per 100,000) during 1998 to 2000 *(99)*. However, it contrasts with the NNIS system data, which found a decline in frequency of healthcare-associated candidemia in ICUs in the United States between 1989 and 1999 *(71)*. Of note, Hajjeh et al. *(99)* found that during 1998 through 2000, only 36% of *Candida* BSIs occurred in the ICU, whereas 28% had onset outside the hospital; however, infection beginning outside the hospital may be a reflection of changing healthcare practices with more immunocompromised patients receiving care as outpatients.

Multiple-cause-of-death data obtained from NCHS found that age-adjusted crude (all-cause) mortality of patients with invasive candidiasis increased steadily from 1980 to peak in 1989 followed by a gradual decline through 1996 *(100)*. Pfaller and Diekema updated this analysis using the same data source and found the rate remained steady at approximately 0.4 deaths per 100,000 population per year from 1997 through 2003 (51). These data suggest the incidence and mortality associated with invasive candidiasis are not declining.

Rees et al. *(101)* reported the results of population-based active laboratory surveillance conducted for invasive mycotic infections during 1992 and 1993 in three California counties in the San Francisco Bay Area; they found the cumulative incidence for these infections was 17.8 per 100,000 per year and *Candida* (7.3 per 100,000 per year) was the most common infection. The case–fatality ratio was 33.9%. The *Candida* species they identified in order of frequency were *C. albicans* (50.9%), *C. parapsilosis* (22.2%), *C. glabrata* (11.7%), and *C. tropicalis* (7.9%). Species-specific case–fatality ratios were *C. tropicalis* (44.1%), *C. albicans* (38.1%), *C. glabrata* (34.7%), and *C. parapsilosis* (16.8%). Major underlying conditions among all patients with invasive candidal infections were nonhematologic malignancies (18.2%), HIV infection (15.3%), diabetes mellitus (13.6%), and chronic lung disease (13.6%) *(101)*. Recent abdominal or cardiac surgery had been performed on 17.9% of patients with invasive candidiasis and was particularly associated with *C. tropicalis* and *C. glabrata* infections. *C. parapsilosis* was the most frequently isolated invasive fungal pathogen in children under 10 years of age (cumulative incidence: 3.3 per 100,000 per year) followed

by *C. albicans* (29.6 per million per year), and for both of these species the race-specific cumulative incidence rates among blacks were more than double those of other racial groups. The majority of infections with *C. parapsilosis* and *C. albicans* in children <10 years occurred in those <1 year. No cases of invasive *C. glabrata* infection occurred in patients under 20 years of age *(101)*. Kao et al. *(102)* also reported results of prospective, active population-based surveillance for candidemia in Atlanta and San Francisco during 1992 to 1993. The average annual incidence of candidemia at both sites was 8 per 100,000 population; the highest incidence (75 per 100,000) occurred among infants ≤1 year old. In 20% of patients, candidemia developed prior to or on the day of admission. Underlying medical conditions included cancer (26%), abdominal surgery (14%), diabetes mellitus (13%), and HIV infection (10%). In 47% of cases, non–*C. albicans* species were isolated, most commonly *C. parapsilosis*, *C. glabrata*, and *C. tropicalis*. Antifungal susceptibility testing of 394 isolates revealed minimal levels of azole resistance among *C. albicans*, *C. tropicalis*, and *C. parapsilosis*.

Most recently, the CDC has conducted active, population-based laboratory surveillance from 2008 to 2010 in two locations in the United States: Baltimore City and County, Maryland (population: 1.4 million) and Metropolitan Atlanta, Georgia (population: 3.8 million). After 1 year of surveillance, an increase in incidence rates was found over prior surveillance (14/100,000 in Atlanta and 31/100,000 in Baltimore) *(103)*. Prevalent underlying medical conditions included surgery in the 3 months prior to candidemia (55%), diabetes (30%), cancer (24%), or liver-related diagnoses (22%). The case-fatality rate was 30% in Atlanta and 26% in Baltimore. In Atlanta, the species-specific incidence of candidemia rose dramatically from previous rates in 1992 to 1993 for both *C. glabrata* (4.5 vs. 1.0/100,000) and *C. parapsilosis* (3.2 vs. 1.8/100,000). In Baltimore, the incidence of candidemia due to *C. parapsilosis* doubled from previous rates from 1998 to 2000 (5.5 vs. 2.5/100,000). These preliminary data suggest that the incidence of candidemia is increasing and that the increase is being driven by increases mainly in *C. glabrata* and *C. parapsilosis*. Ongoing surveillance in sentinel sites around the United Statesis essential to help monitor and understand changes in epidemiology.

Reservoirs and Sources of Infection

Candida species may enter the blood via several routes; the major routes are intubation, intravenous catheterization, and intestinal translocation. The last route becomes important when the burden of yeast microorganisms exceeds a certain but as yet undetermined threshold in humans. A prospective study involving biweekly quantitative stool cultures from very low birth weight (≤1,500 g) infants during the first 6 weeks of life revealed a threshold (8×10^6 *Candida* species CFU/g of stool) beyond which 50% of the patients developed gastrointestinal symptoms *(104)*. More than half of these same patients also developed invasive infection within the following weeks. These results may be of particular importance, because they provide a basis for developing and evaluating effective interventions for the prevention of candidemia originating from the gut in these high-risk pediatric patients.

In most hospitalized *Candida*-infected patients, the likely source of the infecting strains is *Candida* species from the patient's own endogenous fungal flora of the gastrointestinal tract and skin. Clinical studies using newer molecular typing techniques have confirmed that patients' endogenous colonizing *Candida* species strain(s) may be the cause of invasive disease *(105–107)*. Long-term indwelling intravascular catheters, in particular CVCs, provide another portal of entry for endogenous pathogenic *Candida* species. Finally, despite the isolation of *Candida* species from a variety of hospital environmental sources, including air, food, fomites, and environmental surfaces, these have not been implicated as sources for healthcare-associated *Candida* species infections.

Modes of Transmission of Infection

Healthcare-associated transmission of *Candida* species may result from either extrinsic or intrinsic contamination of solutions or devices. Carriage of *Candida* species on the hands of hospital personnel may cause extrinsic contamination of central lines and devices, parenteral hyperalimentation fluids, and other intravenous solutions and medications. Outbreaks of healthcare-associated *Candida* species infections have been reported often in special care units and attributed to cross-infection (Table 40-1). Outbreaks of healthcare-associated *C. parapsilosis* fungemia, in particular, have been traced to contaminated intravascular lines and pressure-monitoring devices and/or parenteral hyperalimentation fluids (Table 40-1). Extrinsic contamination of a new intravenous anesthetic agent without a preservative was also responsible for an outbreak of postsurgical *C. albicans* fungemia and endophthalmitis *(11)*. In a multistate outbreak of *C. parapsilosis* endophthalmitis, the vehicle identified was an intrinsically contaminated ophthalmic irrigating solution *(7)*. Antifungal susceptibilities of outbreak isolates found them to have a uniform pattern that differed from those of control isolates *(108)*. In the outbreak of candidemia in an NICU reported by Sherertz et al. *(109)*, infants' BSIs were traced to the administration of *Candida* species–contaminated retrograde medication syringe fluid. Pertowski et al. *(10)* investigated an outbreak of sternal wound infections in patients following cardiac surgery and found that exposure to a particular scrub nurse in the operating room with a history of recurrent vulvovaginal candidiasis was significantly associated with case-patients. Molecular subtyping of case patients' isolates was performed and these results suggested a common source; however, no isolates from the scrub nurse were available. Following reassignment of the scrub nurse outside the operating room, the outbreak ceased. Also, a distinctly unusual source, a multidose bottle of liquid glycerin used for per-rectal administration, was identified by Welbel et al. *(12)* in an outbreak of *C. parapsilosis* BSIs in neonates.

More specific evidence regarding healthcare-associated *Candida* species transmission has been provided by several investigators who have used new molecular typing methods to study isolates from infected patients, hospital personnel, and the hospital environment. In an outbreak of *C. tropicalis* sternal surgical site infections in patients undergoing cardiac surgery, a staff member carrier was identified who had contact with all the case-patients and

who was colonized (nares and hand) by a *C. tropicalis* strain with a DNA type identical to that of the case-patient isolates and different from those of control *C. tropicalis* isolates *(29)*. In another report, three of four infants infected over a 3-month period from an unspecified source in a NICU acquired the same strain of *C. albicans (110)*. In a third report, 5 of 98 bone marrow transplantation unit (BMTU) patients studied prospectively acquired *C. parapsilosis* exogenously during their admission; although isolates of a single DNA type were isolated from four patients, the hands of three hospital staff members, and two environmental surfaces in the BMTU, no common source could be identified, and a total of three different DNA types were demonstrated for the outbreak isolates *(111)*. In a prospective study of 98 patients admitted to a university hospital's medical ICU and BMTUs, prolonged stay in the unit and prior antimicrobial use were each identified as significant risk factors for healthcare-associated *C. glabrata* colonization *(112)*. Molecular subtyping analysis of *C. glabrata* isolates obtained from patients, healthcare workers' hands, and the environment further suggested that exogenous healthcare-associated acquisition of these isolates may have occurred from sources in the hospital environment, and indirect contact may have been important in their transmission *(112)*. Kuhn et al. *(113)* evaluated isolates from a *C. parapsilosis* community hospital outbreak and using DNA fingerprinting confirmed they belonged to one clone compared with clinical isolates from patients with sporadic infections in a separate tertiary hospital. These same investigators found that biofilm expression by the outbreak clone was significantly greater than that of the sporadic clinical isolates. Application of these newer methods of molecular typing to the study of *Candida* species infection should enhance our understanding of the epidemiology of this important healthcare-associated pathogen.

Risk Factors for Infection

Factors that have increased the number of severely immunocompromised hospitalized patients who are at highest risk for healthcare-associated fungal infections include modern pharmacologic treatments for hematologic and other malignancies, including intensive ablative and immunosuppressive chemotherapeutic regimens, broad-spectrum antimicrobial agents, parenteral hyperalimentation, and prolonged treatment of patients in adult and NICUs, frequently with invasive devices such as CVCs. Other important factors contributing to the number of highly immunocompromised hospitalized patients include the AIDS epidemic and an increase in the number of patients with solid organ (kidney, heart, liver) or HSCTs.

Few well-controlled studies have properly assessed predisposing factors for the development of healthcare-associated invasive candidiasis. Karabinis et al. *(114)* studied candidemia in cancer patients and, in a multivariable analysis of a matched case–control study, found that positive surveillance cultures for *Candida* species, central venous catheterization, and neutropenia were significant independent risk factors for infection in these patients. In a matched case–control study by Wey et al. *(115)*, the stepwise logistic regression analysis identified four independent variables that together predicted the acquisition of healthcare-associated candidemia: the number of antibiotics received before infection, prior hemodialysis, prior use of a Hickman catheter, and isolation of *Candida* species from nonblood body sites. A third matched case–control study by Bross et al. *(116)* drew similar conclusions concerning the use of central lines and antibiotics; moreover, the presence of a urinary catheter, azotemia, diarrhea, candiduria, and the transfer of the patient from another hospital also were associated with an increased risk of candidemia. These studies will help determine high-risk populations and preventive approaches that may reduce the incidence of healthcare-associated candidemia.

In another study, Richet et al. *(9)* showed that significantly granulocytopenic patients with acute lymphocytic leukemia were predisposed to candidemia following administration of vancomycin and/or imipenem. This study also found that, in these patients, proliferation of *Candida* species in the gastrointestinal tract as a result of vancomycin therapy was associated with an increased risk for candidemia, and that concurrent prophylactic oral amphotericin B therapy was protective. Thus, in granulocytopenic patients, receipt of specific antimicrobial agents for prophylaxis of bacterial infections may itself predispose these patients to invasive candidiasis. A better understanding of the risk factors for invasive candidiasis will await future studies.

Turner et al. *(117)* examined healthcare-associated candidemia in pediatric patients at two university hospitals over a 5-year period. Forty percent of the patients with candidemia were premature infants, 38% had gastrointestinal and hepatic disorders, and 15% had underlying malignancies. The infection was related to intravenous lines in 90% of cases.

A few studies have examined the role of preexisting colonizing *Candida* species strains in patients who subsequently develop invasive candidiasis. Solomkin et al. *(118)* reported that, in patients undergoing elective abdominal surgical procedures, there was evidence of sequential spread of colonizing yeasts from the abdominal cavity to the bloodstream and other body sites. Pittet et al. *(119)* used electrophoretic karyotyping to delineate *Candida* species strains isolated from critical care unit patients. In this study, *Candida* species carriage was found to be patient specific rather than site specific; each patient was colonized with *Candida* species with identical karyotype patterns. Colonization always preceded infection that occurred a mean of 25 days after initial surveillance cultures grew yeast. These investigators further determined that, among surgical patients heavily colonized with *Candida* species, the three significant risk factors for candidemia were the length of previous antibiotic therapy, an Acute Physiology and Chronic Health Evaluation (APACHE II) score >20, and the degree of *Candida* colonization *(119)*. In another study, Reagan et al. *(110)* used restriction endonuclease digests of chromosomal DNA and a DNA probe to demonstrate the sequence of initial colonization of patients with *Candida* species followed by their infection with strains considered identical with these techniques. These studies highlight the importance of using molecular epidemiologic tools for further understanding of the pathogenesis and mode of transmission of candidal infections.

Infections with *Candida* species that are resistant to antifungal agents used in prophylaxis for severely immunocompromised patients were initially identified with the widespread use of fluconazole in the therapy of nonhospitalized AIDS patients, which was associated with the emergence of *Candida* species strains resistant to the drug. As early as 1991, a report of a significant association of fluconazole prophylaxis and *C. krusei* opportunistic infections was documented among patients in the Johns Hopkins University's Hospital BMTU *(28)*. These *C. krusei* isolates demonstrated innate resistance to fluconazole. In a follow-up study from this institution, the administration of early empiric amphotericin B plus flucytosine therapy to febrile neutropenic BMTU patients colonized with *C. krusei* was associated with a reduction in the proportion of *C. krusei* fungemias in patients receiving fluconazole *(120)*. However, in the same study, a higher proportion of fungemias attributable to fluconazole-resistant *C. glabrata* was noted among patients receiving fluconazole. Since these preliminary studies, several epidemiologic reports have shown that the widespread use of fluconazole-suppressive therapy for patients at high risk for disseminated *Candida* species infections in these and other hospital critical care units has presaged the emergence of infections caused by less pathogenic but innately resistant *Candida* species (*121*,122,123).

HEALTHCARE-ASSOCIATED *CANDIDA* SPECIES INFECTIONS IN SPECIAL PATIENT POPULATIONS

Neonatal Candidiasis

Prenatally acquired *Candida* species infection resulting in congenital cutaneous candidiasis in premature neonates has been discussed (see above), and the condition must be distinguished from neonatal invasive candidiasis.

Colonization with *Candida* species in hospitalized neonates is thought to result most commonly from acquisition of microorganisms that are part of the maternal vaginal flora. The infant's gastrointestinal tract then becomes the predominant site of colonization with these fungal microorganisms. Alternatively, hospital personnel may be colonized with *Candida* species on their hands; transmission of these yeasts from personnel to infant and from infant to infant via the hands of NICU personnel may be important. In a prospective study of *Candida* species colonization of hospitalized infants, Reef et al. *(124)*, using molecular typing techniques, found evidence that acquisition of *Candida* species was healthcare-associated rather than maternally derived. Another unusual mode of acquisition of *Candida* species was demonstrated in an NICU outbreak of *C. parapsilosis* fungemias that was traced to probable extrinsic contamination of a multiuse bottle of liquid glycerin *(12)*.

Neonatal invasive candidiasis is predominantly a disease of low birth weight infants, in particular, very low birth weight infants. Because of modern advances in medical technology since the 1960s, NICUs have proliferated and have contributed to the prolonged survival of more critically ill infants. *C. albicans* is the most frequently identified fungal species to cause disseminated disease in neonates; however, potentially fatal infection may also be due to *C. tropicalis* and *C. parapsilosis*, and rarely *C. glabrata*, *C. guillermondii*, and *C. lusitaniae*. In a review of 111 cases of candidemia in their NICU during 1981 to 1995, Kossoff et al. *(125)* noted a more than 11-fold increase; a shift in the prevalent *Candida* species from *C. albicans* to *C. parapsilosis*, and a significantly higher mortality associated with *C. albicans* than with *C. parapsilosis*.

Both prior colonization with *Candida* species and these infants' degree of underlying immunologic immaturity are important in the subsequent development of fungal infection. Oral thrush and perineal rash are the most frequent clinical presentations of *Candida* species involvement in this population. Invasive disease, which is usually fungemia, occurs in approximately 1% to 3% of NICU infants. Risk factors identified as important for the development of fungemia in this population include intravascular catheters, total parenteral nutrition, prior receipt of antimicrobial agents, necrotizing enterocolitis and surgery specific for this condition, and medications such as steroids and aminophylline *(126)*. Recently, pulmonary hemorrhage and intrauterine growth restriction were identified as independent risk factors for fungemia in neonates *(127)*.

Invasive candidiasis in infants usually has a nonspecific clinical presentation *(128)*. Signs of respiratory deterioration and apnea predominate (70%); however, other manifestations include temperature instability, irritability, lethargy, carbohydrate intolerance, abdominal distention, and rash. Despite the tendency for blood cultures in these infants to be only intermittently positive, the rate of positivity may be higher than that seen for adults; in critically ill neonates, the incidence of catheter-related BSIs can be as high as 18 cases per 1,000 catheter days *(129)*. In addition, the clinical and laboratory definitions of catheter-related infection established for adults may not be easily applied to children. Difficulty obtaining blood samples in infants and young children may mean there are only results from blood samples obtained via the catheter available to guide patient management (130). As with adults, antifungal therapy should be initiated when yeast is isolated from a blood culture or when suspicion of fungemia is high (130). The selection of an appropriate antifungal agent depends on the microorganism that is isolated and the drug characteristics, including pediatric dosing information, toxicities, route of administration, and formulations (130). Meningitis in neonates is a well-recognized complication of *Candida* species sepsis, with an incidence ranging from 27% to 59% *(127)*. Therefore, a critical requirement for all fungemic infants is the performance of a CSF tap to examine CSF; these cultures may be positive without positive blood cultures *(128)*.

Evidence of *Candida* species meningitis requires early institution of antifungal therapy and may affect both the choice and duration of antifungal therapy and the infant's prognosis and follow-up. In addition, positive urine cultures may be found in 50% of infants with disseminated candidiasis and may be the initial indicator of disseminated infection *(127)*. However, in infants, the presence of yeast skin contamination may invalidate a urine specimen collected in a bag as a diagnostic tool for *Candida* species urinary tract infection, and suprapubic aspiration may be needed. When such an aspirate is culture positive

for *Candida* species, antifungal therapy may be indicated *(128)*. The importance of a screening ophthalmologic examination for infants with suspected *Candida* species fungemia is underscored by the finding that endophthalmitis occurs in as many as 50% of these infants *(131)*. In infected infants, the classic ophthalmologic lesion is described as a yellow-white, fluffy patch of retinitis with indistinct margins that may develop more gradually than lesions caused by bacterial sepsis. Resolution of the infection usually follows the introduction of systemic amphotericin B therapy; however, prolonged therapy is needed to prevent recurrences *(131)*.

The hematologic profile in infants with invasive candidiasis may also be nonspecific. Thrombocytopenia ($\leq$100,000/mm^3) may occur in up to 70% of infants with fungemia *(128)*, and the leukocyte count may be variable. Abnormal liver function test results may suggest hepatic involvement in infected infants *(128)*.

Reports of healthcare-associated outbreaks of *Candida* species infections have identified various sources for these infections in infants. In an investigation of a cluster of *C. albicans* fungemias involving seven preterm infants in a Canadian NICU, Vaudry et al. *(132)* failed to identify any significant risk factors for these infections in a case–control study, and further laboratory evaluation of the case-patient isolates using DNA restriction enzyme digests identified two different strains. A small outbreak of fungemias caused by *C. parapsilosis* in an Albany, New York, hospital was traced to defective filters for hyperalimentation fluids, and outbreak strains showed a single electrophoretic karyotype *(133)*. A pseudo-outbreak caused by *C. guillermondii* resulted from flushing needles with a contaminated heparin solution *(20)*. Contaminated retrograde intravenous medication was found to be the cause of an outbreak of *Candida* species fungemia involving five infants in an NICU, and molecular typing revealed identical *C. albicans* strains from patients and medication syringe fluid *(109)*. A report by Fowler et al. *(134)* of an outbreak of *C. lusitaniae* infections used molecular subtyping methods to establish that person-to-person transmission of the yeast had occurred among neonates in their NICU. Roilides et al. *(135)* reported a 4-year trend with increased isolation of non–*C. albicans* species as causes of fungemia in the absence of routine use of antifungal drug prophylaxis in their NICU. When these investigators studied a cluster of *C. tropicalis* colonization and fungemia cases using molecular subtyping methods, they concluded that cross-colonization was the likely mechanism for transmission possibly via transient hand colonization of personnel.

Postsurgical Infections

Patients demonstrating a variety of postsurgical invasive infections caused by *Candida* species have been described by several investigators. In most reported patients, these infections have been associated with surgical procedures involving all levels of the gastrointestinal tract *(136)*. However, there have also been reports of unusual outbreaks of postsurgical *Candida* species endophthalmitis and candidemia traced to intrinsically contaminated ophthalmologic irrigating solution and extrinsic contamination of an intravenous anesthetic agent without preservative (Table 40-1). Localized infections caused by *Candida* species in postsurgical patients have included sternal surgical site infections, abdominal abscesses, peritonitis, anastomotic breakdown, and intestinal necrosis; however, candidemia and disseminated candidiasis may also occur. Cultures of blood and deep incisional or organ/space surgical sites may be positive for *Candida* species in infected postsurgical patients. However, postoperative patients tend to be a heterogeneous population that is often critically ill with underlying medical conditions, which often makes it difficult to ascribe a specific role to the surgical procedure in the development of invasive candidiasis. Important underlying conditions in these patients may include malignancies and gastrointestinal, cardiac, and renal system disease; such patients may also have multiple exposures to risk factors for candidemia and invasive *Candida* species infections (e.g., vascular catheters, hemodialysis, total parenteral nutrition, and broad-spectrum antimicrobial agents and corticosteroids). *Candida* species has been isolated from CSF in patients following neurosurgery, most commonly in association with shunts. Pancreatic surgery may also be associated with an apparent increased likelihood of *Candida* infection. Hospitalized patients with burn wounds demonstrate frequent wound colonization with *Candida* species and are at particularly high risk for candidemia and potentially fatal disseminated candidiasis.

ANTIFUNGAL SUSCEPTIBILITY

Compared with other fungi, treatment of candidiasis can be better guided by *in vitro* susceptibility testing. Because the susceptibility of *Candida*, in general, is predictable based on species identification, it is currently not recommended to routinely test all *Candida* isolates for susceptibility (137). The 2004 Infectious Diseases Society of America (IDSA) guidelines recommend that susceptibility testing is most helpful in management of deep infection due to non–*C. albicans* species of *Candida* (137). In this setting, especially if the patient has been treated previously with an azole antifungal agent, the possibility of microbiological resistance must be considered. The 2009 IDSA guidelines recommend laboratories perform routine testing against fluconazole for *C. glabrata* isolates from blood and sterile sites and for other *Candida* species that have failed to respond to antifungal therapy or in which azole resistance is strongly suspected (38).

Although standards have been established by the Clinical and Laboratory Standards (formerly the National Committee for Clinical Laboratory Standards) for *Candida* species, interpretive breakpoints exist only for fluconazole, itraconazole, and voriconazole *(138,139)*. Furthermore, evidence supporting the association with MIC and clinical outcome of invasive candidal disease is limited (e.g., fluconazole breakpoints were based predominantly on mucosal candidiasis data). One further limitation of antifungal susceptibility testing for *Candida* is the variability in interpretation of results (e.g., misinterpretation of trailing growth at high drug concentrations) *(140)*.

Based on *in vitro* susceptibility testing performed on bloodstream isolates from around the world, *C. albicans*, *C. tropicalis*, and *C. parapsilosis* are considered to be susceptible to existing antifungal agents *(99,141)*. *C. glabrata* has

emerged as an important problem, sometimes even more commonly isolated than *C. albicans* in some institutions. Although it may be susceptible to fluconazole, this species can easily develop acquired resistance, particularly in patients who have received prior fluconazole prophylaxis or treatment *(71,142)*. *C. krusei* is intrinsically resistant to fluconazole and often demonstrates susceptibility to amphotericin B and flucytosine, although it remains susceptible to caspofungin, voriconazole, posaconazole, and ravuconazole *(143)*. In the severely immunocompromised patient population where fluconazole prophylaxis or therapy has been instituted, *C. krusei* has been problematic *(28)*. Some strains of *C. lusitaniae* can be resistant to polyene agents (amphotericin B, and nystatin) although they remain susceptible to triazoles (fluconazole, itraconazole, voriconazole, posaconazole, and ravuconazole) *(141,144)*. *Candida rugosa* has demonstrated decreased susceptibility to amphotericin B, nystatin, and fluconazole *(143)*. This property, as well as its propensity to colonize skin, may help explain this species emergence to cause difficult-to-control outbreaks of infection in hospitals *(145,146)*.

Results of antifungal susceptibility tests of *C. parapsilosis* clinical isolates (given the limitations of current methods) have generally shown them to be susceptible to amphotericin B, and this has been the most frequently used antifungal. Fluconazole is the most frequently administered alternative therapy to amphotericin B although clinical resistance in *C. parapsilosis* has rarely been reported. In addition, fluconazole has been widely used for targeted prophylaxis in infants who are either <1,000 g or ≤27 weeks. *In vitro* resistance to voriconazole is rare; however, resistance to the drug has developed among clinical strains previously exposed to fluconazole, and outbreak strains with reduced susceptibilities to both fluconazole and voriconazole have been identified *(13)*. The MIC levels for the echinocandins are significantly higher for *C. parapsilosis* than those for the other *Candida* species, and there have been reports of both echinocandidin treatment failures and "break through" infections with *C. parapsilosis* in individuals receiving echinocandins for other indications. In addition, a recent report has suggested an association between increasing caspofungin use and an increased incidence of *C. parapsilosis* candidemia *(16)*. Thus, echinocandins should be used with caution in invasive *C. parapsilosis* infection.

TREATMENT

In high-risk patients and patients in whom the diagnosis of invasive candidiasis is suspected or confirmed, the administration of antifungal drugs may be for prophylactic, empiric, preemptive, or specific therapy. A more aggressive approach to the management of candidal infections with antifungal agents has become the standard because of the potentially high mortality and morbidity associated with these infections and the wide availability of azole anticandidal agents as well as the echinocandins, which are less toxic than amphotericin B.

Echinocandins are the newest class of antifungals. They have a unique mechanism of action, and exhibit activity against a broad range of *Candida* species and strains, including those resistant to the azoles and polyenes. Few studies have directly compared the three approved echinocandins (caspofungin, micafungin, and anidulafungin) for efficacy, but the existing data have not suggested major differences to date. All the echinocandins possess excellent tolerability and safety, and although there are some pharmacokinetic differences, they are relatively minor and generally do not influence drug selection. Consequently, echinocandins are now considered to be the first-line treatment of invasive candidiasis in critically ill patients.

The choice of initial antifungal therapy in a patient who has proven or suspected invasive candidiasis is dependent upon several important considerations *(147)*. What is the patient's recent history of azole exposure? What are the susceptibility patterns of *Candida* spp. in this particular healthcare setting? What are the predominant *Candida* spp. in this particular unit/location and in this particular situation? What are the patient's comorbidities and underlying disorders? How acutely ill is this patient? Is there clinical evidence to suggest involvement of the CNS, cardiac valves, liver, spleen, or kidneys? Is there a patient history of intolerance to an antifungal agent? Each of these questions must be addressed specifically to make an informed choice relative to the most suitable antifungal agent.

The 2009 IDSA treatment guidelines for invasive candidiasis have clarified the indications and use of echinocandins, higher dosing of fluconazole, and lipid formulations of amphotericin B, each of which provides a safer alternative to conventional amphotericin B therapy with its associated toxicities (38). These guidelines identify echinocandins (caspofungin, micafungin, or anidulafungin) as a first-line therapy option for patients with moderately severe to severe nonneutropenic or neutropenic invasive candidiasis. The guidelines identify fluconazole as another first-line treatment option for patients with mild-to-moderate disease (i.e., hemodynamically stable patients) and no prior azole exposure, but state that echinocandins are the preferred choice for patients at elevated risk for infection with a fluconazole-resistant pathogen due to prior azole therapy. An echinocandin is also favored in nonneutropenic or neutropenic patients if the isolate is identified as *C. glabrata* or *C. krusei* (which exhibit increased resistance to triazoles).

The 2009 IDSA guidelines also provide recommendations for the treatment of *Candida* infection of the cardiovascular system, CNS, urinary tract, or vulvovaginal region, as well as candida osteoarticular infection, candida endophthalmitis, nongenital mucocutaneous candidiasis, neonatal candidiasis, and chronic disseminated candidiasis (38). There are some important changes in the most recent guidelines from earlier 2000 and 2004 IDSA guidelines. The most recent guidelines identify voriconazole as a suitable alternative treatment option for nonneutropenic or neutropenic patients with candidemia. In addition, traditional amphotericin B is no longer recommended as first-line therapy for nonneutropenic or neutropenic patients with established candidemia, although lipid formulations of amphotericin B are recommended as first-line treatment for nonneutropenic and as treatment for neutropenic patients. These changes are due to the increased incidence and severity of nephrotoxicity associated with

traditional versus lipid formulations of amphotericin B and the associated cost of this adverse side effect. The 2009 IDSA guidelines recommend either traditional or lipid formulations of amphotericin B as first-line empiric treatment for neutropenic patients or as alternative empiric treatment for nonneutropenic patients with suspected candidiasis (38). Major changes from earlier versions of the guidelines include the introduction of all three echinocandins as first-line or primary treatment options for nonneutropenic or neutropenic patients with candidemia or nonneutropenic patients with suspected candidiasis and the recommendation of voriconazole (as well as caspofungin or lipid formulations of amphotericin B) as a first-line empiric treatment option for neutropenic patients with suspected candidiasis.

The 2009 IDSA guidelines generally do not make any distinction among the available echinocandins (caspofungin, micafungin, or anidulafungin) (38). However, caspofungin was the first member of the class approved for use in the United States and has the largest database, as well as the greatest number of approved indications. Caspofungin is the only echinocandin with an indication for use as empiric treatment of presumed fungal infections in febrile, neutropenic patients and pediatric patients. Similarly, micafungin is the only echinocandin currently approved for the prevention of invasive candidiasis in patients undergoing hematopoietic stem cell transplantation. The efficacy of all three echinocandin agents for treatment of candidemia has been demonstrated in clinical trials including caspofungin was found to be noninferior to amphotericin B deoxycholate for treatment of nonneutropenic and neutropenic patients with invasive candidiasis *(148)*, anidulafungin was found to be noninferior to fluconazole for treatment of candidemia *(149)*, and micafungin was shown to be noninferior to both liposomal amphotericin B and caspofungin) in two separate studies *(150,151)*.

The 2009 IDSA guidelines recommend removal of CVC when candidemia is documented, if at all possible (38). The data to support this are strongest among nonneutropenic patients and show that catheter removal is associated with shorter duration of candidemia *(152)* and reduced mortality in adults *(152,154)* and neonates *(155)*. The management of intravascular catheters in neutropenic patients is more complicated than in nonneutropenic patients, the data for catheter removal is less compelling, and significant access problems may be a consequence of catheter removal (38). Intravascular catheter removal is strongly recommended in neonatal candidiasis, and there is evidence that delayed removal or replacement of a CVC for infants with candidemia places them at increased risk of prolonged infection, mortality, and long-term irreversible neurodevelopmental impairment *(155,156)*. The guidelines provide recommended candidemia treatment performance measures that include the need to perform ophthalmological examinations in all patients with candidemia to exclude *Candida* endophthalmitis (in neutropenic patients, this should be performed after recovery of the neutrophil count), the need to start antifungal therapy on all candidemia patients within 24 hours after the blood culture is positive for yeast, and the requirement that follow-up blood cultures be obtained for all patients with candidemia to ensure clearance of *Candida* from the bloodstream (38).

PREVENTION AND CONTROL

Effective control and prevention strategies for healthcare-associated *Candida* species infections must use available epidemiologic information, be targeted at patients who are at highest risk for these infections, and aim at interrupting or preventing transmission of infection. Strategies for control and prevention of *Candida* HAI differ importantly from guidelines for the control and prevention of healthcare-associated mold infections.

Proper implementation and strict adherence to established infection control guidelines remain the best means to prevent healthcare-associated candidiasis. Specific measures to prevent intravascular fungal infections include strict aseptic technique in the insertion and maintenance of intravenous lines. All the established risk factors for developing healthcare-associated bacterial BSIs also apply to candidemia, and established prevention guidelines for the prevention of BSI should be applied routinely to prevent candidemia (see also Chapter 19). CDC's HICPAC has no specific guidelines for the prevention of candidemia in general hospitalized patients apart from the approaches outlined in the "Guidelines for Prevention of Intravascular Catheter-Related Infections" (157). Regardless, there are several factors that can be considered if a healthcare setting detects a persistent problem with *Candida* BSIs or other forms of healthcare-associated candidiasis.

Reducing gastrointestinal colonization. Colonization with *Candida* is the overriding risk factor associated with developing healthcare-associated candidiasis. Removing the endogenous reservoir should reduce a patient's risk for subsequent disease substantially. Oral nonabsorbable antifungal drugs, including oral amphoterin B suspension, nystatin, and clotrimazole troches, might reduce superficial colonization and control local mucosal candidiasis, but have not been shown to reduce invasive candidiasisis (158). Utilizing systemic antifungals before there is any evidence of active disease (prophylaxis) is one well-studied method to accomplish this. Mounting evidence on the efficacy of preventing candidemia in the subset of patients at highest risk for invasive disease has resulted in specific recommendations by HICPAC and IDSA and an expert panel for the HSCT population (158,159) and the neutropenic population (160). Because candidiasis usually occurs in the period after transplantation but before engraftment, fluconazole, the drug of choice, should be started on the day of HSCT and continued until at least engraftment (158,159). The appropriate duration of prophylaxis is not known, but at least one study has shown there is a survival benefit when prophylaxis is extended for at least 75 days *(161,162)*. Because autologous recipients generally have a lower risk for invasive fungal infection than allogeneic recipients, only autologous recipients with particular conditions (underlying hematologic malignancies, prolonged neutropenia, and mucosal damage from manipulation, or recent treatment with fludarabine or 2-CDA) should receive antifungal prophylaxis (158,159).

Solid organ transplant recipients, especially patients undergoing orthotopic liver transplantation, have also been identified to be at high risk for invasive candidiasis (38,137,*163–165*). Various antifungal therapies, including amphotericin B deoxycholate, itraconazole, liposomal

amphotericin B, and fluconazole, have been studied as prophylactic regimens post transplantation (160). At this time, IDSA recommends that high-risk liver (with at least two risk factors for invasive fungal disease), pancreas, and small-bowel transplant patients receive antifungal prophylaxis in the early postoperative period (38). Prophylaxis in patients receiving liver transplants who are considered low risk as well as patients receiving kidney or heart transplantations is not currently recommended (38).

Prophylaxis may be warranted in ICUs with very high incidence rates of invasive candidiasis compared with normal rates of 1% to 2% *(166)* where aggressive infection control procedures are failing to reduce rates (38,137,*167,168*). Selected ICU patients who are at highest risk (incidence >10%) may also benefit from antifungal prophylaxis *(169)*. However, studies to date have not shown a survival benefit associated with this strategy *(170,171)*. The use of prophylaxis in ICUs with only low risks of candidiasis may be inappropriate due to the increased risk of adverse drug events as well as selection of resistant microorganisms *(172)*. For example, it is possible that the proportion of infections with *Candida* species exhibiting reduced susceptibility to fluconazole, such as *C. glabrata* and *C. krusei*, may increase as a consequence of the introduction of fluconazole prophylaxis *(173–175)*.

A patient population in which the role of antifungal prophylaxis is under increasing study is the neonatal population, specifically extremely low birth weight infants (<1,000 g). Although several studies have documented decreased rates of infection with antifungal prophylaxis *(156,176–178)*, there are many unanswered questions with regard to which variables are most apt for selection of patients requiring prophylactic treatment and there is no consensus among practitioners on the specific subset of patients in which this approach should be used *(71,179)*. IDSA currently recommends routine fluconazole prophylaxis for premature infants and infants with extremely low birth weights in nurseries that have a high incidence of invasive candidiasis (38). Fewer studies have evaluated this approach in surgical ICU patients. A recent meta-analysis evaluating these studies determined overall there was no survival benefit among treated patients compared with untreated patients *(174)*.

Preventing cross-transmission. Currently, Standard Precautions should be utilized for all patients with candidemia (157). Although transmission via healthcare workers' hands may be the pathway for some acquisition of *Candida*, most candidemia is thought to be derived from the patient's own flora, so enhanced precautions to prevent person-to-person spread are not justified. If local authorities identify a microorganism of epidemiologic concern (e.g., a particular *Candida* species of high virulence or resistance), Contact Precautions may be justified. However, outbreaks of candidemia that have involved cross-transmission have been associated with substandard hand hygiene and have been interrupted by improved compliance with Standard Precautions *(13)*. Efforts to improve hand hygiene, such as those described in HICPAC guidelines for hand hygiene (180), are therefore relevant to prevention and control of candidemia. Use of waterless antiseptic agents (alcohol-based solutions) has gained acceptance. Importantly, studies have shown that alcohol-based hand washes are effective against *Candida* species *(71,181)*, but efficacy may vary based on the concentration of alcohol in the products, the amount of contact time, and the burden of yeast present *(182,183)*. Other hand-hygiene antiseptic agents such as chlorhexidine (2% and 4% aqueous), iodine compounds, iodophors, and phenol derivatives also have some activity against fungi (180).

Antifungal prophylactic strategies using the oral azole drugs have been extensively studied, in high-risk granulocytopenic or HSCT patients, and fluconazole has been shown to be effective not only for the prevention of superficial and/or invasive candidal infections (see below), but also for prolonging overall patient survival *(147)*; however, this therapy may also select for less susceptible or resistant *Candida* species. The usefulness of newer antifungal agents and classes has also been evaluated. Micafungin is an alternative prophylactic agent, shown in one study to be comparable with fluconazole for preventing possible or documented fungal infection *(184)*; however, its use is limited by the necessity for intravenous infusion and cost (158). The optimum duration of prophylaxis is unknown but should, at a minimum, include the period of risk of neutropenia (38).

The experimental prophylactic therapies such as the cytokines, including granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), may lessen the extent and duration of the patient's chemotherapy-induced immunosuppression (granulocytopenia). However, a meta-analysis showed that the use of growth factors did not reduce the attack rate of invasive fungal disease *(185)*, and, therefore, these are not recommended for prophylaxis against invasive fungal disease (158). Further, a recent trial showed that early G-CSF corrects neutropenia but does not reduce sepsis in extremely preterm infants *(186)*. Cytokine administration to patients, together with antifungal agents, as well as transfusion of cytokine-upgraded phagocytes, are promising immunotherapeutic modalities for further research.

Routine surveillance cultures have also been suggested to aid in determining which high-risk patients will develop invasive candidiasis. Sandford et al. *(187)* assessed the usefulness of surveillance colonization cultures for predicting the development of systemic fungal infection in patients with prolonged granulocytopenia. These researchers found that, despite the frequent occurrence of stool colonization with *Candida* species (80% of study patients), this finding was not a reliable predictor for the development of invasive candidiasis in these patients. The data also suggested that any benefit conferred by surveillance cultures applied only to *C. tropicalis*–infected patients and not to *C. albicans*–infected patients. Colonization in particular high-density colonization is the most universally accepted predictive variable with regard to invasive candidiasis. However, it remains to be clarified whether colonization can be used in isolation to identify high-risk patients or if it should be combined with other variables indicating high risk and if determination of multisite colonization is required or whether detecting colonization at one or two specific sites (e.g., candiduria) is sufficient for identification of high-risk patients *(179)*. Definitive evidence of a correlation between candiduria and invasive candidiasis is currently still lacking as the few

published studies thus far have yielded conflicting results. Nevertheless, candiduria may be reliably considered as a surrogate marker for high density of colonization, thereby representing a more practical, and less resource-intensive screening marker than is currently possible using parameters such as the multiple site-colonization index *(179)*. Future studies are needed to better elucidate the role of these cultures and validate risk predictive models using a combination of clinical risk factors and *Candida* colonization parameters (188). There is no evidence to support routine use of surveillance cultures for asymptomatic HSCT recipients in the prevention of candididemia outside of an outbreak setting *(189,190)*.

MOLECULAR TYPING OF *CANDIDA* SPP.

Molecular epidemiology has proven useful for implicating the gastrointestinal tract as the most important endogenous reservoir for candidal infections *(110,191–194)*, documenting transmission via hands of healthcare workers *(13,195–198)* and for confirming the source (e.g., contaminated infusates, biomedical devices) during outbreak investigations *(15,29,193,199,200)*. In addition, molecular typing methods have documented that strains of *Candida* surviving on environmental surfaces within the hospital can also be acquired by patients in the hospital *(111,201)*.

Molecular typing methods are rapidly evolving. A variety of methods have been described in detail elsewhere *(201,202)*. Techniques used in the past include those based on restriction fragment length polymorphism with Southern blot hybridization, electrophoretic karyotyping, multilocus enzyme electrophoresis, and PCR-based techniques (random amplified polymorphic DNA). Newer techniques such as (MLST) has performed at least comparably to other established DNA fingerprinting techniques for *C. albicans (203–205)*. It is emerging as a powerful tool for subtyping *C. albicans* since it has a high degree of resolution, can characterize large numbers of isolates rapidly, and does not require subjective interpretation of banding patterns *(203–205)*. MLST is also available for *C. glabrata* and *C. tropicalis*. Other methods, including use of microarrays, which offer the hope of reproducible, high-throughput typing, are under development.

CONCLUSION

Healthcare-associated *Candida* species infections continue to present clinicians with considerable diagnostic and therapeutic challenges. The epidemiology of invasive candidiasis is complex and, although incompletely elucidated, is characterized by considerable regional and temporal variability. Of particular concern is an overall increase in incidence and an increase in the proportion of *C. glabrata*, infections, which is associated with reduced susceptibility to azole antifungal agents. The management of invasive candidiasis has been aided by the availability of several new effective antifungal agents. However, although the poor clinical outcomes associated with invasive candidiasis are, in part, related to the severity of underlying host factors, optimization of treatment-related factors is also important. In particular, the most difficult challenge is early initiation of effective antifungal therapy, given the lack of sensitivity and delay inherent in conventional culture-based diagnostic techniques. New non–culture-based rapid and specific diagnostic tests for invasive fungal infections in severely immunocompromised patients and validated clinical risk-predictive models are required to better target prophylactic, preemptive, and empirical antifungal strategies. In addition, the successful application of molecular typing methods in outbreak investigations has improved documentation of modes of transmission of healthcare-associated *Candida* species pathogens, and, together with new diagnostic and therapeutic advances, they may aid considerably in the development of effective prevention strategies for these important infections.

AUTHORS' NOTE

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC. Mention of a product or company name does not constitute endorsement by CDC.

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CHAPTER 41

Filamentous Fungi

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Healthcare-associated infection by filamentous fungi was a minor issue for infection control until the frequency of these diseases began to increase in the 1970s (1,2,*3*). This increased incidence is attributed to a larger immunocompromised population in relation to advances in invasive medical technology and highly immunosuppressive therapies (1,*3*). These infections have very high mortality rates and are also associated with significant morbidity in the hospital in relation to therapy and diagnostic procedures. The increased incidence, high mortality, and recent advances in diagnosis and therapy have made these infections a more attractive and "surveillance-worthy" target for infection control programs. Important observations have been made regarding the incidence of these diseases and the presence of their causative agents in the hospital environment. This chapter focuses on the cause, epidemiology, and prevention of these infections while addressing infection control considerations.

CAUSE AND FORMS OF DISEASE

Although there are many reports of virtually any fungal species causing some form of healthcare-associated disease in humans, the most often encountered diseases caused by filamentous fungi are invasive aspergillosis and mucormycosis (1,*4*,5). There are also numerous reports of agents of hyalohyphomycosis such as *Acremonium* spp. and *Fusarium* spp. (1,*6*,7,*8*,*9*), but these are usually associated with an outbreak related to the use of contaminated patient-care materials or in the case of *Fusarium* with environmental sources and dissemination from sites of onychomycosis (10). Their frequency is much lower than *Aspergillus* and the Zygomycetes; thus, this chapter concentrates on the latter.

Aspergillus spp. are the most often encountered filamentous fungi in clinical practice, causing invasive, allergic, and toxic diseases. They are ubiquitous filamentous fungi found in soil, plant debris, and air. There are over 180 described species, although only 20 or so have been reported to be pathogenic for humans (1,2). Table 41-1 summarizes the *Aspergillus* spp. that are most commonly isolated from clinical specimens. Invasive disease can be found in almost any organ, but the most commonly affected are lungs, brain, paranasal sinuses, heart, and bones. *Aspergillus* fungemia is very rare, even in the setting of disseminated disease. It occurs in <10% of cases *(11)*. Aspergillosis can also be related to medical devices such as intravenous or peritoneal catheters and prosthetic materials (*12*–*14*,15). Invasive aspergillosis occurs almost exclusively in patients with a high degree of immunosuppression, such as that seen in leukemia and in bone marrow and solid organ transplantation. However, there are recent reports of invasive pulmonary aspergillosis in otherwise immunocompetent hosts and in patients with chronic obstructive pulmonary disease. Its incidence has been on a steady rise, as evidenced by epidemiologic and postmortem studies. Mortality is very high, reaching nearly 90% in some series of disseminated disease or in deeply immunocompromised patients, and therapy often requires intensive medical treatment with amphotericin B (or its lipid formulations), caspofungin, or voriconazole, alone or in combination, in addition to aggressive surgical debridement when appropriate (2).

Fusarium species are becoming exceedingly important in medical practice, particularly for centers that care for cancer and transplant patients. This agent is usually regarded as an agent of onychomycosis and has been implicated in an extensive outbreak of fungal keratitis related to contaminated ophthalmologic solutions; however, it can cause invasive and disseminated disease, particularly in immunocompromised patients (16). While this mold can produce invasive lung involvement, the typical presentation will be that of disseminated disease characterized by fever and disseminated skin lesions of violaceous appearance. As opposed to disseminated aspergillosis, disseminated fusariosis is one of the few mold infections that can have positive blood cultures. Healthcare-associated infection and transmission are rare, but as with other mold pathogens, environmental contamination has been implicated. Mortality is extremely high, despite antifungal therapy.

The terms *mucormycosis* or *zygomycosis* comprise a class of filamentous fungi that cause highly invasive disease in humans. The terms can be used interchangeably. The class Zygomycetes includes three orders: Mucorales, Entomophthorales, and Mortierellales. The most often encountered clinical pathogens fall in the order Mucorales, and their species are shown in Table 41-1. They are all ubiquitous fungi found in soil and decaying fruits, vegetables,

TABLE 41-1

Aspergillus spp. and Zygomycetes as Causes of Healthcare-Associated Infection

Aspergillus spp.	*Zygomycetes*
Common	**Mucorales**
Aspergillus fumigatus	*Absidia* spp.
Aspergillus flavus	*Apophysomyces* spp.
Aspergillus terreus	*Cokeromyces* spp.
Aspergillus niger	*Cunninghamella* spp.
Aspergillus nidulans	*Mucor* spp.
Rare	*Rhizomucor* spp.
Aspergillus oryzae	*Rhizopus* spp.
Aspergillus ustus	*Saksenaea* spp.
Aspergillus avenaceous	*Syncephalastrum* spp.
Aspergillus candidus	**Entomophthorales**
Aspergillus carneus	*Basidiobolus* spp.
Aspergillus caesiellus	*Conidiobolus* spp.
Aspergillus clavatus	**Mortiellerales**
Aspergillus quadrilineatus	*Mortierella* spp.
Aspergillus restrictus	
Aspergillus sydowi	
Aspergillus versicolor	

TABLE 41-2

Risk Factors for Invasive Aspergillosis and Zygomycoses

Risk Factor	*Aspergillosis*	*Zygomycoses*
Prolonged neutropenia	X	X
Cytotoxic chemotherapy	X	X
Bone marrow transplantation	X	X
Solid organ transplantation	X	X
Congenital or acquired immunodeficiency	X	X
Hematologic malignancy	X	X
Renal failure	X	X
Diabetes (ketoacidosis)		X
Chronic obstructive pulmonary disease	X	
Steroids and tumor necrosis factor blockers	X	X
Iron overload and chelators		X
Trauma	X	X

and food. These microorganisms affect immunocompromised patients, such as those with diabetic ketoacidosis, iron overload, malnourishment, leukemia, bone marrow transplant, solid organ transplant, and burns. They are also seen in patients with acquired immunodeficiency syndrome and patients receiving immunosuppressive therapies such as corticosteroids or tumor necrosis factor blockers (1,*4*,5). Although they can affect almost any organ or body system, the most common forms of invasive disease are rhinocerebral, pulmonary, cutaneous, and gastrointestinal. They have also been associated with medical devices such as intravascular and peritoneal catheters. Mortality is very high and prognosis is poor, even in the face of aggressive treatment.

FILAMENTOUS FUNGI IN HEALTHCARE: ECOLOGY AND EPIDEMIOLOGY

The body of information on healthcare-associated reservoirs, transmission, and infection by filamentous fungi is constantly growing. Although the early years of studying this problem were characterized by debate, today there is little question that these microorganisms are present and can be transmitted in the hospital. Healthcare-associated acquisition of infection by filamentous fungi is extremely important for centers that have a large immunocompromised population, such as cancer or transplant centers, and great efforts and advances have been undertaken to control them.

Acquisition of these diseases is a function of a susceptible host and the presence of a pathogenic microorganism in the environment. Table 41-2 summarizes host risk factors for invasive aspergillosis and zygomycosis. As seen in the table, varying degrees of immunosuppression and underlying illness are required for the host to be susceptible.

As for the presence of the microorganisms in the hospital environment, it is now known that the main source for them is environmental contamination, which can include various surfaces, air, and water (1,*4*,5,*12*,15,*17*,*18*,19,20). Disturbances in the hospital environment, such as construction, can cause wide dissemination of the microorganisms and even outbreaks. Much of the evidence linking aspergillosis to the healthcare-associated environment comes from outbreak investigations (7,*21–25*).

Patterson et al. (26) defined healthcare-associated aspergillosis as that occurring more than 1 week after admission or <2 weeks after discharge. Setting those temporal limits allows for community-acquired cases to be excluded from any analysis. Most cases are pneumonias; thus, the most likely route of infection is by direct inhalation of spores by a susceptible host. Although the primary source of *Aspergillus* spp. spores is soil and decaying vegetation, its main form of healthcare-associated spread is through hospital air (*12*,15,*18*,19,20,*27*). The spore concentration in outdoor air ranges from 0.2 to 15.0 spores/m^3, and the density of spores in hospital air is a direct function of the level of filtration that is used in a particular unit (1,*3*,*14*,20,*21*,*28*). High-efficiency particulate air (HEPA) filtration and laminar airflow (LAF) are highly effective methods to reduce spore content in hospital air (*3*,19,*28*), but the quality of output air is a function of the quality of the input air and the filtration system cannot effectively control spores generated within the hospital environment. Assessment of hospital air for fungal contaminations is often done using two methods: particle counts and air cultures. Particle counts are very sensitive for *Aspergillus* spores (2–5 μm diameter), but not very specific. Air culture using fungal culture media at 35°C is very useful for identifying real pathogens, but it is more expensive and time-consuming and results are not available for several weeks. Thus, one often uses particle counts initially and reserves air cultures for special situations. The relationship between hospital air spore burden and development of aspergillosis

is controversial. However, most of the research indicates that there may be a direct relationship between spore density and disease. Although no firm threshold value has been established, spore concentrations >1/m^3 are thought to be associated with an increased incidence of disease in susceptible immunocompromised hosts (1,20,*22*,*28*). Extensive molecular epidemiology studies have linked the strains isolated from the patients to those found in the hospital environment (1,*13*,*18*,*21*). Other sources of *Aspergillus* in the hospital may include food, plants, and flowers. A recent source of concern has been hospital water. Anaissie et al. (10,*17*,*29*,*30*,31,*32*) have reported isolation of spores in hospital water and showers identical to those isolated from the patients, both for *Aspergillus* and *Fusarium* spp.

The reservoir and modes of transmission for the Zygomycetes are similar to those of *Aspergillus* (1). Nevertheless, there are numerous reports of infection by direct inoculation from contaminated materials, such as bandages, intravenous or peritoneal catheters, and even tongue depressors. Because outbreaks of zygomycosis from these sources have been reported, such sources should be considered when a cluster of infections resulting from Zygomycetes occurs in a hospital (1,*4*,5,*33*).

PREVENTION: ENVIRONMENTAL AND PHARMACOLOGIC INTERVENTIONS

Preventive strategies work best when the hosts at highest risk are protected with the interventions that have shown the best efficacy and safety. This is as true for healthcare-associated filamentous fungal infections as for any other area of medicine. Interventions that protect against these infections can be classified in two categories: environmental and pharmacologic. Table 41-3 summarizes current preventive strategies for healthcare-associated acquisition of filamentous fungal infections. Environmental measures are safe and generally presumed effective in preventing these types of infections, although their cost can range from very affordable (e.g., plain surgical masks) to highly expensive (e.g., modifications in hospital infrastructure and physical plant). Pharmacologic measures have been extensively studied, and they do not necessarily pertain to the specific prevention of healthcare-associated acquisition of these diseases but to general prophylaxis of fungal infection in susceptible hosts.

As discussed previously, *Aspergillus* is ubiquitous in the environment, but there are certain conditions that may cause it to overgrow or disseminate: humidity and construction. Environmental control measures are designed to avoid these two phenomena and minimize patient exposures to spores. The simpler measures include avoiding, limiting, or containing construction in patient care areas; using plain surgical masks or high-efficiency masks (there are no clear data to support one over the other) when patients are transported through construction areas (34); prohibiting live plants and flowers in patient rooms; disinfecting showers and wet surfaces; and repairing faulty air handlers (31). The more sophisticated and highly effective measures include HEPA air filtration and LAF, which are generally reserved for the rooms or wards housing bone marrow transplant patients or patients undergoing induction chemotherapy. These measures have data to support their use, but their high cost makes them only worthwhile for programs or facilities with a high volume of high-risk patients, such as cancer and transplant centers (*3*,19,*22*).

TABLE 41-3

Preventive Measures in High-Risk Hosts for Healthcare-Associated Infections Caused by Filamentous Fungi

- High-efficiency particulate air filtration
- Laminar airflow rooms
- Limitation or containment of hospital construction
- Use of plain surgical masks or high-efficiency masks when traveling outside protected environments, particularly through construction areas
- Mold remediation for air ducts, carpets, wall panels, showers, etc.
- Antifungal prophylaxis in high-risk hosts
- Control of underlying risk factors
- Limitation of duration of neutropenia with less immunosuppressive regimens

Pharmacologic prophylaxis has also been shown to be effective and safe in selected populations at high risk. Again, these interventions are not specific to healthcare-associated transmission, but they are becoming the standard of care for selected immunocompromised populations, which include induction chemotherapy, patients with prolonged neutropenia *(35)*, organ transplant recipients, hematopoietic stem cell transplant recipients, and patients with hematologic malignancies (36,*37*,38). Current prophylaxis options relevant to filamentous fungi include amphotericin B (intravenous, low dose at 0.1 mg/kg daily or full doses at 0.7–1.0 mg/kg weekly), nebulized amphotericin B and its lipid-based preparations *(39–41),* and the use of new agents such as voriconazole *(42)*, posaconazole *(43)*, and the echinocandins (*44*).

INFECTION CONTROL CONSIDERATIONS

As stated previously, the frequency of these infections is on the rise, and the problem becomes relevant mostly for centers that handle large volumes of immunocompromised patients. These centers should organize active surveillance programs to detect clusters of filamentous fungal infection, which may indicate environmental contamination. Such centers should consider HEPA filtration and LAF units and have construction, environmental sampling and cleaning, and patient transport policies designed to minimize exposure. It is also helpful to have prophylaxis protocols in place for the patients at highest risk.

Environmental sampling is not routinely recommended, but may be indicated during investigations of suspected clusters or outbreaks of infection. There are no standards for indoor quality of air in hospitals. As noted previously, particle counts and air cultures for molds are useful tools in those selected situations in which one must identify and

remediate contaminated areas. The principal goal of testing is to ensure that the hospital's air filtration equipment is functioning correctly and, thus, delivering the cleanest air possible for the system.

For general acute-care hospitals, appropriate general healthcare-associated infection surveillance should be enough to detect clusters of fungal infections. Investigation of such clusters of infection should include a search for possible reservoirs for the filamentous fungus, evaluation of the hospital ventilation system, moisture problems, and sites where outside air may be mixing with the inside air (see also Chapters 82–84).

As medical technology and interventions advance and patients live longer, these filamentous fungal infections will become more common. Infection control programs will increasingly acknowledge their relevance as healthcare-associated infections.

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PART D. Viral Infections

CHAPTER 42

Influenza Viruses

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Influenza continues to be an important cause of morbidity and mortality in hospitalized and long-term care patients, particularly among the elderly and those with chronic underlying diseases. Effective strategies for influenza prevention must be multifaceted because of the uniqueness of the influenza viruses, including their seasonal nature, antigenic drift, and antigenic shift. Because all known influenza A subtypes exist in aquatic bird reservoirs, influenza is not an eradicable disease *(1,2)*. Instead, prevention by vaccination and containment are the most realistic public health strategies for influenza control. Continued public health surveillance of influenza in humans and in animal reservoirs is a key element of these prevention and control strategies *(1)*. In healthcare settings, the best approach to seasonal influenza prevention is a vaccination program starting in the fall of each year or as soon as the vaccine is available. Limitations for prevention by vaccination include inconsistent use and underuse of vaccines and problems with incomplete immunity despite vaccination, especially in the elderly, people with chronic underlying illnesses, immunosuppression (e.g., human immunodeficiency virus [HIV] infection and bone marrow suppression), and young children (3).

BACKGROUND

The subtypes of influenza A virus are classified on the basis of their surface antigens, called hemagglutinins (H) and neuraminidases (N). There are three hemagglutinins (H1, H2, and H3) and two neuraminidases (N1 and N2). Immunity to these antigens reduces the likelihood of infection and reduces the severity of illness if it does occur. However, antigenic drift and antigenic shift (i.e., subtle and marked changes, within a subtype, respectively) make long-lasting immunity difficult to achieve. Of the two antigenic changes, antigenic drift is the more gradual, with the H and N subtypes retaining some similarity as changes occur. Antigenic shift is a more abrupt change in H or N subtype, which occurs at longer intervals (e.g., approximately every 10 or more years). When the marked changes of antigenic shift occur, infection or vaccination with one strain may not necessarily induce immunity to distant strains, even though they are of the same subtype. Influenza B is more antigenically stable than influenza A and undergoes antigenic drift, but not the major structural changes of antigenic shift.

Effectiveness of influenza vaccine is determined by the closeness of the vaccine-induced antibody to the H and N surface antigens of influenza A and B. Influenza vaccine loses its protective effects as more major shifts of influenza H and N surface antigens or subtypes occur.

The nomenclature for influenza strains is a useful way to better understand that particular strain. The standard way of describing strains includes the serotype, host of origin (human unless otherwise specified), geographic origin, strain number, year of isolation, and the H and N designation.

Recommendation for trivalent influenza vaccine (TIV) components is based on surveillance data related to epidemiology and antigenic characteristics *(4)*, serological responses to previous vaccines, and the availability of candidate strains and reagents (3,*4*). For the 2010–2011 influenza season, TIV will include a component of the recently emerged H1N1 strain *(4)*. For the H1N1 component, an A/California7/2009-like virus (the pandemic strain) will replace the Brisbane/59/2007 strain. For H3N2, the A/Perth/16/2009-like virus will replace A/Brisbane/10/2007. For type B, the B/Brisbane/60/2008-like strain (the same as 2009–2010) will be used.

VACCINATION AND INFLUENZA-RELATED VIRUS MORBIDITY AND MORTALITY

The so-called high-risk groups for influenza and its complications include older persons (i.e., 65 years of age or older), very young children, and persons of any age with certain underlying health conditions, who are at increased risk for hospitalization, death, and other complications. During major epidemics, hospitalization rates for high-risk persons may increase two- to fivefold. Despite this, only about 30% of people aged 65 years or older are vaccinated

with influenza vaccine every year (3). Many outbreaks are reported from nursing homes and long-term care facilities *(5–7)*, in part because of underuse of vaccine in these vulnerable, closed populations (see Chapter 97). In addition to underuse of vaccine, many high-risk people fail to develop a protective antibody response to vaccination *(5,6)*. Outbreaks have also occurred in general hospitals, psychiatric units, and medical and pediatric services (3). This underuse of vaccine is a major contributor to outbreaks of influenza in healthcare facilities with associated morbidity and, on occasion, mortality.

As the population ages, the risk of seasonal influenza death increases. Thompson et al. reported that the death rate from influenza rose markedly in the 1990s, and in 2001 it exceeded the number of deaths due to acquired immunodeficiency syndrome (AIDS) *(7)*. Annual estimates of influenza-associated deaths increased significantly between the 1976–1977 and 1998–1999 seasons, with a mean of 20,000 and 36,000 deaths, respectively. Ninety percent of respiratory and circulatory deaths occurred in persons aged 65 years or older. Since its emergence in the 1960s, type A (H3N2) epidemics have caused approximately 400,000 deaths in the United States alone, and >90% of these deaths have occurred in people older than 65 years *(8)*. Prior to the reemergence of influenza A (H1N1) in 2009, the H3N2 had the most severe overall impact (*2*,9). An unexpected trend with the 2009 pandemic influenza H1N1 strain, on the other hand, was a higher attack rate in people younger than 65 years, outside the traditional high-risk groups (10). Early data from the 2009 pandemic influenza A (H1N1) outbreak in Mexico indicated that attack rates among persons aged 65 years or older were lower than those in other age groups and that anti-influenza A antibodies that cross-react with 2009 H1N1 could be detected in up to one third of healthy adults aged older than 60 years (*11*,12,*13*).

Despite this new trend with pandemic influenza A (H1N1), it is important to keep in mind the impact of influenza on elderly and chronically ill patients. Gross et al. characterized two typical nursing home outbreaks of seasonal influenza A *(5,6)*. One began in November, peaked in February, and ended in April. The outbreak progressed slowly and was complicated by concurrent infections with respiratory syncytial virus, parainfluenza virus, and *Mycoplasma pneumoniae*. The patient population in this case had an immunization rate of 59%, affording it some degree of herd immunity. The authors contrast the pattern of slow spread in this closed, partially immunized population to the more explosive outbreaks described in open, unimmunized populations (e.g., acute care settings and psychiatric services) (*8*,9). In the outbreak, influenza illness was significantly more common in the unvaccinated group, as was mortality (17.7% in the unvaccinated group and 7.2% in the vaccinated group). When controlled for sex and severity of illness, influenza vaccine reduced mortality by 59% in this closed, partially vaccinated population *(6)*.

Patriarca et al. developed a useful model to project morbidity, mortality, and costs associated with type A influenza illness in nursing homes *(14)*. The model used demographics similar to the real world of long-term care: 100 residents and a 60% rate of vaccination in the fall of the prior year. In this model, the combination of previous vaccination and amantadine during outbreaks was associated with significantly fewer cases compared with vaccine alone, probably because of the <100% efficacy of vaccine. The authors predicted an increase in herd immunity as more patients were vaccinated beyond the 60% receiving it initially, and when 70% received vaccine, the risk of an outbreak approached zero. They concluded that influenza control programs in nursing homes are beneficial, clinically sound, and cost-effective and have a modest increase in program costs with the addition of amantadine. More recent studies have shown that vaccination of both healthcare providers (HCPs) and patients is associated with fewer deaths among nursing home patients *(15)* and elderly hospitalized patients *(16)*. These data support the Advisory Committee on Immunization Practices' (ACIP) target of 90% vaccine use in populations at risk (3) and the 2005 requirement from Centers for Medicare and Medicaid Services (CMS) that nursing homes participating in the CMS programs offer all residents influenza and pneumococcal vaccines and document the results *(17)*. Each resident is to be vaccinated unless contraindicated medically, the resident or a legal representative refuses vaccination, or the vaccine is not available because of shortage. This information is to be reported as part of the CMS Minimum Data Set, which tracks nursing home health parameters (*18*,19).

CLINICAL MANIFESTATIONS

Typical influenza illness in the adult is characterized by sudden onset of fever, myalgia, sore throat, headache, retroorbital pain, and nonproductive cough. Unlike most other viral respiratory infections, influenza causes myalgias and other constitutional symptoms that can last a week or more. However, the sensitivity and the positive predictive value of fever, cough, and/or other symptoms for the diagnosis of influenza virus infection in severely ill or hospitalized patients are lower than those in the community *(20)*. The use of these common symptoms for treatment decisions and infection control management will probably be insufficient to contain a healthcare-associated outbreak, because many influenza cases will remain unidentified.

Some patients with influenza A may develop additional complications of primary influenza pneumonia or secondary bacterial pneumonia most often resulting from *Streptococcus pneumoniae* or *Staphylococcus aureus (21)*. These complications are not associated with influenza B infection, which is usually a milder illness.

Influenza in adults is first and foremost a respiratory disease. The term "intestinal flu" in adults is generally a misnomer *(22)*. The illness in children, on the other hand, may have a major gastrointestinal component or may mimic sepsis *(22,23)*. In an influenza A outbreak on a pediatrics ward, 7 of 12 infected children (58%) developed pulmonary infiltrates and 5 of the 7 went on to develop a secondary bacterial pneumonia. In the young infant, influenza may mimic sepsis with fever and no localizing findings *(23)*.

DIAGNOSIS

Diagnostic tests available for influenza include viral isolation (culture), rapid antigen testing, nucleic acid amplification testing by the polymerase chain reaction (PCR)

TABLE 42-1

Summary of Diagnostic Tests for Influenza

Method	*Influenza Types Detected*	*Acceptable Specimens*	*Time for Results*
Virus isolation (culture)	A and B	Nasopharyngeal swab, throat swab, nasal wash, bronchial wash, nasal aspirate, sputum	3–10 d
Immunofluorescence	A and B	Nasopharyngeal swab, nasal wash, bronchial wash, nasal aspirate, sputum	2–4 h
Polymerase chain reaction	A and B	Nasopharyngeal swab, throat swab, nasal wash, bronchial wash, nasal aspirate, sputum	2–4 h
Enzyme immunoassay	A and B	Nasopharyngeal swab, throat swab, nasal wash, bronchial wash	2 h
Serology	A and B	Paired acute and convalescent serum samples 2–4 wk apart	2 wk or more
Rapid diagnostic tests			
Multiple manufacturers	Depends on manufacturer—may distinguish between A and B or may be positive for influenza virus, type not specified	Nasal wash, nasopharyngeal swab, throat swab, and other specimens, depending on manufacturer	≤15 min

(Adapted from Centers for Disease Control and Prevention. H1N1 flu: interim guidance for the detection of novel influenza A virus using rapid influenza diagnostic tests. Available at *http://www.cdc.gov/h1n1flu/guidance/rapid_testing.htm*. Accessed May 9, 2011.)

method, and immunofluorescence (3,24) (Table 42-1). The two latter tests are the most useful laboratory techniques for prospective, real-time diagnosis of influenza. Sensitivity and specificity of these tests may vary with the laboratory performing the test, the type of test used, and the type of specimen tested. The preferred specimens for testing are nasopharyngeal specimens whenever possible; these are typically more sensitive than throat swab specimens (25). Clinical judgment plays an important role, and as with any diagnostic test, results should be evaluated in the context of the available clinical information.

A positive rapid diagnostic test allows for more timely institution of therapy and infection control precautions. However, the specificity (90%–95%) and the sensitivity (50%–75%) of rapid tests vary by manufacturer and are lower than those for viral culture. Because of the lower sensitivity of rapid tests, providers should consider confirming negative tests with PCR testing based on their clinical judgment.

Rapid tests differ in several important respects. Some distinguish between influenza A and B viruses, and others cannot. Some tests are waived from requirements under the Clinical Laboratory Improvement Amendments of 1988. Most tests can be used with a variety of specimen types (Table 42-1), but the accuracy of the tests may vary based on the type of specimen collected (e.g., throat vs. nasal swabs). The additional advantage of PCR testing over rapid tests is their ability to provide specific information regarding circulating influenza subtypes and strains. If PCR testing is not readily available locally or via reference laboratory, immunofluorescence tests or virus isolation are good alternatives.

Acute- and convalescent-phase serologies (antibody determination) are a helpful epidemiologic or public health tool retrospectively, but may be neither widely available nor useful for clinical real-time decision making or for prospective surveillance.

Diagnosis of influenza can also be made using epidemiologic parameters in combination with clinical and laboratory findings. When influenza is prevalent in the community, adult patients with acute febrile respiratory illness can be assumed to have influenza virus (3,*26*), keeping in mind that other viral respiratory illnesses such as respiratory syncytial virus and adenovirus can overlap with influenza disease (3). This approach to diagnosis and empiric therapy may be necessary during periods of widespread influenza activity when laboratory capacity is exceeded, as was the case with the novel H1N1 influenza in 2009–2010 *(27)*.

EPIDEMIOLOGY

Surveillance and Monitoring

The Centers for Disease Control and Prevention (CDC) conducts influenza surveillance year round in the United States as part of a worldwide collaborative surveillance system (*2*,3). This activity monitors a variety of state and local health departments, public health and clinical laboratories, sentinel physician practices, and reports of pneumonia and influenza deaths from a sampling of vital statistics offices throughout the United States. These so-called FluView data are reported weekly on the Internet *(28)*.

Once influenza establishes itself in the community, sporadic cases may be seen in both HCPs and patients. In healthcare settings, employee absenteeism for influenza-like illness (ILI) often precedes an outbreak by several weeks, suggesting transmission from healthcare worker

(HCW) to patients *(2,13,29)* or the opposite *(29,30)*. Either way, healthcare-associated influenza increases hospital days and costs of hospitalization; in one study the cost was $3798 per infected patient in 2002 US dollars *(29)*. Cost-effectiveness studies of adults younger than 65 years indicate that vaccination can reduce both direct medical costs and indirect costs from work absenteeism *(31)*, resulting in 13% to 44% fewer HCP visits, 18% to 45% fewer lost workdays, 18% to 28% fewer days working with reduced effectiveness, and a 25% decrease in antibiotic use for ILI *(31)*. Among healthy persons aged 18 to 64 years, vaccination can save an estimated $60 to $4000 per illness, depending on the cost of vaccination, the influenza attack rate, and vaccine effectiveness against ILI *(32)*. Among studies of healthy young adults, >70% of the costs prevented were associated with reductions in lost work productivity *(32)*.

In healthcare settings, prospective monitoring and surveillance of influenza-like respiratory illness are of greatest value when accompanied by an influenza vaccination program to prevent illness in HCPs. Monitoring local or regional influenza and respiratory virus surveillance data can provide key indicators of the need for heightened awareness of influenza in healthcare settings.

Influenza as an Emerging Infectious Disease

In April 2009, a novel H1N1 influenza A virus, the so-called pandemic H1N1/09 virus (former designations include swine influenza, novel influenza, swine-origin influenza A [H1N1] virus [S-OIV], Mexican flu, and North American flu), was identified in Mexico (*2*,9,10). The virus subsequently reached pandemic level 6—the World Health Organization's highest designation—based not on mortality, but on geographic distribution *(33)*. This represents the first influenza A virus pandemic since the emergence of H3N2 (Hong Kong flu) in 1968. Although the pandemic H1N1/09 virus originated from the triple-reassortment swine influenza (H1) virus circulating in North American pigs, it is not epidemic in pigs. The initial waves of the H1N1/09 virus were relatively short-lived, and concerns remain that it may become more aggressive during spreading, based on the historical behavior of pandemic H1N1 strains (9,*34*).

Novel influenza viruses have the potential to initiate global pandemics if they are sufficiently transmissible among humans (*1*,9,*34*). Recent experience with the avian H5N1 influenza A strain—first identified in 1995 in Asia—supports the value of continued public health surveillance and containment *(35)*. Both the avian H5N1 and H1N1/2009 outbreaks demonstrate that influenza is still a serious public health issue and that global epidemiologic surveillance is an important public health tool for prevention and control of influenza, and early detection by global surveillance played an important role in tracking and containing these outbreaks.

Modes of Transmission

Influenza A and B viruses are among the most communicable viruses of man and have produced explosive epidemics. Transmission of both influenza A and B in healthcare settings is well documented. In healthcare settings, HCPs, patients, or visitors can be a reservoir of infection. Once infection is established and infection is being transmitted, infection control interventions, including vaccination, need to include all three groups as part of an outbreak control plan.

Humans are reservoirs of infection, and person-to-person transmission is thought to occur primarily via fomites (droplet spread) and hands contaminated with virus (3,19,*34*). Larger droplets require closer person-to-person contact for virus transmission, generally <3 ft separating two persons. These large droplets are produced by coughing or sneezing and can infect the susceptible host directly or indirectly. Direct transmission involves direct inoculation of mucous membranes of the eye or nose. Indirect transmission refers to contamination of the donor's hands, which spread infectious material to the skin or mucous membranes of a susceptible host.

In other cases, small-particle aerosols (<10 μm median diameter) containing infectious virus particles are produced and disseminated by coughing or sneezing. These small-diameter infectious virus particles can be transmitted over long distances (>6 ft). The aerosol mode of transmission may be responsible for the explosive nature of influenza transmission, with one infected person shedding large numbers of infectious virus particles and subsequently infecting a large number of susceptible people (3,*35*).

CONTROL AND PREVENTION OF INFLUENZA

Control of influenza requires herd immunity, which requires that large numbers of people in a particular group at risk be immune to infection (9,*14*). There are two approaches to reduce the impact of influenza infection: inactivated influenza vaccine (immunoprophylaxis) and antiviral drugs (chemoprophylaxis). Antiviral drugs are a useful adjunct when herd immunity is not present because of underuse of vaccine and/or inadequate protective antibody response to vaccination (36).

Vaccination

As influenza viruses continue to evolve through antigenic shift and antigenic drift, new strains emerge to which the population is susceptible. Therefore, annual vaccination is recommended using the current TIV for that year, even if the current vaccine has one or more antigens administered in the previous year's formulation (3,*4*). This is because immunity declines over a year's time, and an annual booster dose is required to maintain immunity to influenza strains that appear in the general population each year.

Influenza vaccination is the cornerstone of prevention and control of healthcare-associated influenza. Vaccine efficacy (i.e., the rate of reducing influenza infections in those who receive it) ranges from 80% to 90% in healthy individuals *(2)* to 50% in some nursing home populations (3).

During the preparation of TIV, the vaccine viruses are made noninfectious (i.e., inactivated or killed) (37). Only subvirion and purified surface antigen preparations of TIV (often referred to as "split" and subunit vaccines, respectively) are available in the United States. TIV contains killed viruses and thus cannot cause influenza. It is administered intramuscularly by injection for use among persons aged 6 months or older, including those who are healthy and those with chronic medical conditions. The

live attenuated influenza vaccine (LAIV) discussed below has the potential to cause mild signs or symptoms (e.g., runny nose, nasal congestion, fever, or sore throat). This formulation is administered intranasally by sprayer and is licensed for use in nonpregnant women aged 2 to 49 years; safety has not been established in persons with underlying medical conditions that confer a higher risk for influenza complications (37).

Beyond the obvious benefits of decreasing the risk of influenza transmission to patients, influenza vaccination of HCPs contributes to increased worker productivity and decreased absences (38). Using trivalent, seasonal vaccine, 264 HCPs from two Baltimore teaching hospitals were enrolled in a randomized trial of influenza vaccine versus placebo (meningococcal vaccine). Subjects were followed for clinical illness and were tested for serologic evidence of influenza A and B infections at baseline and at the end of the influenza season. The investigators conducted 359 person-winters of serologic surveillance (99.4% follow-up) and 4746 person-weeks of illness surveillance (100% follow-up). Twenty-four (13.4%) of 179 control subjects and 3 (1.7%) of 180 influenza vaccine recipients had serologic evidence of influenza type A or B infection during the study period. Vaccine efficacy against serologically defined infection was 88% for influenza A ($p = .03$).

In general, the passive approach to vaccination that announces vaccine availability in anticipation of employees being vaccinated does not achieve meaningful vaccination uptake. More active approaches include making vaccine available to staff on all shifts on patient units and education of HCPs that dispels misinformation and emphasizes the importance and safety of influenza vaccination.

A program that administered TIV in a neonatal intensive care unit (NICU) targeting parents of patients was attributed to an increase in vaccine uptake in NICU staff *(39)*. Among parents, 95% were vaccinated (with informed consent). Of 120 neonatal HCPs, 112 (93%) were screened during the 2005–2006 season; 80 (67%) were vaccinated, compared with 49 (41%) prior to the implementation of this program ($p = .03$); 54 (45% of the study population, which included senior neonatologists, fellow and resident physicians, nurses, respiratory therapists, X-ray technicians, and clerical staff) received TIV in the NICU, compared with the 17 (14%) of 120 HCWs the previous year; and 20 (46%) of 43 HCWs of the nursing staff were vaccinated in the NICU, whereas only 3 (7%) of 43 HWCs were vaccinated outside the unit.

Overall, the effort was judged an effective means of increasing the vaccination rate among NICU HCWs. Still, attending physicians had the lowest vaccination rate (1 of 7 [15%]), and most cited efficacy issues and/or side effects as reasons for deferral. Nurses refused vaccination most often because of fear of injection (20 of 43 [46%]).

To increase vaccination uptake, educational efforts for nurses should emphasize the risk of influenza transmission to neonates as motivation for vaccination. Physician-directed efforts should include tolerability of vaccine side effects. LAIV, administered intranasally, should be considered to increase vaccination rates among healthy HCPs who have fear of injections.

However, vaccination on patient units is not always a guarantee of success. Weinstock et al. reported on their efforts in a bone marrow transplant unit *(40)*. After an outbreak on the unit in January 1998, they took a "new, more rigorous approach" during the following influenza season. Their approach focused on HCP education accompanied by vaccination on the transplant unit. Vaccine uptake improved from 12% in the prior season to 58%. The 42% of staff who remained unvaccinated is particularly sobering in view of an influenza outbreak in patients on the unit the year before. While this increase is significant, this degree of vaccine acceptance probably falls short of the optimal herd immunity needed to impact influenza prevention.

One study reviewed vaccine use in HCWs systematically by comparing responses to questionnaires from vaccine recipients and nonrecipients. Vaccine recipients were significantly more likely to believe that influenza disease and its complications were more serious to high-risk patients, that influenza vaccine was effective and uncommonly associated with side effects, and that influenza vaccination was important for HCPs to decrease transmission to high-risk patients *(41)*. The authors concluded that these issues were the major educational components of a vaccination program for HCWs. However, a European study showed that even educational interventions targeted to specific HCPs' misinformation or misunderstandings only increased vaccine use by HCWs in three targeted departments from 13% to 37% *(41,42)*.

The challenge for healthcare facilities involves overcoming barriers to unacceptably low rates of vaccination of both HCWs (including physicians) and patients. The general public and HCPs alike have misconceptions that the vaccine can cause illness (37) (e.g., that vaccine can "cause the flu" and/or the—[GBS]). The possible link between influenza vaccine and GBS first emerged during the nationwide swine influenza vaccination program (A/New Jersey/76) in 1976 and was raised again during the H1N1/2009 vaccination campaign (43).

Influenza vaccines are made from egg-grown viruses that are rendered inactive as part of the vaccine-manufacturing process and cannot cause influenza (3,37). Also, education programs should include a reminder that influenza vaccine provides immunity to influenza only and that it does not provide protection from other respiratory viruses such as respiratory syncytial virus or the rhinoviruses (37).

GBS appears to have been unique to the A/New Jersey/76 vaccine strain, with an overall rate of 4.9 to 5.9 cases of GBS per million vaccinees among 45 million people vaccinated *(44)*. The nature of the association of A/New Jersey/76 vaccine with GBS remains unclear *(45)*, but the association is likely multifactorial, according to more contemporary analyses (*45*,46). In retrospect, the data on the swine flu vaccination program of 1976 did made a case for a "slight increase" in the risk of GBS *(45)*. That experience was an aberration, since the risk increased only in 1976 and only among civilians in the United States. Vaccines containing swine flu virus that were prepared in England and the Netherlands were associated with no such increase in risk. Moreover, 1.7 million US servicemen who received double doses of the vaccine against swine influenza had no adverse effects *(45)*.

One argument for a direct relation between GBS and preceding infections derives from experience with the enteric pathogen *Campylobacter jejuni*, which precedes GBS in

30% to 40% of cases as detected by serologic tests, even in the absence of enteritis *(45)*. The hypothesis is that *C. jejuni* is a contaminant in chicken eggs that may also contaminate influenza vaccine during the vaccine-manufacturing process. The presence of a lipopolysaccharide antigen on some *C. jejuni* strains is shared with ganglioside epitopes of peripheral nerves. The connection between campylobacter infection and the GBS supports a theory of cross-reactivity, or "molecular mimicry," in which the immune response directed toward an infectious agent spills over to involve a neural antigen *(47)*.

However, in recent years, GBS has not been reported as a complication of H1N1 monovalent vaccine use (37). One reason may be that vaccine formulations in years subsequent to the 1976 H1N1 vaccine have not been associated with vaccine-associated GBS (*2*,37,46).

With underuse of vaccine in major populations at risk (i.e., HCPs, the elderly and chronically ill, and persons likely to spread influenza to high-risk people), influenza prevention programs in many healthcare settings are often haphazard and incomplete and, instead, react when clusters or outbreaks of infection occur. Even though a substantial number of HCWs and patients have not been vaccinated at the time of the first report of influenza, the arrival of influenza in the community and/or hospital is still a good time to vaccinate these groups, keeping in mind that the time from vaccination to protective antibody response is about 2 weeks.

Other Strategies to Improve Vaccination Uptake

Despite the efficacy of vaccine and a public health commitment to childhood and adult immunization, fewer than 30% of persons aged 65 years or older receive the influenza vaccine each year (3). The collective experience of public health and infection control experts is that promoting influenza vaccination, or any other kind of vaccination, requires more than just posters announcing the availability of vaccine (3,*41*,*42*). A recent review of strategies for management of influenza in the elderly provides a comprehensive review of this important subject *(42)*.

Beyond recommending universal influenza vaccination, other more active strategies are being discussed and adopted in some healthcare settings. Standing orders for vaccination is an effective strategy for increasing influenza vaccine uptake in patients (3,*18*). In 2002, CMS relaxed their physician signature requirement for influenza and pneumococcal vaccination, allowing nurses and pharmacists to administer vaccination using standing orders in accordance with state rules on the matter (*17*,*18*,19). In a university ambulatory setting, larger numbers of patients whose physicians used standing orders for influenza vaccination received vaccine compared with patients whose physicians did not (63% vs. 38%, respectively) *(48)*. Guidance on standing orders is available for mass vaccination clinics as well *(18)*.

Efforts should be made to administer vaccine where people receive their medical care, generally physicians' offices, clinics, and urgent care settings, to name a few. Vaccine administered during an inpatient admission avoids another "missed opportunity." Other elements of a successful vaccination program are education for HCWs, a plan for identifying the highest risk patients (often by review of medical records), and efforts to remove administrative and financial barriers that prevent people from receiving vaccine (3). In primary care settings, computer-generated reminders to physicians have been effective *(49)*. Physicians who received such reminders as a part of a study were twice as likely to vaccinate their patients as those physicians who did not receive the reminders.

The optimal time to receive seasonal influenza vaccine is during October and November, or as soon as vaccine becomes available. However, because of vaccine distribution delays, the ACIP recommends a staggered approach so that early vaccination efforts focus on persons at greatest risk followed by other high-risk people as more vaccine becomes available (3).

In HCPs, vaccine should be administered in the workplace (e.g., patient units, at large conferences, cafeterias, ambulatory clinics, and physician private offices) to maximize participation. Making influenza vaccine available to employees is no guarantee of acceptance. However, offering free vaccine, addressing employee concerns about vaccine safety and adverse events, and making vaccination more convenient and accessible to employees reduce some of the barriers to an effective program for HCWs.

Simultaneous use of other vaccines with influenza vaccine is safe, effective, and eliminates the need for a return visit for additional vaccines. Influenza vaccine can be included as part of any healthcare encounter that includes other adult or childhood vaccinations. Because the target groups for influenza and pneumococcal vaccines overlap, both vaccines can be administered at the same time at different sites without increasing side effects of either vaccine (3). Children at high risk for influenza may receive influenza vaccine at the same time as measles—mumps—rubella, Haemophilus influenzae B, pneumococcal, and oral polio vaccines. Vaccines should be administered at different sites on the body, and influenza vaccine should not be given within 3 days of administration of pertussis vaccine (3).

Innovative Influenza Vaccination: LAIV

The LAIV is another option for HCPs who are healthy, younger than 50 years old, and not pregnant. This vaccine, delivered by an intranasal spray, has been shown to be equivalent to the injectable trivalent formulation in terms of safety and efficacy *(50)*.

Healthcare professionals who provide care to newborn infants (including neonatal intensive care patients), pregnant women, persons with a solid organ transplant, persons receiving chemotherapy, and persons with HIV/AIDS may receive LAIV if otherwise eligible (51). However, LAIV should not be used for HCPs who care for patients undergoing bone marrow transplantation. Although these immunocompromised patients have not been shown to be harmed by use of LAIV among HCPs, the recommendation against the use of LAIV in HCWs with this type of patient contact is an extra precaution for fragile immunocompromised patients. HCWs with this type of patient contact who receive LAIV should wait for 7 days after being vaccinated before returning to caring for bone marrow transplant recipients. No special precautions (e.g., masks or gloves) are necessary for healthcare personnel who have been vaccinated with the LAIV and who do not work with patients undergoing bone marrow transplantation (51).

Influenza Vaccination as a Measure of Quality

Healthcare administrators should consider the level of vaccination coverage among HCPs as a measure of a patient safety/quality program and consider obtaining signed declinations from personnel who decline influenza vaccination for reasons other than medical contraindications. Influenza vaccination rates among HCPs within facilities should be regularly measured and reported, and ward-, unit-, and specialty-specific coverage rates should be provided to staff and administration. Studies have demonstrated that organized campaigns can attain higher rates of vaccination among HCPs with moderate effort and by using strategies that increase vaccine acceptance (3).

Efforts to increase vaccination coverage among HCPs are supported by various national accrediting and professional organizations and in certain states by statute (3,*52*). The Joint Commission on Accreditation of HealthCare Organizations (2007) has approved an infection-control standard that requires accredited organizations to offer influenza vaccinations to staff, including volunteers and licensed independent practitioners with close patient contact. In addition, the Infectious Diseases Society of America has recommended mandatory vaccination for HCPs, with a provision for declination of vaccination based on religious or medical reasons. Some states have regulations regarding vaccination of HCPs, that require that healthcare facilities offer influenza vaccination to HCPs or require that HCP either receive influenza vaccination or indicate a religious, medical, or philosophic reason for not being vaccinated (3).

Other Approaches to Influenza Vaccination

The increased H1N1 influenza activity of 2009–2010 has resulted in a reevaluation of our approach to influenza vaccination. Previously, the ACIP recommended that annual influenza vaccination should include all people aged 6 months or older. Beginning with the 2010–2011 influenza season, the ACIP recommends that everyone who is 6 months or older should receive influenza vaccine *(53)*. This recommendation is an effort to expand protection against influenza to more people, seeks to remove barriers to influenza immunization, and signals the importance of preventing influenza across the entire population *(53)*. This new recommendation comes against a backdrop of incremental increases in the numbers and groups of people recommended for influenza vaccination in recent years and lessons learned from the H1N1 pandemic. Key points in favor of this new guidance are shown in Table 42-2.

Because of the benefits to patients and employees, and the additional implications for increased employee productivity, healthcare settings of any type should offer influenza vaccine to all employees, regardless of their degree of patient contact. Babcock et al. have described a mandatory influenza vaccination program in a large healthcare system in St. Louis, MO, which included approximately 25,000 employees (54). This approach resulted in vaccine uptake of 98.1%, with exemptions allowed for health or religious reasons only. Interestingly, a large number of employees who had previously signed a waiver declining vaccine accepted vaccination once it was mandated. While mandatory vaccination raises the issue of duty to patients versus employee autonomy, the St. Louis experience suggests that duty to patients, patient safety, and quality of care take precedence. In his accompanying editorial, Pavia calls the mandate a clear effort to protect patients from healthcare-associated influenza and describes some of the barriers to implementing such a program, including recent legal challenges (55).

TABLE 42-2

Rationale for Recommendation for Universal Influenza Vaccination

- Previous recommendations for seasonal vaccination already applied to about 85% of the US population
- Protection of people 19–49 y of age, who were hard hit by the 2009 H1N1 pandemic virus, which is likely to continue circulating into next season and beyond
- Many in currently recommended "higher risk" groups are unaware of their risk factor or that they are recommended for vaccination
- Conveys a practical, simple, and clear message regarding the importance of influenza vaccination
- Experience during 2009 H1N1 pandemic indicates that some people who do not have a specific recommendation for vaccination may also be at higher risk of flu-related complications, including those who are obese, postpartum, and in certain racial/ethnic groups

(From Centers for Disease Control and Prevention. CDC's advisory committee on immunization practices [ACIP] recommends universal annual influenza vaccination. Press release: Feb 24, 2010. Available at *http://www.cdc.gov/media/pressrel/2010/r100224.htm.* Accessed May 9, 2011.)

Others have described the role of mandatory influenza vaccination in a larger context (*56*,57). Using mandatory school vaccination programs as a starting point, Malone and Hinman offer an historical and balanced discussion of the public health benefits of vaccines versus individual rights, including the legal precedents supporting mandatory vaccination *(56)*. Orenstein et al. discuss the matter from a different viewpoint, but make a compelling case for vaccines as public health tools (57). Jefferson offers a counterpoint to the mandatory influenza vaccination, citing a gap between policy and evidence *(58)*.

Antiviral Agents for Influenza

Two classes of antiviral drugs are approved by the U.S. Food and Drug Administration (FDA) for treatment and prevention of influenza virus: M2 ion channel blockers (adamantanes) and neuraminidase inhibitors (NAIs). Historically, these agents are adjuncts to vaccination and not a substitute (*59*,60). The M2 blockers are effective against influenza A viruses, but not influenza B viruses, which lack the M2 protein. The use of the M2 blockers has been associated with the rapid emergence of drug-resistance mutations of the M2 protein among human influenza A viruses of H3N2 subtype; and in H1N1 subtype, viruses circulating in certain geographic areas (60,*61*).

Since 1960s, H3N2 has tended to dominate in prevalence over H1N1, H1N2, and influenza B, at least prior to the reemergence of the pandemic H1N1/2009 strain. Measured resistance to the standard antiviral drugs amantadine and rimantadine in H3N2 has increased from 1% in 1994

to 12% in 2003 to 91% in 2005 (9). Adamantane resistance has also been detected in A (H5N1) viruses in Southeast Asia (10,*11*). This rapid increase in resistance has reduced the usefulness of this class of drugs for the management of influenza A infections, and since 2005, CDC has not recommended their use *(61,62)*; the emergence of resistance to oseltamivir in seasonal influenza viruses circulating during the 2008–2009 season also led to changes in CDC recommendations *(63)*.

Two NAIs, oseltamivir (Tamiflu [Hoffman-La Roche]) and zanamivir (Relenza [GlaxoSmithKline]), are FDA-approved drugs for use against type A and type B influenza infections *(64,65)*. The two drugs differ structurally so that oseltamivir is orally bioavailable, whereas zanamivir must be inhaled. A third NAI, peramivir (BioCryst, Inc.), is formulated for intravenous administration and is undergoing clinical trials *(66)*. A fourth, called A-315675 (Abbott Laboratories) has only been investigated in preclinical studies.

The dosages, indications, and duration of use for the FDA-approved drugs are summarized for patients older than 1 year in Table 42-3 and for children younger than 1 year in Table 42-4.

TREATMENT

When administered within 2 days of illness onset to otherwise healthy adults, these can reduce the duration of uncomplicated influenza illness (67).

In 2009, the FDA issued an Emergency Use Authorization for peramivir, which may be used in certain hospitalized adult and pediatric patients with confirmed or suspected 2009 H1N1 influenza *(66)*. It is the only intravenous option for the treatment of patients with 2009 H1N1 influenza. Other guidance for use of these agents is discussed in more detail elsewhere (67).

TABLE 42-3

Dosing of Oseltamivir and Zanamivir for Treatment and Prevention for 2009 H1N1 Influenza

	Ages 1–12 y	*Ages 13 ≥ 65 y*
Oseltamivir tablets[a]		
Treatment twice daily × 5 d	<15 kg, 30 mg	75 mg
Prophylaxis once daily × 10 d	16–23 kg, 45 mg	
	24–40 kg, 60 mg	
	>40 kg, 75 mg	
Zanamivir inhalation[b]		
Treatment twice daily × 5 d	NA, <7 y	10 mg, ≥7 y
Prophylaxis once daily × 10 d	NA, <5 y	10 mg, ≥5 y

Note: Zanamivir is manufactured by GalxoSmithKline (Relenza—inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamilflu—tablet). This information is based on data published by the Food and Drug Administration (FDA), which is available at www.fda.gov.
NA, not approved.
[a]A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.
[b]Zanamivir is administered through inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of correct use of the device.
(Adapted from Centers for Disease Control and Prevention. Guidance on the Use of Influenza Antiviral Agents During the 2010–2011 Influenza Season—Use of Antivirals. Available at *http://www.cdc.gov/flu/professionals/antivirals/antiviral-use-influenza.htm*. Accessed May 9, 2011.)

PROPHYLAXIS

Antivirals for prevention of influenza are not a substitute for vaccination, although they are critical adjuncts for prevention and control. Influenza antivirals are approximately 70% to 90% effective in preventing illness from influenza infection (3,60). Because of widespread resistance of both H1N1 and H3N2 to the adamantanes, the NAIs, oseltamivir and zanamivir, are the first-line drugs for influenza prevention (3). When used as prophylaxis, these agents can prevent illness and still permit subclinical infection and the development of protective antibody against circulating influenza viruses (3). Both drugs have been studied extensively among nursing home populations as a component in influenza outbreak control and can limit the spread of influenza within chronic care facilities

TABLE 42-4

Recommended Doses of Oseltamivir Oral Suspension for Infants Younger than 1 Year of Age

Age (mo)	*Dose (mg)*	*Volume per Dose, 12 mg/mL*	*Treatment Dose (5 d)*	*Prophylaxis Dose (10 d)*
6–11	25	2 mL	2 mL twice daily	2 mL once daily
3–5	20	1.6 mL	1.6 mL twice daily	1.6 mL once daily
<3	12	1.0 mL	1.0 mL twice daily	Not recommended unless critical

(Data from US Food and Drug Administration. Emergency use of Tamiflu in infants less than 1 year of age. Available at *http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm183870.htm.* Accessed May 9, 2011.)

(3,*59*). Both NAIs, zanamivir and oseltamivir, are approved for prophylaxis, and community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (3,*64*,*65*).

To be maximally effective, preventive treatment must be taken each day during the period of peak influenza activity in the community. This approach contributes to managing the development of resistance and helps avoid unnecessary costs and supply chain issues (3,60). Persons for whom prophylaxis is indicated are high-risk persons vaccinated after influenza activity has begun, HCPs who are unvaccinated or were vaccinated after influenza activity has begun who provide care to high-risk patients, immunosuppressed persons who may not respond to vaccination, and persons for whom vaccine is contraindicated (e.g., persons with allergy to egg protein) (3).

None of the four antiviral agents has been demonstrated to be effective in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Data are limited and inconclusive concerning the effectiveness of influenza antivirals for treatment of persons at high risk for serious complications of influenza (3,60). Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations compared with adults (3,60). One study compared oseltamivir with the adamantanes and did not identify any new safety signals in terms of neurotoxicity *(68)*, although later, central nervous system toxicity was identified in children in Japan taking oseltamivir. The US FDA advises that persons receiving NAIs be monitored for abnormal behavior and notes that a direct link between behavioral changes and oseltavmivir has not been established *(69,70)*.

Other Therapeutic Options

Recently, the statin class of lipid-lowering agents was reported to be associated with decreased mortality in hospitalized patients with seasonal influenza *(71)*. The use of statins for influenza was first proposed in 2006 as part of the treatment for H5N1 avian influenza *(72)*. Fedson's hypothesis is that influenza is associated with inflammation and an increased risk of cardiovascular diseases. Therefore, the anti-inflammatory and immunomodulatory effects of statins might also help patients with influenza.

More recently, in a retrospective review, statin use was associated with reduced mortality in patients hospitalized with laboratory-confirmed seasonal influenza *(71)*. In these patients, 17 of 801 (2.1%) treated subjects died of influenza or its complications. In the untreated group, 64 of 1999 (3.2%) of the subjects died of influenza or its complications; this represents a 54% decreased risk of death, considering other risk factors, such as age and use of antiviral drugs. The investigators concluded that their results were not sufficient to recommend statins for treatment of influenza. Instead, these data need to be confirmed by more rigorous studies.

OUTBREAK CONTROL

Antiviral administration as an outbreak control measure requires considerable coordination to implement with a minimum of delays (3,*73*). For outbreak control, it is recommended that in closed populations such as nursing homes, patients with influenza taking one of these drugs for treatment be isolated or cohorted from the asymptomatic patients who are taking antivirals for prophylaxis (3,*59*,60,*74*). High-risk individuals can still be vaccinated after an outbreak of influenza A has begun. Because the development of antibodies in adults after vaccination takes 2 weeks, prophylaxis should be administered during the 2 weeks following vaccination while waiting for maximum vaccine antibody production (3,60).

Children being vaccinated for the first time may need 6 weeks for antibody development after vaccination or 2 weeks after the second vaccine dose. In either case, influenza antivirals do not interfere with antibody response after vaccination (3).

LIMITATIONS ON ANTIVIRAL USE

Outbreak-initiated use of influenza antivirals is usually problematic *(73,74)*. Often, the spread of influenza among patients and HCPs outpaces the best intentions and efforts to provide prophylaxis and treatment to those who might benefit from it (3). Additional considerations involve drug availability, distribution, staff education, compliance, and financial considerations.

It is not known whether these drugs are effective if they are given >48 hours after the onset of illness, although CDC guidance in response to the pandemic H1N1/2009 strain during the 2009–2010 influenza season offered a more flexible approach for initiating therapy later in very ill patients *(75)*. This means that unless rapid diagnostic techniques are readily available, treatment decisions will be based on clinical and/or epidemiologic diagnosis of influenza because of delays in establishing a laboratory diagnosis of influenza A.

Side effects include mild central nervous system symptoms (nervousness, anxiety, insomnia, and difficulty in concentrating) or gastrointestinal symptoms (anorexia and nausea). These side effects often improve after a week on the drug or can be reduced by an appropriate dosage adjustment (3). Dosage adjustments are needed for these drugs in patients with renal or hepatic failure (3,60).

In addition to known resistance of influenza A H3N2 to adamantanes, sporadic resistance has been reported to the NAIs as well *(61–63,76)*. It is advisable, therefore, to monitor local, regional, and national resistance trends to support proper drug selection.

ISOLATION PRECAUTIONS AND INFECTION CONTROL

The components of a comprehensive approach for healthcare-associated influenza infection, detailed extensively as a result of pandemic H1N1 2009 influenza (77), include immunization of HCWs and patients at high risk, early identification, isolation and/or cohort isolation (cohorting) of infected patients and personnel, and the flexibility to offer vaccine later in the year when influenza is first identified in the community or hospital (3,*75*). In addi-

tion, isolation in private rooms with negative pressure, if possible, is best for known or suspected cases of influenza.

Cohorting may be useful when larger numbers of patients or personnel are infected with influenza (3,*35*). Cohort isolation attempts to separate different groups of people in an effort to reduce disease transmission (3,*35*). In this case, cohorts of infected and uninfected individuals are identified and separated as a means of reducing spread of influenza. Because most facilities have only a limited supply of private rooms or rooms equipped with negative pressure, more than one patient with proven influenza may be cohorted or isolated together. Depending on the severity of the outbreak, it may also be necessary to restrict ill HCWs from work, curtail visitation, and reschedule some elective admissions and surgical procedures (3,*35*).

Obviously, the infection control fundamentals, especially hand hygiene, are critical and should not be overlooked *(78)*. Droplet Precautions, with a mask, preferably a fit-tested disposable N95 respirator, for direct patient contact (i.e., within 3 ft of the patient) are recommended whenever possible (3,*35*,77).

Precautions for patients with influenza should be maintained for 7 days or the duration of clinical illness, whichever is longer. Because the duration of clinical illness in antiviral-treated patients is shortened if the drug is given in a timely fashion (i.e., within 48 hours of onset of illness), the period of isolation precautions, especially the use of a mask, may be shortened accordingly.

CONCLUSION

The approach to prevention and control of influenza in healthcare settings relies heavily on vaccine use as the cornerstone of an infection control program for influenza. This is in conjunction with early identification, isolation, and/or cohort isolation. To reduce the risk of an outbreak, vaccine use must be high enough to yield some degree of herd immunity. Therefore, the ACIP recommendation of 90% vaccine use is appropriate when one considers the scientific basis from outbreak experience and sophisticated projection models.

Antiviral drugs are an important adjunct to vaccine during outbreak periods to increase the potential for developing herd immunity, especially when vaccine use is less than optimal. When vaccine use is low and/or influenza infection occurs, additional measures such as restriction of personnel, visitors, and certain procedures may also be indicated.

Despite the ACIP's new recommendation for universal vaccination, innovative programs promoting HCP education and awareness are still needed to reach this goal in healthcare settings. Mandatory influenza vaccination programs, although controversial and debated, play a role in improving patient safety and quality of care further. Whether voluntary or mandatory, either vaccination option requires administrative and financial commitment at a time of limitations on healthcare resources. The return on investment, however, will come over the long term in the form of reductions in morbidity, mortality, and hospital use, and the added benefit of more appropriate use of essential infection control program resources.

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CHAPTER 43

Varicella-Zoster Virus

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HISTORICAL BACKGROUND AND CURRENT SCOPE OF THE PROBLEM

Varicella is a vesicular exanthema caused by primary infection with varicella-zoster virus (VZV) and is commonly termed chickenpox in English because of the itching observed, derived from the Old English word *gican*, meaning to scratch *(1)*. Herpes zoster (HZ) is the clinical syndrome of segmental vesicular exanthema and pain associated with reactivation of latent VZV infection in a dorsal nerve ganglion. This is commonly called "shingles" in English because of the way the rash encircles the body, derived from the Latin word *cingulum*, meaning a girdle *(2)*. Varicella had been known for centuries as a relatively benign infection of childhood. It was first differentiated from smallpox in recorded medical texts in the ninth century AD by the Persian physician Rhazes, who noted that the mild pustular skin eruption was not protective against smallpox *(3)*. From an epidemiological standpoint, much of what we know and practice regarding management of disease prevention derives from the clinical descriptions that linked varicella and HZ *(4,5)*.

It is with modern medicine that these two entities took on new significance. With the advent of immunosuppression, severe VZV infection, with visceral dissemination after both primary and reactivated infection, became common *(6,7)*. Because of the resultant morbidity and mortality associated with VZV infection, immunologic and chemotherapeutic antiviral methods were developed to minimize this outcome in high-risk individuals. Today, the availability of anti-VZV chemotherapy and VZV vaccination assists in minimizing or preventing the complications of this important healthcare-associated infection. It is important that persons involved in the control of healthcare-associated infections remain knowledgeable about these methods of intervention as well as about the vast informational background upon which many of the recommendations are based.

DISTINCTION BETWEEN VARICELLA AND HERPES ZOSTER

Prior to the modern methods for virologic diagnosis, clinical observation had suggested that the causative agents of varicella and HZ were related *(8,9)*. Varicella was observed to occur not only following exposure to zoster, but also after vesicle fluid was purposely inoculated into susceptible children *(10)*. In addition, the pathologic description of the two clinical entities was similar (*11*,12). The major significant advance in understanding the nature of these agents was contributed by Weller (13,*14*,*15*), who demonstrated the method for isolation and serial propagation of VZV. These investigators demonstrated that virus isolates made from persons with chickenpox or zoster were identical in terms of cytopathic effect (CPE) in tissue culture (13) and antigenic analysis *(14,16)*. Subsequently, others demonstrated that the VZV strains isolated from these two clinical syndromes were identical by morphology *(17,18)* and by DNA analysis *(19,20)*.

NATURE OF VZV

VZV Strain Clades

Like the other members of the herpes virus family, VZV is an enveloped virus that contains double-stranded DNA within its protein core. The viral particle is an icosahedron, and the complete enveloped virion measures between 150 and 200 nm in diameter, while the naked particle is about 95 nm in diameter. The VZV genome contains approximately 125-kb pairs *(21)*, with approximately 71 open reading frames. There is a geographic distribution of sequence variations of VZV, and these are grouped into clades (22,23). The VZV vaccine strain Oka is a clade 2 strain, and the ability to distinguish VZV outbreaks by clade type has become an important epidemiologic tool *(24,25)*.

The CPE of VZV infection appears as syncytial cells with intranuclear inclusion bodies (13). In clinical disease, a similar inclusion body is observed in infected tissue, and, as noted, this CPE is identical for both chickenpox and HZ *(15)*. Electron micrographic analysis of vesicle fluid from children with chickenpox demonstrates cell-free enveloped virions *(17)*. It is presumed that VZV acquires an envelope by budding out of the nucleus and into a cytoplasmic Golgi vesicle *(26)*. The membrane of these Golgi vesicles contains viral glycoproteins, and thus the virus obtains the surface glycoproteins to which the immune system will be targeted. The molecular aspects of VZV replication has been reviewed (27).

IMMUNE RESPONSE TO VZV INFECTION

The antibody response to VZV has been measured by several methods with varying degrees of sensitivity since the initial isolation of the virus. In the 1950s and 1960s, the usual procedure was the complement fixation (CF) test. Although most children developed VZV antibody by the second week of illness, CF antibody is present in only approximately 80% of adult populations in which the serostatus would be expected to be >90% positive, indicating that CF antibody is lost over time *(28)*. Thus, the CF test is a poor assay to determine humoral immune status in the general population. Instead, the use of an indirect fluorescence antibody for membrane antigen (FAMA) method that uses VZV-infected cells as a substrate *(29,30)* permits the determination of the humoral immune status in high-risk populations *(31)*. This has been widely used for effective approaches to control of healthcare-associated VZV infection. In addition, enzyme-linked immunosorbent assays (ELISAs) *(32–35)* are available that are at least as sensitive as the immunofluorescence assays *(34)*.

VZV encodes nine glycoproteins, of which gB, gE:gI, and gH:gL are abundantly expressed, are important in virus infectivity, and serve as targets of the immune response (36). The humoral immune responses to these glycoprotein antigens can be assessed by immunoprecipitation reactions between crude radiolabeled VZV antigens *(37)*, by ELISA *(38,39)*, and by latex agglutination (LA) *(40)*. Using these methods, antibody to at least one of the major VZV glycoproteins is easily demonstrable within 1 week after onset of chickenpox. By 2 weeks, antibodies to two more viral glycoproteins are present. The amount of glycoprotein antibody reaches a peak by 4 to 8 weeks, before a gradual decline occurs over the years after the episode of chickenpox *(37)*. The LA assay has a sensitivity and specificity similar to the FAMA assay, and, because it can be performed in minutes and is commercially available, this assay can be particularly helpful to the healthcare epidemiologist *(40,41)*.

Cellular Immunity to VZV

It is well recognized that iatrogenic or natural reduction in cellular immunity is associated with both severe varicella and increased reactivation of latent VZV *(42–47)*. Cellular immunity to VZV has been classically measured by VZV-specific lymphocyte proliferation assays *(48,49)* and by quantitative measures of cytotoxic T lymphocytes *(50,51)*. Susceptible individuals fail to have an *in vitro* response either to crude VZV antigens or to individual VZV protein, but those with prior history of chickenpox develop a cell-mediated immune response to the individual VZV glycoproteins *(48)*. Analyses suggest that VZV proteins gI (ORF68) and immediate-early protein 62 (IE62; ORF62) are important for induction of a protective immune response to VZV *(50)*. Several methods for quantitative T-cell immune assays are available in research laboratories, as described *(52–54)*.

CLINICAL MANIFESTATIONS OF VZV INFECTION

Primary Infection: Varicella

In healthy children, the clinical features of VZV infection present as a mild exanthema often associated with prodromal malaise, pharyngitis, and rhinitis, appearing at a median time of 15 days after exposure (*55*,56). The rash is characterized as a vesicular eruption that emerges in successive crops over the first 3 to 4 days of illness, usually with concomitant exanthema. Each skin vesicle appears on an erythematous base, thereby giving rise to the descriptive "dewdrop on a rose petal." It can be difficult to see this stage of infection because of the rapid progression of the skin changes. A quick progression from stage to stage is characteristic of varicella in the otherwise healthy child and allows it to be distinguished from certain other vesicular eruptions and from varicella in the immunosuppressed person. Within 12 hours, the initial lesion becomes an umbilicated papule, and the crusted area then undergoes leukocyte infiltration and develops into a pustule. This then evolves into a hardened, crusted papule. The exanthema usually begins on the head, quickly progresses to the trunk and arms, and finally appears on the legs. Because of the rapid progression of individual lesions, it is common to see all stages of the exanthema, including macules, vesicles, papules, and crusts, in the same region of the skin. Fever can be expected to be elevated for the first 4 days of the exanthema, and much of the morbidity is associated with the extent of the cutaneous exanthema *(55)*.

Reactivation Infection: Herpes Zoster

In 1900, Head and Campbell (57) described the anatomic pathology of this syndrome and its precise localization to sites of single dermatomes, which permitted a mapping of the cutaneous distribution of the spinal nerves. Immunosenescence *(51)* and stress *(58)* are associated with risk factors for HZ. The clinical morbidity of HZ is determined in large part by the spinal ganglion involved. The most common area of involvement is the trunk, presumably because this is the area of greatest VZV infection during the primary infection, followed by cranial dermatomes and then by cervical and lumbar dermatomes (57,*59*,60). The involvement of cranial nerves is usually associated with the most clinically severe syndromes.

The pain associated with this disease is usually its major complication, although motor incapacitation can also be significant in the symptom complex (61,62). The pain of HZ, called postherpetic neuralgia, occurs with increasing frequency in older persons and can be a significant problem, lasting for many months *(59,63–65)*. This is presumably due to the fact that virus reactivation occurs in the dorsal spinal ganglion, which becomes a site of intense inflammation, often with hemorrhagic necrosis of nerve cells and eventual destruction of portions of the ganglion and with poliomyelitis of posterior spinal columns and leptomeningitis *(66)*. Certainly there is intense inflammation and nerve damage manifested clinically by meningitis and myelitis, with or without paresis of limbs, face, gut, or urinary bladder *(64,66–72)* in some cases. Recently, the role of the IE62 of VZV, which is a major transactivator of viral genes, has been suggested as an activator of brain-derived neurotrophic factor (BDNF). BDNF is involved in the pathogenesis of neuropathic pain, and antibody to IE62 augmented BDNF activity in neurons in an allodynia model in mice *(73)*. If this is confirmed, the role of inflammation in pain induction during HZ could be mediated via IE62-specific VZV immune responses, and this could become an important target area for improving treatment of postherpetic neuralgia.

Historical Complications and Mortality Rates for VZV Infection

Prior to the licensure of VZV vaccine in the United States in March 1995, there were an estimated approximately 11,000 VZV-related hospitalizations annually in the United States, 80% of which occurred in otherwise healthy children, and approximately 100 deaths per year *(74,75)*. The rate of complications was highest for persons <1 year old and >15 years old. Hospitalization rates relating to varicella, calculated from the Michigan Inpatient Database from 1983 to 1987, were 10 per 1,000 cases below age 1 year, 2 per 1,000 for ages 1 to 14 years, 5 per 1,000 for ages 15 to 19 years, and 8 per 1,000 for age 20 years and above. The types of complications that lead to hospitalization in VZV infection have been reviewed *(74,76–78)* and consisted of bacterial superinfection of skin, dehydration, pneumonia, encephalitis, and hepatitis. Bacterial skin infections and bacterial pneumonias occur in the youngest groups; prior to the antibiotic era, severe bacterial infections, including osteomyelitis, were not uncommon in association with varicella. With the development of antibiotics, but prior to the recognition of an association between aspirin and Reye's syndrome *(79)*, the major fatal complications of VZV infection in childhood were encephalitis and Reye's syndrome. Encephalitis occurred in approximately 1 in 11,000 cases in the age group 5 to 14 years and is described below. Reye's syndrome was associated with varicella and formerly occurred at a rate as high as 1 in 6,600 cases in certain regions of the United States *(80)*. With the reduction in occurrence of Reye's syndrome after varicella, VZV-associated mortality decreased from an average of 106 deaths per year in 1973 to 1979, to 57 per year for the period 1982 to 1986 (81) and finally to 43 per year in 1990 to 1994 *(82)*. This reduction also coincided with the prohibition of aspirin use in children with chickenpox and then with the availability of acyclovir and of varicella-zoster immune globulin (VZIG), and undoubtedly each contributed to this reduced mortality. The pre-VZV vaccine age-specific case-fatality ratios were reported as 6.23/100,000 at ages <1 year, 0.75/100,000 at ages 1 to 14 years, 2.72/100,000 at ages 15 to 19 years, and 25.2/100,000 for ages 30 to 49 years (81). Mortality rates in the postvaccine era have fallen dramatically (see "VZV Vaccine," below).

Bacterial Infections

Clusters of severe, occasionally fatal, group A streptococcal infection have historically been associated with varicella, and therefore aggressive management of bacterial infection is warranted *(82,83)*. Although not usually considered a healthcare-associated infection, pyoderma, the most frequently observed bacterial complication of varicella *(77,78)*, should be considered a healthcare-associated infection if it complicates the course of the hospitalized patient with VZV infection. This problem can be minimized by attention to good hygiene, including daily bathing with bacteriostatic soap, trimming of children's fingernails to minimize excoriation of itchy skin, and early recognition and treatment of superinfection.

Respiratory Tract Infection

In addition to the occasional laryngitis and laryngotracheobronchitis that can occur during varicella, bacterial superinfection can also involve the lower respiratory tract, producing pneumonia and bronchitis. Treatment should be directed toward the usual respiratory pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus (78)*. Viral pneumonia is more likely to be a problem in older persons with varicella. In persons of ages 15 to 19 years, varicella-related pneumonia occurred in 1 in 3,000 cases, but in adults, clinically significant disease has been reported in 1 in 375 cases of varicella *(80)*. Asymptomatic pulmonary disease with radiographic changes has been reported to occur in 16% of adults *(84)*.

Mucositis

Varicella is a generalized infection involving all epithelial areas, including mucosal surfaces of respiratory, alimentary, and genitourinary systems. Involvement of the bladder and urethra can result in severe dysuria with functional bladder obstruction. Urinary analgesics and bladder drainage may be required.

Gastrointestinal Complications and Reye's Syndrome

When death occurs during VZV infection, the gastrointestinal system is often involved. Bleeding requires specific attention, particularly in the immunosuppressed subject. In addition, vomiting is not a usual part of the clinical course of this infection, and this symptom should alert the physician to look for abdominal or central nervous system (CNS) complications. As with other viral infections, surgical emergencies such as appendicitis and intussusception can occur during varicella. Mild hepatic involvement is seen in most children with varicella and is usually manifested by asymptomatic elevation of hepatic enzymes, for which no treatment is necessary *(85)*. As noted above, Reye's syndrome was described in association with varicella, often with concomitant use of aspirin in the child older than 5 years *(79,86,87)*. Reye's syndrome and other metabolic diseases must be excluded in any child with varicella in whom there is vomiting and changes in mental status *(88)*.

Encephalitis/Myelitis

VZV is trophic for epithelial tissue, and the CNS is not spared from this trophism, with encephalitis and myelitis appearing as important complications of VZV infection. It is important to note that with both varicella and HZ, neurologic disease can occur either before or after the acute infection *(89,90)* and can even occur with VZV reactivation in the absence of skin eruption, an entity called *zoster sine herpete (91)*. Several CNS syndromes, including aseptic meningitis, polyneuropathy, myelitis, and encephalitis, have been observed in normal persons in association with otherwise occult VZV infection *(92)*. VZV infection involving the CNS is of two types: cerebellar or cerebral complications during varicella and cranial or peripheral nerve complications during HZ. Cerebral complications present equally as either cerebral or cerebellar abnormalities, the latter being more benign *(69,89,90)*. Cerebellar ataxia is the most common syndrome associated with varicella encephalitis in children and is generally a benign entity that is thought to be due to postinfectious demyelination *(89,90,93)*. In older teenagers and adults, encephalitis occurred in approximately 1 in 3,000 cases of varicella *(80)*. Rarer CNS syndromes, such as granulomatous angiitis and stroke-syndromes, have been observed following HZ,

but these are poorly understood syndromes that have not been etiologically related to reactivation of VZV. As with varicella, CNS disease in immunodeficient persons is an important problem in HZ, and progressive CNS disease can occur in persons with HIV infection (*94–96*,97).

Bleeding Disorders

Bleeding disorders can occur during varicella and are due to disseminated intravascular coagulation, vasculitis, or idiopathic thrombocytopenic purpura. The syndrome of purpura fulminans must be treated with supportive therapy and with antibiotic therapy until bacterial sepsis is ruled out. Anaphylactoid purpura can follow an otherwise uncomplicated course of varicella and must be managed with appropriate attention to the status of renal function and the possibility of occult intra-abdominal hemorrhage. Idiopathic thrombocytopenic purpura can occur during active infection or during convalescence and usually responds to treatment with intravenously administered immune globulin *(98)*.

Infection in the Immunocompromised Host

The era of aggressive anticancer chemotherapy and acquired immunodeficiency syndrome has been associated with progressive VZV infection (*4*,*5*,*94–96*,97,*99*,*100*). VZV infection in the immunosuppressed individual is associated with progression of infection from skin to internal organs. Severe skin eruption occurs with or without hemorrhage; there is high fever and spread of virus to visceral organs, producing hepatitis, pneumonitis, pancreatitis, small bowel obstruction, and encephalitis *(100,101)*. A major manifestation of visceral dissemination in addition to fever is severe abdominal and/or back pain *(101,102)*. In the preantiviral era, visceral dissemination occurred in 30% of children with chickenpox while on active cancer therapy *(100)*. Pneumonitis occurred between 3 and 7 days after onset of chickenpox in 25% of such patients; without antiviral therapy, the overall mortality rate in such patients was approximately 7%. In the placebo-controlled trials of antiviral agents in similar patients, a fatal outcome occurred in 17% and visceral dissemination occurred in 52% of the placebo groups (*103*,104,*105*). In addition to viral dissemination, bacterial superinfection was a problem in these patients, and bacteremia accounted for significant morbidity during VZV dissemination *(100)*.

The severity of HZ is less predictable in patients receiving immunosuppressive agents. Historically, VZV will reactivate in 35% to 50% of persons with Hodgkin's disease, and those undergoing bone marrow transplantation during the first year of treatment *(106,107)* and persons undergoing other forms of chemotherapy are at increased risk for zoster *(108,109)*. The rates have not changed with intensive anticancer chemotherapy, and antiviral therapy significantly reduces this morbidity (62). When used early in reactivation, acyclovir can usually eliminate mortality (104,110,*111*).

PATHOGENESIS OF VZV INFECTION AND DISEASE

Pathogenesis of Chickenpox

The events that lead to the clinical syndrome of chickenpox are thought to be similar to those that were first proposed by Fenner to explain an animal model of viral exanthem *(112)*. In this schema, virus enters the host from an exogenous source and spreads locally to a site of initial augmentation and then, by a primary viremia, to a location of subsequent viral growth. After several days of replication, the virus then spreads by means of a second viremia to the skin and mucosal surfaces, where the exanthema and enanthema occur *(112)*. The entire time course for such virus replication and spread varies from 10 to 21 days, the range observed for the incubation period of varicella (*55*,56,*113*). The existence of the primary viremia has not been documented, but the secondary viremia is well described *(114)*. Virus spreads to endothelial cells of the skin and then infects the basal and deep malpighian layers of the epidermis. The role of T-cell tropism of VZV in the transmission of virus to skin and nerve ganglia has been proposed *(115)*. In addition, the VZV glycoprotein E contains an N-terminal region important for binding to the insulin-degrading enzyme (IDE) of cells in skin and other organs and glycoprotein E/IDE could be the critical ligand—receptor necessary for spread to the skin (36,116). Once in the skin, ballooning degeneration of these cells occurs and local collection of extracellular edema results in unilocular and multilocular vesicles (*2*,12). In addition to swelling of infected cells, multinucleation occurs, forming the basis for the Tzanck assay, and condensation of viral proteins within the nuclei results in intranuclear inclusions.

Pathogenesis of Herpes Zoster

The two important events in the pathogenesis of HZ are the development of latent VZV infection in dorsal spinal ganglia following primary VZV infection *(18,117,118)* and subsequent reactivation of latent VZV with disruption of ganglionic structure and spread to the areas distributed by this spinal nerve *(71,119)*. The virus is thought to reactivate in either the ganglion cell or the perineuronal cells *(120)*; when reactivation occurs, the virus then spreads within the ganglion and within the distribution of that spinal nerve. Because of VZV tropism for nervous tissue, in persons with profound immunodeficiency, VZV can spread transsynaptically within specific neuronal systems, producing necrosis of brain *(121)*. In addition, recent studies have shown that VZV is present in saliva of HZ patients *(25)*, and this is associated with acute stress, as has been shown in astronauts during space flight *(58)*. As noted above, the immune system plays a role in pathogenesis as suggested by an intense inflammation at the initial site of virus reactivation *(66)* and a resultant tissue reaction that leads to nerve damage with pain syndrome and to damage in the epidermal structures with the functional abnormalities *(68)*. The hypothesis that an IE62-specific antibody response induces BDNF and leads to the neuropathic pain syndrome remains to be confirmed *(73)*.

Of concern for healthcare-associated infection control, a generalized vesicular rash appears during the first week of HZ in approximately 10% of normal adults (*59*,60,*122*), suggesting that failure to control the virus at the initial site of reactivation permits spread of virus, much as in chickenpox. This rash consists of a single crop of vesicles that lacks the polymorphism of chickenpox, unless continued dissemination occurs *(123)*. Furthermore, in

recipients of marrow transplantation, disseminated vesicular exanthema without primary dermatomal skin eruption can follow reactivation *(106)*.

DIAGNOSIS OF VZV INFECTION AND IMMUNITY

Diagnosis by Direct Antigen or by DNA Detection

VZV infection can be diagnosed reliably on clinical grounds alone when there is a history of close exposure to chickenpox or HZ in the past 10 to 21 days and a vesicular eruption consistent with chickenpox (Table 43-1). However, in many situations, particularly those involving immunocompromised persons, no clear historical data support the diagnosis. In this situation, since treatment will be of paramount importance, laboratory diagnosis is necessary. For HZ, the clinical appearance of rash consistent with HZ on clinical grounds can be confirmed by polymerase chain reaction (PCR) in approximately 75%, and zosteriform herpes simplex infection occurs in 3% to 4% (61).

The earliest method for diagnosis was light microscopic examination of the vesicle contents to demonstrate multinucleated giant cells when stained with Wright–Giemsa stain. This method, called a Tzanck prep, has now been superseded by a fluorescent antigen detection assay, which is available in a commercial kit for confirmation of the diagnosis. This assay consists of a direct fluorescent antigen stain of samples of cells that are scraped from the base of a vesicle and dried onto a glass slide. Rapid diagnosis by antigen detection can also be performed on punch biopsy specimens of vesicular lesions. These tests take only 1 to 2 hours and can quickly differentiate between vesicular rashes caused by VZV or herpes simplex virus infection.

The most specific method for diagnosis of VZV infection is by DNA hybridization techniques or by PCR (124). PCR is the more sensitive assay and can discriminate between vaccine strain VZV and wild clades of VZV, and this is now the preferred tool for the healthcare epidemiologist, once the diagnosis is established by rapid antigen detection using VZV-specific monoclonal antibodies.

TABLE 43-1

Diagnosis of Varicella-Zoster Virus (VZV) Infection

History of exposure to varicella or herpes zoster in past 3 wk
Physical examination of rash indicates
For varicella: lesions in all stages of development from vesicle on red base to umbilicated pustule to crusted lesion
For zoster: dermatome distribution of lesions
VZV-antigen detection using lesion scraping
Culture of vesicle or PCR for VZV (optional if antigen-positive)
Antibody assay on acute/convalescent paired sera (optional if antigen-, culture-, or PCR-positive)

PCR, polymerase chain reaction.

Viral Culture for Isolation of VZV

For confirmation of laboratory diagnosis or to obtain the virus strain for research purposes, VZV infection is isolated in cell culture (13). Vesicular fluid is collected in sterile capillary tubes or tuberculin syringes, which are subsequently evacuated into culture medium. The medium is then layered over cultured cells, and in 3 to 5 days, CPE is visible in the monolayer. In human fibroblast cells, the CPE consists of multiple foci of swollen, rounded refractive cells. A definitive diagnosis of VZV infection is made by immunostaining of the infected monolayer with a VZV-specific monoclonal antibody.

Detection of Susceptibility to VZV

The simplest method for reliably determining susceptibility to varicella is to take a history for previous chickenpox. A positive history from adults correlates with serologic confirmation 97% to 99% of the time *(125–127)*. A positive history of previous chickenpox in a child with recent household VZV exposure is associated with subsequent disease in only 7% *(55)*. Conversely, a negative history from an adult does not correlate with serostatus in 72% to 93% *(125–128)*. Thus, serologic tests of immunity are most useful in adults with a negative history of chicken pox. The FAMA, radioimmunoassay, ELISA, LA, and hemagglutination antibody assays, because they are sufficiently sensitive, are reliable methods for demonstration of prior infection with VZV *(33,34,38)*. For this reason, these tests are widely used as presumptive evidence of immunity following exposure to chickenpox, for preemployment evaluation, or for follow-up after vaccination. It should be noted that these assays are not reliable in persons who have received blood products and who might have acquired passive antibody. As mentioned above, the CF test, because it is an insensitive test for antibody, should not be used for determination of prior infection. The immediate availability of the radioimmunoassay, ELISA, or FAMA assays can be problematic when the question of susceptibility must be determined quickly, as is usually the case in matters relating to healthcare-associated infection. The LA assay is commercially available *(40)* and reliably determines immune status to VZV *(40,41)*. A VZV skin test, which has shown promise as a test of susceptibility, is not generally available *(129,130)*.

EPIDEMIOLOGY OF VZV INFECTIONS

Transmission and Communicability of VZV

Early observations suggested that chickenpox was an airborne disease *(131,132)*, but this was subsequently confirmed using sophisticated methods of air-flow analysis *(133,134)*. The spread of infectious VZV from a person with chickenpox is by air droplets from nasopharyngeal secretions, which usually requires face-to-face exposure but can also occur via air currents to susceptible individuals without direct contact *(133,134)*. For HZ, the accumulation of VZV in hospital rooms *(135)* and the presence of VZV in saliva of HZ patients *(25)* may play a role in spread of infection.

The period of infectivity is generally considered to be between 48 hours prior to exanthema and 4 days after exanthema, a range derived from published observations

of chickenpox in cohorts of children quarantined for other infections. In this setting, it was rare to observe spread of chickenpox from a child who exposed other ward-mates >2 days prior to the onset of rash (56,*136*). Although there is a single report that infectivity could occur 4 days prior to exanthema *(137)*, this case is suspect and would be the exception to the common experience, which suggests that exposure for >1 day prior to exanthema is unlikely to be infectious (56,*136*). The usual recommendation is to consider the period of infectivity as 48 hours prior to rash until the skin lesions are crusted.

HZ can cause spread of VZV by direct contact with lesions or by exposure to airborne infectious material *(25)*. The incubation period for chickenpox following exposure to zoster *(113)* is the same as that following exposure to varicella (56) (median time 15 days, range 10–21 days). However, the clinical varicella attack rate following household HZ is only 25% among history-negative children *(113)*, compared to an attack rate of 87% following exposure to household chickenpox *(55)*.

Age-Specific Incidence of VZV Infection

Postvaccine era incidence of varicella in the United States is not known with certainty, but using index counties as representative, the number of cases and the complications requiring hospitalization have been reduced by 80% (138). Historically, the estimated incidence of chickenpox in the United States in the prevaccine era was based on the size of the birth cohort and on the assumption that nearly everyone developed chickenpox over a lifetime. Thus, for example, with approximately 4 million births in the United States annually, approximately 3.7 million cases of varicella occurred each year *(74)*. More than 90% of all cases of varicella occurred in persons under the age of 15 years, and nearly half of all cases in children occurred between the ages of 5 and 9 years. Age-specific incidence data were reported for the years 1980 to 1990 from the National Health Interview Survey, indicating that 33% of cases occurred in preschool children of ages 1 to 4 years, in whom the incidence was 82.2/1,000/year (*74*,81). In the age group 5 to 9 years, the incidence was estimated to be 91.1/1,000/year *(74)*.

In the pre-HZ vaccine era, it is estimated that there were approximately 1,000,000 cases of HZ in the United States per year (62). Based on public records, the incidence of HZ is constant for each age group through midadulthood. Thereafter, the incidence of zoster increased with age such that persons in their 80s have a 1 in 100 chance per year of developing zoster *(65)*. When adjusted for prior occurrence of varicella, there is a known association of HZ in children who have acquired varicella prior to their first year of life *(139)*. In the VZV vaccine era, with less circulating wild-type VZV, there is the potential for increased rates of HZ in the non-HZ-vaccine immunized adult population (62,*140*), and it remains to be determined whether this is a real concern that would stimulate wider use of the HZ vaccine.

VARICELLA-ZOSTER VACCINE

Background

The VZV vaccine is the single most important tool in prevention and control of healthcare-associated VZV infection. The live attenuated VZV vaccine was developed by Takahashi in 1974 *(141)* and was prepared by attenuation of a VZV isolate (Oka strain) in human embryonic cells and then in human diploid fibroblasts (142). The vaccine virus, which is a clade 2 virus, is biologically different from wild VZV in its growth characteristics, DNA restriction enzyme profile *(143,144)*, and single nucleotide polymorphisms (23). The Oka-strain vaccine was used extensively in Japan in healthy children and was effective for the prevention of varicella after exposure and for curtailment of outbreaks of VZV infection prior to its near-world-wide approval *(141,145)*.

Recommended use of VZV vaccine

A live attenuated VZV vaccine (Varivax) was approved in the United States in 1995 (146). Vaccine is administered at any routine visit at or after age of 12 months for susceptible children, that is, those without prior history of prior chickenpox, and susceptible persons ≥13 years old should receive two doses at least 4 weeks apart *(147)*. The vaccine is particularly important in chickenpox history-negative teens and adults, especially college students, healthcare and daycare workers, prisoners, military recruits, nonpregnant women of childbearing age, and international travelers. For adolescent and adult patients, serologic testing for VZV antibody is usually cost effective prior to vaccination *(148,149)*. The vaccine is not recommended for infants younger than 1 year, for immunosuppressed persons, for those receiving salicylate therapy, for pregnant women, or for persons allergic to components of the vaccine, including neomycin, gelatin, and monosodium glutamate *(147)*. Severe VZV vaccine infection has been observed in immunodeficient children *(94,96,97)*. Despite this, VZV vaccine can be administered in HIV-infected children *(150)*, and, because of the likely severity of chickenpox in children with acquired immunodeficiency syndrome, the vaccine is recommended for consideration on a case-by-case basis for asymptomatic or mildly symptomatic patients with age-specific CD4 T-lymphocyte percentages of 25% or more. Other immunosuppressed individuals such as solid organ transplant recipients who are on continuous iatrogenic immunosuppression are not recommended for receipt of VZV vaccine, and it is unlikely that these patients will have an effective immune response to the vaccine *(151)*. However, in children with leukemia studied in the United States, vaccination given to those in remission produced a 5-year seropositivity of 70% and an attack rate of chickenpox after household exposure to VZV of only 14% *(152,153)*.

The protection of at-risk patients from varicella exposure requires use of VZV vaccine in healthcare workers, and the safe use of this vaccine in this population has been described *(21)*. For healthcare workers, screening for prior VZV infection should be done at the time of employment, and seronegative persons should receive the two-dose VZV vaccine immunization schedule. For patients about to undergo intensive immunosuppression, the healthy family members who have no history of VZV infection or who are seronegative for VZV antibody should be vaccinated. For severely immunocompromised patients, for example, hematopoietic cell transplant recipients, the recommendation states that ideally patients should not have contact with vaccinees at times of severe immunosuppression until ≥4 weeks after completion of vaccine doses *(154)*.

However, in practice, the more important concern is that the patient should not have contact with any vaccinee who experiences a rash after vaccination. At present, transmission from a healthcare worker to a patient has not been documented, and vaccine virus is susceptible to acyclovir which many immunosuppressed patients receive during intense immunosuppression. Thus, most centers allow the employee to start work prior to the completion of VZV immunization as long as they will not have contact with immunosuppressed patients and only when there is no postvaccine rash.

The effectiveness of the VZV vaccine has been reported in long-term follow-up studies (138,*145*,*155*,*156*). A single dose of vaccine results in seroconversion in 97% of susceptible children 1 to 12 years old, in 79% of children 13 to 17 years old, and in 82% of adults. Two doses of vaccine result in seroconversion in 94% of adults *(145,155,156)*. Vaccine effectiveness in preventing chickenpox is approximately 85% and the effectiveness for preventing severe disease is approximately 97%. As noted above, the number of chicken pox cases and hospitalizations has decreased between 1995 and 2000 by approximately 80%, based on analysis of representative counties in the United States (138). Breakthrough varicella occurs in approximately 20% of vaccinees after household exposure, and the risk factors for such breakthrough are close contact with varicella, age ≤14 months at vaccination, and receipt of low titer vaccine *(153)*. In this regard, subjects with low serological immune response to the vaccine appear to reactivate the vaccine virus, resulting in persistent increasing serum antibody titers, suggesting that the vaccine virus persisted *in vivo* and reactivates in the presence of low antibody titers *(152)*. If this is true, the vaccination should result in long-term immunity.

HZ due to vaccine strain virus is very rare but does occur (97,*157*). Chickenpox has been contracted in a child 5 years of age after exposure to a sibling who developed zoster 5 months after immunization with VZV vaccine *(158)*. The inadvertent exposure of susceptible women to VZV vaccine during pregnancy has been monitored since 1995 in the United States, and to date, there has been no congenital varicella syndrome or other VZV-specific birth defects in this group *(159)*. Other aspects of VZV vaccine have recently been reviewed *(160)*.

HERPES ZOSTER VACCINE

Risk for developing HZ is thought to be related, not to low levels of anti-VZV antibody but to inadequate cellular immunity to VZV (61,*161*). Cellular immunity to VZV increases with age after primary VZV infection until age approximately 40 years and then lessens with advancing age *(51)*, consistent with the increased rate of HZ with advancing age *(162)*. It had been shown that persons of age >60 years could respond to VZV vaccine *(163)*, paving the way for a large prospective placebo-controlled study showing that a modified Oka-strain-based VZV vaccine (Zostavax, Merck Inc.), with approximately 14-fold increase in plaque-forming units, would prevent HZ and postherpetic neuralgia (61). This study of 38,546 adults of age >60 years showed that the HZ vaccine reduced the incidence of HZ by 51.3% and reduced the incidence of postherpetic neuralgia by 66.5%. Based on these data, as well as on a thorough analysis of benefit, including economic impact of HZ, the HZ vaccine was licensed in the United States in 2006 (62).

The HZ vaccine is recommended for use in all persons ≥60 years old with no other contraindications (62). The vaccine is given as 0.65 mL/dose subcutaneously in the deltoid region of the upper arm. Contraindications include (a) allergy to components of the vaccine, for example, gelatin and neomycin, (b) immunocompromised persons (see discussion in Ref. 62), (c) pregnant women, (d) concomitant severe acute illness, and (e) use of antiviral medications active against VZV (e.g., acyclovir, famciclovir, and valacyclovir), which cannot be safely stopped for 24 hours prior to vaccination and for 14 days thereafter. A prior history of HZ is not relevant, since the HZ vaccine is immunogenic and safe in those with a prior history of HZ *(164)*. The availability of the HZ vaccine is a new tool for control of VZV spread by HZ exposure and a means of lessening this disease in the older population *(165)*. The HZ vaccine is likely to be approved for use in younger populations.

PREVENTION AND CONTROL OF HEALTHCARE-ASSOCIATED VZV INFECTION

Employee Policy Regarding VZV Infection

The control of healthcare-associated VZV infection begins with the development of a rational employment policy for the healthcare worker (Table 43-2). It cannot be overemphasized that healthcare workers are a significant source of exposure to primary healthcare-associated VZV infection *(125,128,166–168)*; therefore, one of the first lines

TABLE 43-2

Varicella-Zoster Virus (VZV) Policy for Healthcare Workers

Determine history of prior varicella at initial intake interview
Obtain serologic information of immune status for persons with negative or unknown history of varicella and consider such workers susceptible
Seronegative healthcare workers should receive VZV vaccine (alternatively, vaccinate all persons with negative or unknown history of varicella)
Unvaccinated susceptible employees should avoid contact with patients having varicella or herpes zoster
Susceptible or recently vaccinated healthcare workers must report any VZV exposure to the infection control department
After valid exposure:
Susceptible, unvaccinated workers must be furloughed away from direct patient care from days 10 to 21 after exposure; consider administration of VZV vaccine
Recently vaccinated workers can be assigned to patient care responsibility if (a) VZV-seropositive upon retesting and (b) seronegative workers can be retested 5–6 d later and, if still seronegative, furloughed away from direct patient care from days 10 to 21 after exposure

of protection of susceptible patient populations is to minimize spread of infection from hospital workers. This begins with the initial employment history and physical examination, which should include history regarding prior chickenpox *(128)*. If this history is negative, appropriate serologic testing should be performed to confirm antibody status if the employee will be involved in interactions with patients. VZV-seropositive employees will not be at risk for primary VZV infection. VZV history-negative/seronegative employees who receive VZV vaccine should be restricted from patient responsibilities involving VZV-infected individuals and should be counseled to recognize VZV infection and the appropriate isolation methods.

In the past, the practice of furloughing healthcare workers known to be susceptible to VZV, after exposure to this virus, was less than satisfactory because of both cost to the healthcare institution *(84)* and lost time for the employee. With the approval of the VZV vaccine in the United States, there is an opportunity to reduce the potential for employee-mediated healthcare-associated VZV infection. Healthcare institutions are advised to consider the use of the VZV vaccine for control of employee-related healthcare-associated infection (81). In addition to healthy children aged 12 months to 12 years, the vaccine is recommended for healthy adolescents and adults with no prior history of chickenpox (Table 43-3). The vaccine is given in two doses of 0.5 mL subcutaneously 4 to 8 weeks apart. It is recommended for all such healthcare workers, especially those having contact with susceptible children, pregnant women, and immunocompromised individuals.

In the policy recommendation, it is noted that individual institutional policies should be developed in regard to the use of the VZV vaccine, and these will need to consider certain factors about which there is imprecise information. In addition, 5.5% of adolescents and adults develop a rash after the first injection, and there is the rare instance of transmission of virus from healthy vaccinee to susceptible household contact. Hence, it is recommended that recent vaccinees who develop a rash following vaccination avoid contact with immunosuppressed patients. As a practical matter, recent vaccines with or without a rash should avoid contact with high-risk persons (e.g., newborns, pregnant women, and immunocompromised persons). In addition, testing for seroconversion at the completion of immunization is not recommended, because approximately 99% will be seropositive; however, consideration should be given to testing vaccinated healthcare workers at the time of a subsequent VZV exposure, since detection of antibody could become a method for identifying employees who are at minimum risk for breakthrough infection. It should be noted that breakthrough cases of varicella in vaccinated persons are mild, but the rate of transmission of disease from vaccinees who develop varicella is not well studied (81). For this reason, daily monitoring for rash while employees continue at work is suggested for vaccinated healthcare workers, following VZV exposure (81). In addition, VZV serostatus should be determined by LA assay, and seronegative workers should be retested 5 to 6 days later, prior to the 10th day postexposure; if the worker is still seronegative, he or she should be furloughed away from direct patient care during days 10 to 21 postexposure. VZV-seropositive healthcare workers can be assigned patient-care duties but should be monitored daily for rash and removed from such duties if breakthrough rash appears (81). For susceptible healthcare workers who have been exposed to varicella, removal from patient contact is recommended beginning on the 10th day following initial exposure and continuing until day 21 after the last exposure. Although postexposure vaccination has been shown to have a 90% protective effect in children vaccinated within 3 days of close exposure, vaccination is not recommended as a means of limiting healthcare-associated VZV infection after a healthcare worker exposure (81).

TABLE 43-3

Indication for VZV Vaccination[a]

Healthy children aged 12 mo to 12 yr
Healthcare workers
Persons working in day care or pediatric institutions
College students
Prisoners
Military recruits
Nonpregnant women of childbearing age
International travelers

[a]Vaccine (Varivax, Merck) recommended for healthy children over age 12 mo and for healthy adolescents and adults with no prior history of varicella.

INFECTION CONTROL OF VZV INFECTION IN HOSPITALIZED PATIENTS

Initial Containment Response: Isolation Precautions

Prior to the VZV vaccine, pediatric patients, especially those under the age of 5 years, formed a population in which most were susceptible to chickenpox, and VZV infections spread and endured over many months within an institution *(137)*. When immunocompromised pediatric patients existed in the same setting, the need was heightened for control of such healthcare-associated infections *(169,170)*. Guidelines for prevention and control of such infections have been published, and there is advice for managing such problems (81,*171–173*). However, with the use of VZV vaccine, the pediatric inpatient population >1 years old should be immune to VZV, and such institutional outbreaks could be a thing of the past.

If the exposure is from a patient, the patient should be discharged if possible. If this is not possible, then for patients with either varicella or disseminated HZ or for immunosuppressed patients with localized HZ, isolation precautions designed to prevent spread of infection by both air and direct contact are recommended. Optimally, this will consist of a private room with negative air pressure relative to the corridor *(171)*. Immunocompromised individuals with HZ are unlikely to disseminate infection after 24 hours of treatment with acyclovir (110), and for that reason, continued strict isolation is not necessary for this subgroup. The precaution guidelines should be posted on the door to restrict entry for susceptible persons.

Immunocompetent patients with localized zoster should be placed on precautions to prevent transmission by direct or indirect contact with infectious material/drainage from an infected body site. For varicella and disseminated HZ, isolation should remain in effect until all skin lesions are crusted. For localized HZ, Contact Precautions should continue until all drainage from the lesions has ceased.

Secondary Response: Control of Extended Infection

After initiating control of the source of VZV infection, the problem then is to quickly access three types of information: (a) the nature of the VZV exposure and whether this exposure is likely to result in secondary infections, (b) a list of susceptibility of the exposed patients, and (c) a list of patients at risk for life-threatening VZV-related complications. The types of exposures that are likely to lead to varicella transmission are those involving close contact. A close contact is defined as one in which there is >1 hour in the same area indoors with the infected source (e.g., exposure in the same two to four bed hospital room or indoor play area). However, even <1 hour of exposure should be taken seriously when exposure is direct face-to-face contact with the infectious person (81). As noted earlier (see "Detection of Susceptibility to VZV," above), positive or negative history of prior varicella can be highly reliable in the first assessment of who is susceptible. Pediatric admission records should indicate whether the exposed patients have received the VZV vaccine. Serologic tools can be used to clarify the status of those with ambiguous history. Thus, the initial step is to define the hospital area(s) in which a definite VZV exposure occurred and then to focus on which patients in this area are at risk for infection. Finally, among these exposed patients, immunosuppressed individuals are considered to be at high risk for VZV-related complications, and these persons should be given separate attention (see below).

Once this information is available, those susceptible patients who are exposed should be discharged if possible. Those who cannot be discharged should be isolated beginning 10 days from initial exposure through 21 days from last exposure. Those who must remain in the hospital who were not exposed to varicella should be placed in a cohort to keep them away from the VZV-exposed susceptible patients in order to prevent further spread of infection. It has been shown that the use of the VZV vaccination in this situation can stop an extended round of varicella in a pediatric setting *(174)*. At present, however, except for use in children with leukemia under a special protocol, the vaccine is only recommended for use in healthy individuals, and hence this modality is not recommended for healthcare-associated control of VZV in US institutions.

Approach to Protection of Immunocompromised Persons

An institution's policy regarding healthcare-associated spread of VZV infection is designed in large part to minimize the possibility of immunocompromised persons becoming infected with VZV in the hospital. Those at risk are defined as patients who have primary and acquired immunodeficiency disorders, have neoplastic diseases, have recently received immunosuppressive treatment, are premature newborns of varicella-susceptible mothers, or are premature infants born at <28 weeks' gestation or weighing <1,000 g (81). As noted above, these individuals should receive special attention in the form of antiviral prevention. This type of prevention should begin before there is a known problem. The clinic staff and inpatient personnel should become familiar with and enforce visiting policy that minimizes the exogenous introduction of infection into the patient areas. As mentioned, the employee policy should serve to protect the patients from exposure to VZV infection. In addition to employee vaccination, the children with acute leukemia should have access to VZV vaccine, and the infection control office should work with the pediatric hematology clinic to provide vaccination for appropriate clinic patients.

Of greatest concern, of course, are those who are both susceptible and immunocompromised. In the past, these children were provided exogenous antibody to VZV in the form of VZIG, an immune globulin prepared from pooled blood plasma containing high antibody titers to VZV *(28)*. Since VZIG is not generally available, antiviral chemotherapy with acyclovir or valacyclovir could be the only practically available approach for VZV prophylaxis in susceptible high-risk patients after exposure to VZV. Although not approved for this use, acyclovir has been shown to significantly decrease, but not completely eliminate chickenpox when used in healthy children after household exposure *(175,176)* or in the setting of renal transplantation *(177)* or leukemia *(178)*. A cautionary note is made because of a case of fatal VZV infection that occurred weeks after prophylactic acyclovir was stopped in one immunosuppressed child *(179)*. Thus, if there is a decision to use prophylactic antiviral chemotherapy, this should be made on a case-by-case basis, and with the recognition that VZV can remain inactive and then reappear after the suppressive therapy is stopped. When used for this purpose, acyclovir is given at an oral dose of 20 mg/kg (not to exceed 800 mg per dose) four times daily and valacyclovir is given at an oral dose of 1 g three times daily if body weight is >40 kg.

Management of Adult Patients with VZV Exposure

More than 95% of all adults have been infected with VZV, and these persons do not develop disease after repeat exposure to the virus *(125–127)*. Nevertheless, it has been shown by Arvin et al. *(7)* that normal adults frequently are reinfected by VZV after exposure to chickenpox. But, despite this finding, recurrent varicella is sufficiently rare that for practical purposes, it need not be considered in the construction of guidelines for management of healthcare-associated VZV. Susceptible adults do develop chickenpox, provide the source for unexpected epidemics, and are at increased risk for life-threatening complications. The susceptible individual needs to be identified and appropriately managed. One population that is at risk for varicella is adults from subtropical climates, where varicella can occur well into adult life *(180,181)*. Since immigrants from these areas can be found in health-related employment, attention should be addressed to any such person in order to confirm varicella immunity and provide VZV vaccine before that person has contact with high-risk patients.

With the availability of the VZV vaccine, vaccination is recommended for all healthy persons after 12 years of age

who do not have a reliable history of chickenpox at the time of any routine healthcare visit. As noted for healthcare workers, the vaccine is given to adolescents and adults in two doses, subcutaneously, 4 to 8 weeks apart. Vaccination is particularly recommended for susceptible persons (a) who live or work in settings with high transmission of VZV, including day care and institutional settings; (b) who live or work in environments in which VZV transmission might occur, including college dormitories, correctional institutions, and the military; (c) who are nonpregnant women of childbearing age and who will avoid pregnancy for 1 month following each dose of vaccine; and (d) who are international travelers likely to have close contact with local populations (81). If acyclovir is used prophylactically in adults, the VZV vaccine should not be given until after the acyclovir is stopped. As noted with children, the vaccine should not be given to persons with neomycin allergy or to individuals with immunodeficiencies. If the vaccine is to be used for adults for whom there is an immunodeficient child in the family, then the same precautions exist as for hospital employees, and the adult should not stay with the child for the first week postvaccination.

MANAGEMENT OF THE PREGNANT WOMAN AFTER VZV EXPOSURE

Congenital Varicella Syndrome

The congenital varicella syndrome was first described in 1947, and <100 cases have been described *(76,182–185)*. The syndrome consists of low birth weight, cutaneous scarring, limb hypoplasia, microcephaly, cortical atrophy of brain, chorioretinitis, and cataracts. Intrauterine VZV infection can occur following maternal varicella in all trimesters of gestation, but teratogenic or developmental damage results from infection prior to the third trimester *(186,187)*. The rate of transplacental infection is 24%, but clinically apparent disease occurs in only about 2% to 3% after maternal varicella in early pregnancy *(76,182,187)*.

Perinatal VZV Infection

Perinatal infection can occur in late third trimester chickenpox, and newborns are considered at risk if chickenpox occurs in the mother from 5 days before to 2 days after delivery (81,*187*,*188*). The precise risk of severe disease is not known, and the initial report *(188)*, which showed a mortality rate of 31%, is probably inflated compared to the risk in a modern neonatal intensive care unit. The risk of severe VZV infection appears to be a function of the presence of transplacental maternal antibody to VZV in the baby *(186,189)*. In the absence of VZIG, acyclovir prophylaxis should be considered, but the best reported result is with the combination of immunoglobulin and acyclovir *(190)*. Unlike varicella exposure of the neonate, maternal HZ is not a risk since it occurs only in the setting of prior maternal antibody which appears to be protective *(187)*.

Approach to the Pregnant Woman Exposed to VZV

A pregnant woman with significant exposure to VZV infection should be evaluated for susceptibility to VZV with an appropriate antibody assay, if she has a negative or unknown history of varicella as a child. But congenital infection is rare, and the woman should be reassured. The most significant risk is to the health of the mother rather than to the infant *(187)*, and therefore, guidance on management should be directed toward protecting the health of the mother.

ACKNOWLEDGMENT

The author acknowledges the assistance of Ms. Valerie A. Gonzales in the preparation of this manuscript.

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CHAPTER 44

Herpes Simplex Virus

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Herpes simplex virus (HSV), a common cause of morbidity among humans, has two distinct serotypes: HSV-1 and HSV-2. HSV-1 primarily causes cold sores, with oral or labial lesions being the most common manifestation. HSV-1 is presumably transmitted by contact with infected saliva or cutaneous lesions. HSV-2 is found predominantly in the genital areas and causes vesicular lesions with red borders that often appear in crops or clusters with satellite lesions. Both oral and genital lesions are often swollen and painful but eventually crust over and heal. HSV-2 transmission can be reduced with the use of condoms.

Newborns under 1 month of age are especially susceptible, because infection of the skin and mucous membranes by herpes simplex leads to viremia with viral dissemination to multiple organs, including the central nervous system. Newborns usually become infected at birth via contact with maternal cervical—vaginal secretions infected with HSV-2, but occasionally become infected via contact with infected personnel or contaminated equipment in the nursery.

In adults, HSV usually causes an asymptomatic infection, but occasionally HSV-1, or less commonly HSV-2, invades the central nervous system, causing encephalitis. This occurs when virus in the upper respiratory tract migrates along the olfactory nerve through the cribriform plate, most typically into the frontal or temporal lobes. The most common manifestations of herpes infection, however, are cutaneous, mucocutaneous, or oculocutaneous lesions.

BIOLOGY OF HERPES SIMPLEX VIRUS

HSV particles contain a double-stranded DNA genome enclosed in a nucleocapsid surrounded by enveloped glycoprotein. HSV may survive in humans for decades in spite of circulating neutralizing antibodies. After a primary infection, the virus usually remains latent in neuroganglion cells. Reactivation from these cells, with or without symptoms, is the hallmark of HSV infection. Reactivation of HSV may occur frequently over time and can be induced by stimuli noxious to the skin, such as ultraviolet radiation.

EPIDEMIOLOGY OF HERPES SIMPLEX

The prevalence of HSV infections among humans has been determined by virologic and seroepidemiologic surveys. Based on serologic surveys of adults (antibodies to either HSV-1, HSV-2, or both), seroprevalence ranges from 15% to 100% *(1–5)*. Seroprevalence is associated with many variables including socioeconomic status, crowded living conditions, age, geographic location, and sexual practices. Surveys using viral isolation from healthy individuals without HSV disease, to determine prevalence of HSV infection, have found that between 1% and 20% of asymptomatic children and adults are shedding HSV-1 in saliva at any given time. However, in populations in which individuals are cared for or live together for a long time, the prevalence may increase to over 30% *(6)*.

Immunocompromised patients, particularly those with acquired immunodeficiency syndrome or receiving a stem cell or solid organ transplant, will shed HSV either symptomatically or asymptomatically following infection. Estimates on the frequency of asymptomatic infection and seropositive patients after transplantation range up to 80%.

Between 0.1% and 7.3% of men attending sexually transmissible diseases clinics have HSV-2 infections *(7)*. In pregnant women from lower socioeconomic groups, the cumulative incidence of asymptomatic shedding varies between 1% and 4% *(8)*. The cumulative incidence is significantly higher in high-risk populations such as prostitutes, who may have a cumulative incidence up to 12% *(9)*. Asymptomatic genital shedding of HSV-2 is intermittent, and serial studies have found that the virus is not persistently present and varies from individual to individual.

HSV TRANSMISSION IN HOSPITALS

Prevalence of Herpes Simplex Shedding Among Hospital Personnel and Adult and Pediatric Patients

No studies have addressed the prevalence of asymptomatic shedding of HSV among hospitalized adults or children. Among institutionalized children, however, one

6-year study that used serologic testing and viral isolation at a children's home found that, of 70 initially seronegative children, 8 (11.4%) had a primary infection while at the home and 6 were symptomatic *(6)*. In another study in Australia, in a home for children under age 3 years, 29 of 43 seronegative children developed HSV antibodies over 1 year *(10)*. The prevalence of HSV infections among any hospitalized group will depend highly on whether the patients are immunocompromised and on socioeconomic background, the presence of risk factors for HSV, and the history of previous HSV infection. Hence, for practical purposes, hospital personnel should assume that all patients are potentially infectious for HSV.

In 1980, Hatherley and coworkers (11) studied the frequency of asymptomatic HSV excretion in the saliva of 384 asymptomatic members of the staff of an obstetric hospital. HSV was isolated from 10% of the employees.

Healthcare-Associated HSV Transmission

HSV transmission in the hospital is an infrequent but serious problem when it occurs. Documented hospital transmission of HSV has been confirmed in numerous studies, with the virus being transmitted from patient to patient, from personnel to patient, and from patient to personnel.

The patients at highest risk for healthcare-associated acquisition of HSV are infants <30 days of age (see Chapter 52). Several studies have documented acquisition of HSV by hospitalized infants, occasionally with fatal outcomes. The first cluster of cases was reported in 1975 by Francis and colleagues (12), who identified four fatal infections that occurred over a 2-month period in a pediatric intensive care unit. Each patient was infected with HSV-2.

In the late 1970s, DNA fingerprinting of HSV became possible. Halperin and associates (13) first determined that each epidemiologically unrelated strain had a different endonuclease pattern and thatepidemiologically related strains had identical DNA fingerprints. This technique has been applied to a number of outbreaks of HSV infection in the hospital and is a potent epidemiologic tool to confirm HSV transmission.

Infants who acquire HSV infection during the first month of life always do so postnatally. The usual source of acquisition is the maternal genital tract, although infants may acquire HSV-1 from labial lesions of either parent; occasionally, infections have been acquired by nursing infants from breast lesions. In 1978, Linnemann and coworkers (14) observed two infants in a nursery infected within 1 month with HSV-1. The two isolates had identical DNA fingerprints. The source of infection for one child was the father's labial lesion, implying that the second child had acquired HSV virus via horizontal transmission in the nursery.

In 1983, Hammerberg and colleagues (15) described an HSV outbreak in a nursery in which four infants acquired HSV-1 infection over 10 days. DNA patterns of each of the four isolates were identical, indicating the strong possibility of horizontal transmission. In 1984, Van Dyke and Spector (16) reported a case of apparent transmission of HSV-1 from a physician with a labial lesion to an infant who had received endotracheal suctioning for meconium aspiration. This was the first reported case of transmission of HSV from hospital staff to a patient.

In 1986, Sakaoka and associates (17) reported an unusual outbreak in Japan. They identified three infants who were infected with the same HSV-1 isolate, although the three cases occurred over 2.5 years. None of the mothers of these infants had a history of any genital herpes, and HSV could not be obtained from the genital tract of the mothers. All three infants were infected with a strain with the same restriction endonuclease pattern. This suggested that a single individual in the nursery with recurrent asymptomatic HSV may have infected infants intermittently in the nursery. In a second outbreak, the same authors isolated HSV-1 from three infants in the same room of a hospital within 1 month (17). One of the infant's mothers had herpetic lesions at a genital site at delivery. The infant of this infected mother was the source of infection for the other two infants. The three infants had occupied a common radiant warmer, which was thought to be a potential source of HSV transmission.

The DNA technique has also been used to exclude horizontal transmission. Halperin and coworkers (13) reported two infants who were cared for side by side in a hospital nursery who both developed HSV infections with HSV-2. DNA patterns of the two isolates were different, indicating that healthcare-associated transmission had not occurred.

In addition to hospitalized newborns, other patients at risk include surgical patients, particularly burn patients. Any patient with a breakdown in the skin has an increased risk for serious HSV infection because it is easy for HSV to enter the wound and thus the bloodstream. In 1985, Brandt and colleagues (18) used DNA patterns to determine that three HSV wound infections that occurred on a burn unit over 6 weeks were caused by unrelated isolates, although temporarily there appeared to be an outbreak in the unit. In 1981, Adams and associates (19) described two outbreaks of HSV-1 infection in a pediatric intensive care unit, one in early summer and one in late summer. In one outbreak, three nurses had herpetic whitlow (cutaneous infection of the fingertip and/or nail bed). The husband of one of the nurses had an acute HSV gingival stomatitis, and a fourth nurse had acute recurrent oral ulcers associated with HSV infection. DNA analysis of the HSV showed that each nurse was infected with the same isolate. In the second outbreak, two different isolates were transmitted in the intensive care unit. In both outbreaks, a patient was identified as the possible source of infection.

In 1992, Perl and coworkers (20) described an outbreak in a hospital unit caring for adults with cancer. The index patient was a 64-year-old man immunocompromised by lymphoma. He developed perioral HSV-1 infection. He subsequently required intubation, and the physician who intubated him developed herpetic keratoconjunctivitis. The nurse caring for the patient and a family member visiting the man both developed HSV infections with the same strain as the one found in the infected patient. There is one report of a physician acquiring HSV via a needle stick. The needle had be used to deroof a child's HSV infected vesicle (21).

Thus, there is little doubt that HSV infection is a potentially serious problem for both patients and personnel. Personnel are more likely to acquire HSV from immunocompromised patients who shed high titers of HSV for long periods. Outside the hospital a mohel infected two infants with HSV-1 during ritual circumcisions (22).

PREVENTION AND CONTROL

Prevention and control of HSV infections in the hospital is easily accomplished by rigorous adherence to standard hygienic practices. Of nine adults with HSV labialis, Turner and colleagues *(23)* found HSV in the oral secretions of seven and on the hands of six. HSV survives for as long as 2 hours on skin, 3 hours on cloth, and 4 hours on plastics. HSV is an enveloped virus and therefore is easily inactivated by standard denaturing agents such as alcohol, soaps, and detergents. Its survival on fomites and on hands means that rigorous care must be taken to protect both personnel and patients from infection from both environmental surfaces and hands *(24,25)*.

Currently, there is no evidence that hospital personnel with genital infections pose a high risk to patients if infected personnel follow good patient care practices. The risk to patients by personnel with oral labial herpes is unknown. Personnel with nonexposed oral infections, however, can reduce the risk of infecting patients by wearing an appropriate barrier, such as a mask over the lesions and avoiding hand contact with the lesions. Hand washing is absolutely essential to prevent transmission from personnel to patients. Personnel with either oral lesions or active cutaneous lesions on the hands should not care for high-risk patients such as neonates and patients with severe malnutrition, burns, or immunodeficiencies.

Personnel who have exposed active lesions of herpes simplex should not work with newborn infants (term or preterm), burn patients, or immunocompromised hosts until all lesions have dried and crusted. Personnel with herpetic whitlow may be more likely to transmit infection by contact *(26–28)*. For personnel with herpetic whitlow, the effectiveness of gloves in preventing transmission is unknown; in general, personnel with herpetic whitlow should not work with patients while they have active lesions. There is no evidence that the treatment of infected personnel with oral acyclovir, although it may reduce the titer of virus shed, will eliminate the risk of transmission *(24,29,30)*.

Several guidelines for preventing infection of personnel by infected patients have been published. Personnel can prevent infection by avoiding contact with contaminated oral secretions. Such exposure is a hazard for nurses, anesthesiologists, dentists, respiratory personnel, and others who usually have hand contact with the respiratory secretions from patients. Patients in an immunodeficiency state with active HSV infections are more likely to be infectious over a longer period than are immunocompetent individuals. Personnel can protect themselves from such infections by (a) avoiding direct contact with active lesions, (b) wearing gloves on both hands or using no-touch techniques when handling oral and vaginal secretions, and (c) thorough hand washing after patient contact.

Management of Obstetric Patients with HSV Infections

Women on an obstetric ward with proven or suspected genital herpes should be assigned to a private room with a private bath (*31*). Standard Precautions should be used by personnel who have contact with such women. Meticulous hand washing is important. The infant of a woman who has an active HSV infection or who is asymptomatic but HSV culture positive may be allowed to visit the mother, provided the mother washes her hands, wears gloves, and wears a clean gown before handling the child. The patient should sit in a chair while holding the infant, and the neonate should not be placed in a bed with the mother. The patient may walk in the hall if she wears a clean gown, but may not visit the nursery. Mothers with active genital HSV infections should be treated with acyclovir. These precautionary measures should be maintained for at least 7 days. Also, linens from patients with HSV infections should be considered contaminated and promptly and appropriately bagged for transport to the laundry (see also Chapter 55).

Management of Neonates with Active or Suspected HSV Infection

Infants born of mothers with active HSV infections should be cultured for HSV 48 hours after birth and should be kept in special care under close observation in a nursery unit. The infant should be placed on Contact Precautions along with proper disposal and containment of all articles coming in contact with the infant. The infant should be kept in isolation until at least 96 hours have passed since birth and until cultures for HSV including conjunctivae, urine, blood, skin, posterior pharynx, and nose are negative. The infant may go home with the mother and should be followed closely for the first 30 days of life. Prophylactic use of acyclovir in infants exposed to HSV at birth has no known benefit.

Pregnant personnel may care for patients with HSV infections but must observe strict hand washing techniques *(32)*.

CONCLUSION

HSV infections in the hospital are uncommon, but transmission from patient to patient, patient to personnel, or personnel to patient may occur. In a survey done by Perl and associates (20), the annual rates of healthcare-associated HSV-1 infection at a large hospital were between 9 and 15 per 10,000 admissions. When clusters of cases occur temporally within a given unit, transmission should be suspected and isolates gathered and typed by genome analysis to determine the source of the infection. This is important, because occasionally the source is an asymptomatic patient or staff member. HSV transmission is easily prevented by appropriate barrier methods and decontamination of surfaces with standard soaps, detergents, and alcohols. HSV is very labile and easily eliminated from both hands and inanimate surfaces.

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CHAPTER 45

Cytomegalovirus

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During pregnancy, if a woman acquires a primary infection with cytomegalovirus (CMV), the fetus is placed at highest risk for symptomatic congenital disease. Because of this risk and because acquisition of a primary CMV infection is frequently associated with morbidity and mortality in very low birth weight infants, immunocompromised patients, and transplant recipients, concern is often raised about the possible transmission of CMV within hospitals. Several studies of the hospital transmission of CMV have been completed. To accurately interpret these studies and understand the hospital transmission of CMV, one must first develop a basic understanding of the virus and the way it is transmitted within the general population.

BIOLOGY, DIAGNOSIS, AND CLINICAL FEATURES

Human CMV and the other human herpesviruses share certain common features. All human herpesviruses contain large DNA genomes, and CMV has the largest with a DNA molecular weight of 150 million. In addition, they all feature a nucleic acid core, a nucleocapsid, and an envelope glycoprotein derived primarily from the cell membrane when mature virions bud from within one cell to another. This cell membrane makes the virus very susceptible to inactivation by common disinfectants.

A transient viremia is produced by a primary infection with CMV. For immunocompetent individuals, primary CMV infections are usually always asymptomatic, although CMV occasionally causes an infectious mononucleosis syndrome in adults often consisting of fatigue and low-grade fever. For immunocompromised patients, particularly those immunosuppressed because of the acquired immunodeficiency syndrome (AIDS) or stem cell transplantation, CMV infections may cause severe disease in almost any organ system. CMV replicates in all tissues and organs, and when cell-mediated immunity is deficient, reactivation of latent CMV infections is common. The severity and location of tissue inflammation associated with CMV depend on the degree of immunosuppression. Among transplant recipients of solid organs, those who are seronegative before transplantation and acquire CMV via a donor organ or infected blood have the most severe CMV disease after transplantation. This disease is often associated with fever, neutropenia, and accelerated organ rejection.

CMV infections are best diagnosed by recovery of the virus from infected tissues or organs. In tissues with high titers of virus, histopathologic examination may reveal the presence of CMV inclusion cells. In immunocompromised patients, viremia is very common. In immunocompetent individuals, viremia occurs only transiently during a primary infection. The virus eludes antibody neutralization within tissues when it buds from cell to cell, thus causing, in most cases, a focal infection. Viral excretion in saliva or urine of the original infecting strain may resume at any time; therefore, CMV apparently becomes latent. Such latency is most frequently noted in individuals with severely impaired cellular immunity; in these individuals, a secondary viremia may disseminate the virus to all organs and tissues. Not only can a latent infection recur, but reinfection with a second strain of CMV may occur in both immunocompetent and immunocompromised individuals. To date, no studies have revealed the precise frequency of reinfection among immune (seropositive) individuals (1,*2–6*).

EPIDEMIOLOGY

Because CMV is ubiquitous in the human population, nearly all individuals eventually become infected. The percentage of seropositive individuals in central Virginia increases with age approximately 1% or 2% per year, and a mean of about 50% of the population possesses antibodies to the virus *(7)*. Nearly 100% of these individuals are seropositive by age 70. Around the world, the mean seropositivity rate for particular populations varies with location, the frequency of breast feeding, and socioeconomic status; regardless of location, however, nearly all individuals eventually become seropositive *(8–13)*.

One can also examine the prevalence of CMV infection within a particular population by determining the frequency of viral excretion. The rate of excretion for any age group depends on many factors, including geographic location, and is extremely variable. The congenital infection rate worldwide, however, is remarkably constant; in any population, between 0.5% and 2% of newborns will be excreting CMV (14,*15–18*).

For the most part, CMV produces no disease when acquired postnatally. Adults occasionally develop an infectious mononucleosis syndrome. Viremia will persist for a few days or weeks following a primary infection. CMV DNA in the blood detected by polymerase chain reaction and prolonged viral excretion in saliva and urine may persist for weeks or months. After infection, young children excrete CMV in saliva and urine for a period of 12 to 40 months, significantly longer than adults do (1). Immunoglobulin G antibodies to CMV appear 2 to 3 weeks following a primary infection and persist for life in both children and adults.

When, where, and how is CMV transmitted? In up to 2% of all pregnancies, transplacental transmission will occur. In the majority of cases of transmission, the mother is seropositive prior to becoming pregnant, and the infants become congenitally infected *in utero* following a recurrence of the mother's infection. Although primary maternal infection during pregnancy is responsible for only a small percentage of the total number of congenitally infected newborns, it is responsible for the majority of the symptomatic infections and severe handicaps caused by congenital infection (14,*15–18*). Perinatal transmission rather than transplacental transmission accounts for the majority of CMV infections acquired by infants. Breast milk is the most common form of transmission of CMV from seropositive mothers and accounts for up to 50% of transmitted infections; 10% to 20% transmit the infection via cervical and vaginal secretions *(19)*. Also, CMV can be acquired postnatally from other children, as in a day care setting; intrafamilial transmission is frequent following a primary infection in a single family member, with a rate of transmission of about 50% *(20)*.

CMV is frequently excreted in semen and cervical secretions. In addition, CMV infections are more prevalent among those who have multiple sex partners. However, the frequency of sexual transmission of CMV is problematic, because the virus can be transmitted orally or by close and frequent contact.

There is clear evidence of how slowly CMV is transmitted, even under optimal circumstances, which has been documented in studies of CMV transmission among children in day care. Children initially shed CMV at a concentration of about 10^4 plaque-forming units per milliliter of urine following a primary infection; this titer declines slowly thereafter *(21)*. Those under 2 years of age shed CMV for between 6 and 40 months, with a mean of about 2 years (1).

Our group monitored three day care centers in Richmond for 3 years (1). At the three centers, 14%, 27%, and 45% of the children became infected, with the majority becoming infected in the second year of life. The most significant data indicate that even at the center with the highest rate of infection, on average only one child per month acquired a primary CMV infection. Therefore, even under ideal transmission conditions of close, intimate daily contact (i.e., children playing daily together in the same room), the virus is transmitted slowly.

The period for CMV transmission from infected children to their mothers or caregivers is also very slow and depends on the age of an infected child (22). We observed that among the seronegative mothers of infected children, 16 (57%) of 28 mothers with infected children 20 months of age or younger acquired CMV from their children, while only 3 (14%) of 22 mothers with infected children over 20 months of age acquired the infection ($p < .007$). In the group of mothers with infected children <20 months of age, the average interval between identification of the child's infection and transmission to the mother was 8 months (SD = ±6 months).

Caregivers can also be infected with CMV through transmission from children (23–25). We studied 614 caregivers in Richmond, and the rate of CMV infections among caregivers was independently associated with the age and race of the caregiver and the ages of children for whom they cared. The highest rate of CMV infections occurred in women caring for children younger than 2 years independently of age and race (23,24). For the caregivers in our study, the annual seroconversion rate was 11% for a group of 202 initially seronegative women, compared with a 2% rate for hospital employees during the same period.

CMV TRANSMISSION IN HOSPITALS

Prevalence of CMV Excretion among Hospitalized Adults and Children

The above short review of CMV transmission outside the hospital describes the relative rates of transmission and indicates why nearly all the hospital transmission studies have been conducted in pediatric units.

In general, children have higher excretion rates than adults, as indicated by published reports on the prevalence of CMV excretion among hospitalized adults and children. In a home care setting, 8% of children younger than 5 years excrete CMV *(26–29)*. This rate increases to between 9% and 75% for children in day care, depending on the day care center (1,*21,30–39*). Between 1% and 7% of hospitalized children beyond the newborn period shed CMV (*28,29,40–43*,44,45). From 1% to 3% of infants in newborn nurseries shed CMV at any time, although an Egyptian study found 12.5% of 175 infants in a neonatal intensive care unit shedding CMV (44,46–48).

Viremia is rare among healthy adults and <1% are viruric. Likewise, in a study completed on a general oncology ward in Richmond, <1% of adult patients excreted CMV *(49)*. Published data suggest that up to 45% of stem cell recipients may excrete CMV, but this percentage may be decreasing because of the selection of seronegative donors and the frequent use of ganciclovir *(50–52)*. Among AIDS patients, rates of CMV excretion vary widely, but it is probable that at least 25% of symptomatic patients will shed CMV *(53)*. In the 1970s, between 38% and 96% of kidney recipients excreted CMV *(54–60)*, but current rates are probably much lower because immunosuppressive therapy is less intense. Finally, 8% to 35% of pregnant women will excrete CMV from one or more sites in the third trimester *(61,62)*.

An examination of CMV infection at eight different hospital units in two children's hospitals was completed by Demmler and her colleagues (44) in Houston, TX. The group surveyed each unit at least three times and surveyed the chronic care unit 18 times. Infection rates in the units ranged from 3% to 6%, but the chronic care units had much higher rates of CMV infection (15%). In these units, the

children were together for many months, were chronically ill, and had multiple blood transfusions. Overall, infection rates among hospitalized children in Houston were similar to those observed in an earlier study of hospitalized children in Richmond.

CMV on Surfaces

Where is CMV found in a hospital setting besides in the urine and saliva of infected patients? In Houston the Demmler group (44) obtained numerous environmental samples and surface swabs for CMV culture, including toys, Ambu bags, scales, intravenous tubing, crib rails, and thermometers. The swabs did not recover CMV from any inanimate object. However, the virus was isolated from the hands of a patient, a nurse, and a laboratory worker. Hands are a known reservoir for CMV. In Birmingham, AL, a similar survey done in day care centers recovered CMV from the hands of children and caregivers *(63)*.

It is easy to deactivate CMV with products such as soaps, detergents, and alcohol; CMV will also wash off surfaces with plain water (64). The virus is not very stable in the environment (65). CMV has a half-life of 2 to 6 hours on surfaces, but low titers of virus may persist for 24 hours.

Transmission from Patients to Personnel—Published Rates of CMV Infection among Pediatric Nurses and Controls

Table 45-1 lists the published rates of CMV infection among pediatric nurses and control subjects (women without patient contact). Relatively low numbers of primary CMV infections and low numbers of total subjects have affected the results of each survey. In the early 1970s, Yeager (66) first reported data that suggested a healthcare-associated infection risk for pediatric nurses. Her group observed infection in 3 of 31 ward nurses, 2 of 34 nursery nurses, and 0 of 27 control subjects. Studies in Sweden and Philadelphia showed similar results, but low rates of CMV infection were found in studies in Richmond, Birmingham, Houston, and Minneapolis (see Table 45-1).

One observation that has been consistent among all the studies is a relatively low infection rate among the control subjects. When the infection rates (number of persons infected per 100 person-years observed) for each of the studies listed in Table 45-1 were averaged, a higher annual infection rate was found among those who worked in pediatric hospitals than among the control subjects. Ward nurses display an annual average infection rate of 3.1 infections/100 person-years (24 infections for 778 person-years); this does not differ statistically from the 2.1 infections/100 person-years (45 infections for 2,126 person-years) observed for the control group. In nursery nurses the average annual infection rate is 3.9 infections/100 person-years (21 infections for 534 person-years), which is a significantly higher rate than that observed in the control group ($p < .05$; chi-square = 4.8; 1 degree of freedom).

The above analysis should be approached with skepticism for several reasons. First, the statistical analysis depends on the large group of pregnant women who served as controls in the Birmingham study. If this control group had not been available, the analysis would lack sufficient statistical power to detect small differences among groups. Second, in three of the studies, nursery nurses did not acquire CMV from infected infants in their care, according to genome analysis data. This was true of one woman in the Richmond study, of two in the Birmingham study, and of two in the Houston study. Third, one may be comparing

TABLE 45-1

Rates of Primary CMV Infection Among Pediatric Nurses and Control Subjects

		Ward Nurses		*Nursery Nurses*		*Controls (Women Without Patient Contact)*	
Authors	*Location (Reference)*	*Annual Seroconversion Rate*[a]	*Number of Nurses Studied*	*Annual Seroconversion Rate*	*Number of Nurses Studied*	*Annual Seroconversion Rate*	*Number of Women Studied*
Yeager et al.	Denver, CO (66)	7.7 (3/39)[b]	31	4.1 (2/49)	34	0	27[c]
Ahlfors et al.	Malmo, Sweden (67)	6.9 (2/29)	29	—	—	3.0 (1/33)	52
Dworsky et al.	Birmingham, AL (46)	—	—	3.4 (4/118)	61	2.3 (23/1000)	1,549
Friedman et al.	Philadelphia, PA (68)	6.0 (7/117)	115	13 (3/23)	23	2.9 (1/35)	35
Adler et al.	Richmond, VA (47)	4.4 (2/45)	31	1.8 (1/55)	40	—	—
Demmler et al.	Houston, TX (44)	0	48[c]	6.5 (7/107)	70	—	—
Balfour et al.	Minneapolis, MN (69)	1 (2/200)[d]	117	2.2 (4/182)	96	P1.8 (16/867)	519
Balcarek et al.	Birmingham, AL (70)	2.3 (8/348)[e]	183	—	—	2.1 (4/191)	105
All studies		3.1 (24/778)[f]	506	3.9 (21/534)	324	2.1 (45/2,126)	2,260

[a]Seroconversions per 100 person-years observed.
[b]Numbers in parentheses are the number of women seroconverting per total number of person-years observed. Not all women were monitored for 1 y.
[c]Not included in the total number of nurses per women studied or in the summary of all studies, because the person-years per subject could not be calculated.
[d]Renal transplantation/dialysis nurses.
[e]A mixture of nurses and other women with patient contact.
[f]See text for statistical comparisons.

very dissimilar groups when combining studies because nurses engage in many different activities, and these activities and their relative frequencies may vary widely among hospitals. Fourth, the highest rate of infection occurs in nursery nurses, and these nurses care for children with the lowest rate of CMV excretion. Summarizing the data in Table 45-1, under the worst circumstance the rate of CMV infection for nursery nurses is probably no more than three times higher than the rate for control subjects (relative risk = 1.83; 95% confidence interval = 1.01–3.04).

Patient-to-Patient Transmission

A powerful tool for studying CMV transmission is DNA genome analysis of viral DNA. Table 45-2 lists the results of studies that applied this technique to epidemiologic studies of CMV in the hospital. Between 1982 and 1985, my colleagues and I monitored the number of children in the newborn nursery in Richmond who were shedding CMV virus and the periods they were viruric while hospitalized (47). We monitored 40 seronegative women over the course of this study. One of this group seroconverted, but she shed an isolate that had a DNA genome pattern different from 34 of the isolates excreted by the children in the nursery for that period. Also, no infant-to-infant transmission occurred.

In Durham, it was believed that a house officer had acquired CMV from a child in her care, but the DNA of her isolate differed from that of the isolate shed by the child *(71)*. Surveys revealed similar observations for nurses in Houston and Birmingham (46,*72*).

In 1983, Spector (73) used DNA analysis of viral isolates to conclude that two babies in a neonatal nursery in Oakland had probably acquired CMV from another infected infant in that nursery. Infants became infected after being located side by side for approximately 6 weeks. They received care from common caregivers, but did not receive blood from common donors.

In another study in Houston, Demmler and her team (44) studied the DNA patterns of 27 viral isolates, 24 from children and 3 from nurses, derived from 18 sets of samples obtained for culture from children and staff on a pediatric chronic care unit. Four children produced two pairs of identical isolates. Because one pair of children had shared a common blood donor, it is uncertain whether the CMV was acquired from the blood donor or via horizontal transmission. The second pair of children who shed identical isolates had been given care for 20 weeks or more side by side in the same unit, and they had not received blood from a common donor. One nurse had cared for both children for 3 weeks. Therefore, it is reasonable to assume that these children shed isolates with identical DNA patterns because patient-to-patient transmission occurred.

Based on analysis of genome DNA, there have been no documented instances of CMV transmission from patients to hospital caregivers, but, at least in the two reports cited above, patient-to-patient transmission probably did occur. In both cases, patient-to-patient transmission occurred in chronic care units with children crowded side by side for long periods; this is an institutional setting similar to that of day care.

PREVENTION AND CONTROL

According to published data, CMV transmission from patients to hospital personnel occurs rarely, if at all, and has never been documented. An analysis of the seroconversion data shows that there may be an annual infection rate 1% to 4% greater for nursery nurses than for the general population, but, as noted above, there are many problems with this type of analysis of published data.

CMV may be transmitted between hospitalized patients, but transmission is easily prevented. Soap and water readily inactivate the virus, and simple handwashing techniques should prevent transmission. One study we completed showed that susceptible pregnant women but not nonpregnant women could protect themselves from acquiring CMV from their infected child by following simple hygienic precautions (74). Thus if strictly adhered to, standard precautions will protect both patients and personnel *(75,76)*. One should not be concerned about patient-to-patient transmission unless dealing with immunocompromised patients or premature infants. In either of those situations, one should be very careful about the kinds of contact these patients have with other patients and personnel; one should adhere to frequent and adequate handwashing techniques and to standard precautions.

It is not necessary to routinely test hospital personnel for CMV immunity either before or during pregnancy

TABLE 45-2

CMV Transmission Studies Using Analysis of Viral DNA

			Number of Isolates Studied		*Number of Isolates*	
Authors	*Location (Reference)*	*Type of Unit*	*Children*	*Nurses*	*Different*	*Identical*
Wilfert et al.	Durham, NC *(71)*	NICU[a]	1	1	2	0
Yow et al.	Houston, TX *(72)*	NICU	1	1	2	0
Spector	Oakland, CA (73)	NICU	7	0	4	3
Dworsky et al.	Birmingham, AL (46)	NICU	1	1	2	0
Adler et al.	Richmond, VA (47)	NICU	34	1	35	0
Demmler et al.	Houston, TX (44)	Chronic care	24	3	25	2

[a]NICU, neonatal intensive care unit.

because of the low incidence of infection. If, however, a pregnant woman working in a healthcare setting is especially concerned about CMV, serologic testing for immunity can be done. Seronegative pregnant women who are susceptible should be especially attentive to good hygiene at work and at home if they care for a young child at home (74). Serial serologic testing during pregnancy should be offered as an option to concerned pregnant seronegative healthcare workers.

Pregnant women also should not be furloughed or transferred with the idea that their exposure frequency would decrease on different units. They should instead assume that all patients may be infectious and are best advised to practice frequent handwashing and strictly adhere to standard precautions. Standard precautions apply to blood and all body fluids, secretions, and excretions. Pregnant hospital personnel should assume that all body fluids are possibly infectious. As stated above, they should practice frequent handwashing after patient contact. When they perceive that they are most likely to be exposed to body fluids or when they are handling urine and respiratory secretions, they should wear gowns and gloves.

While CMV is seldom, if ever, transmitted via respiratory droplets, the polymerase chain reaction—a very sensitive method for detecting minute quantities of DNA—has detected CMV DNA in the filtered air near immunosuppressed patients with CMV pneumonia and other respiratory infections *(77)*. Because the infectivity of aerosols from such patients is unknown, use of a mask by pregnant women is appropriate when prolonged or frequent exposure to aerosolized urine or respiratory secretions is likely to occur.

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CHAPTER 46

Hepatitis Viruses

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Three hepatitis viruses are of clinical significance in healthcare settings in the United States because of healthcare-related transmission: hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). This chapter discusses the epidemiology, clinical presentation, diagnosis, and prevention of transmission of these viruses, focusing on transmission from patient to patient in healthcare settings. Transmissions from patient to patient in dialysis settings, through transfusion or transplantation, and to and from healthcare personnel are covered elsewhere.

Patient-to-patient transmission of HAV, HBV, and HCV has been detected in a variety of healthcare settings, both in developed and less developed countries (1,*2–8*). Such transmission generally occurs indirectly through lapses in infection control practices of caregivers, and almost all of the transmissions reported were preventable through adherence to recommended practices for infection control.

Worldwide, exposures associated with healthcare delivery account for many HBV and HCV infections. Therapeutic injections, which are commonly overused and administered in an unsafe manner in developing and transitional countries, are estimated to account for over 21 million new HBV infections and 2 million new HCV infections each year *(9)*. Historically, in the United States, surveillance data have suggested that healthcare-associated HBV and HCV transmission was unusual; however, mounting data compiled from public health outbreak investigations suggest that transmission of viral hepatitis related to healthcare procedures is more common than previously recognized *(8,10,11)*.

HEPATITIS A

Epidemiology

Hepatitis A is caused by HAV, an RNA virus, classified as a picornavirus (12). HAV infection can cause both acute disease and asymptomatic infection, does not cause chronic infection, and confers lifelong immunity from future HAV infection *(13)*. HAV is transmitted primarily by the fecal–oral route, by either person-to-person contact or ingestion of contaminated food or water (12).

While hepatitis A occurs worldwide, major geographic differences exist in its endemicity and resulting epidemiologic features. The degree of endemicity is closely related to sanitary and living conditions and other indicators of the level of development. Historically, most US cases have resulted from person-to-person transmission, and infection often occurred in the context of community-wide and child daycare center outbreaks (12,*14*). In a majority of reported cases, risk factors for infection have not been identified *(10,14,15)*.

The national incidence rate of hepatitis A has declined steadily since the introduction of licensed hepatitis A vaccines in the United States in 1995 and the issuance of the first public health recommendations for the use of vaccine to prevent transmission of HAV in 1996 *(16)*. In 2007, a total of 2,979 acute symptomatic cases of hepatitis A were reported; the national incidence (1.0 case per 100,000 population) was the lowest ever recorded *(10)*. The most frequently reported risk factors for hepatitis A were international travel (18%), and sexual and household (8%) or other (9%) contact with another person with hepatitis A. (Risk factors are not mutually exclusive.) The majority of cases have no risk factor data available. After asymptomatic infection and underreporting were taken into account, an estimated 25,000 new infections occurred in 2007 *(10,17)*.

Rarely, HAV infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of their infection, before they are symptomatic or jaundiced (1,*18–29*). Transmission has not been reported to occur after inadvertent needlesticks or other contact with blood, although transmission of HAV among injection drug users (IDUs) may be through both percutaneous and fecal–oral routes (12,*30*).

Depending on conditions, HAV can be stable in the environment for months *(31)*. Heating foods at temperatures >185°F (85°C) for 1 minute or disinfecting surfaces with a 1:100 dilution of sodium hypochlorite (i.e., household bleach) in tap water is necessary to inactivate HAV *(32)*. Laboratory studies have demonstrated that HAV can survive on human hands for up to 4 hours and that the quantity of HAV transferred from hands to animate and inanimate surfaces can be increased by the application of pressure and friction *(33)*. This study suggests that human hands and environmental surfaces may serve as sources of HAV dissemination.

Clinical Illness

The average incubation period for hepatitis A is 28 days (range 15–50 days) *(34)*. Typically, acute hepatitis A starts abruptly with symptoms that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. The severity of clinical disease associated with HAV infection increases with age. In children <6 years of age, most (70%) infections are asymptomatic; if illness does occur, it is usually anicteric *(35)*. Among older children and adults, infection is usually symptomatic, with jaundice occurring in >70% of patients *(36)*. Signs and symptoms usually last <2 months, although 10% to 15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months *(37)*.

Fulminant hepatitis is a rare complication of hepatitis A; the case-fatality rate for all ages is 0.3% to 0.6%, but reaches 1.8% among adults >50 years *(10)*. Persons with chronic liver disease who acquire hepatitis A are at increased risk for acute liver failure and death *(10,38)*. Other complications include cholestatic hepatitis, with very high bilirubin levels that can persist for months, and relapsing hepatitis, in which exacerbations can occur weeks to months after apparent recovery. Chronic infection does not occur following HAV infection (12).

In infected persons, HAV replicates in the liver, is excreted in bile, and is shed in the stool. Feces can contain up to 10^8 infectious virions per milliliter and are the primary source of HAV *(39,40)*. Fecal excretion of HAV and, hence, peak infectivity are greatest during the incubation period of disease before the onset of jaundice or elevation of liver enzymes *(39,40)*. The concentration of virus in stool declines after jaundice appears; once disease is clinically obvious, the risk of transmitting infection is decreased. However, some patients admitted to the hospital with HAV, particularly immunocompromised patients, may still be shedding virus because of prolonged or relapsing disease, and such patients are potentially infectious *(41)*. Fecal shedding of HAV, formerly believed to continue only as long as 2 weeks after the onset of dark urine, has been shown to occur as late as 6 months after diagnosis of infection in premature infants (who are more likely to be anicteric). Children and infants can shed HAV for longer periods than do adults, up to several months after the onset of clinical illness *(28)*. Viremia occurs soon after infection and persists through the period of liver enzyme elevation *(42,43)*. The amount of virus in the blood is several orders of magnitude lower than that in stool *(42–44)*. Although virus has also been found in saliva during the incubation period in experimentally infected animals, transmission by saliva has not been reported *(44)*.

Diagnosis

Hepatitis A cannot be differentiated from other types of viral hepatitis on the basis of clinical or epidemiologic features alone. The diagnosis of acute HAV infection is confirmed during the acute or early convalescent phase of infection by the presence of immunoglobulin M (IgM) anti-HAV. In most persons, IgM anti-HAV becomes detectable 5 to 10 days before the onset of symptoms and can persist for up to 6 months after infection *(43,45)*. Immunoglobulin G (IgG) anti-HAV, which also appears early in the course of infection, remains detectable for the lifetime of the individual and confers lifelong protection against infection *(13)*. Although commercial tests are available for the detection of IgM and total (IgM and IgG) anti-HAV in serum, IgM HAV testing should be limited to persons with evidence of clinical hepatitis or to those who have had recent exposure to an HAV-infected person to avoid the possibility of false-positive test results *(46)*.

HAV RNA can be detected in the blood and stool of most persons during the acute phase of infection by using nucleic acid amplification methods, and nucleic acid sequencing has been used to determine the relatedness of HAV isolates *(47)*. However, these methods are available in only a limited number of research laboratories and generally are not used for diagnostic purposes.

HAV Transmission in Healthcare Settings

Transmission of HAV from patient to patient in healthcare settings has been reported infrequently, usually occurring when the source patient had unrecognized hepatitis and was fecally incontinent or had diarrhea (1). Other risk factors for HAV transmission include activities that increase the risk of fecal–oral contamination, such as eating or drinking in patient-care areas, inadequate hand hygiene after handling an infected patient and/or the patient-care environment, and sharing food, beverages, or cigarettes with patients, their families, or other staff members. Healthcare-associated hepatitis A outbreaks are summarized in Table 46-1 in chronological order of the date they were reported. The table shows the number of patients, staff, and family contacts infected, the country and healthcare setting in which each outbreak occurred, and factors contributing to transmission such as asymptomatic viral shedding, gross fecal environmental contamination, and hospitalization during the prodrome of hepatitis A *(18,20,22,23,25–29,48–61)*. The majority of reports are from the 1980s, with the last published report from 2002. Two illustrative outbreaks will be described in greater detail.

Several outbreaks have occurred in neonatal intensive care units (NICUs), often involving transfusion of neonates with infected blood and subsequent transmission of HAV infection to other infants and staff *(22,23,26–29,48)*. The first such reported outbreak resulted from exchange transfusion of blood from a donor in the prodrome of hepatitis A *(18)*. (The donor became ill 4 weeks after donation.) The infant had received an exchange transfusion at birth for Rh incompatibility and developed subclinical HAV infection. She was subsequently nursed on a surgical ward for treatment of *Staphylococcus aureus* osteitis for 4 weeks, during which period she had to be turned every hour. Transmission to her mother, to nine staff who provided care to the index patient, and to one other patient on the same ward as the index case was documented.

In many of the NICU outbreaks, lapses in infection control practices, including smoking, eating, and drinking in patient-care areas, not wearing gloves as appropriate when providing patient care, and inadequate hand hygiene, facilitated transmission of HAV from patient to patient and from patient to staff, contributing to propagation of the outbreaks *(22,23,26–29,48)*. NICUs provide a setting that has been conducive to further spread of HAV once it

TABLE 46-1

Healthcare-Associated Hepatitis A Outbreaks

Year	*Author (Reference Number)*	*Infection Source in Index Patient*	*Factors in Transmission*	*No. of Patients Infected*	*No. of Staff Infected*	*No. of Family/ Household Contacts Infected*	*Country/Setting*
1977	Centers for Disease Control and Prevention (49)	International travel	E, P, U	2	12	3	United States/Pediatric ward
1981	Orenstein (50)	C	E, P, U	0	4	0	United States/Pediatric ward
1981	Seeberg (18)	T	A, I	1	9	1	Sweden/Pediatric ward
1982	Goodman (51)	N	E, P, U	1	6	0	United States/Surgical ward
1983	Khanchit (20)	T	E, U	2	12	1	United States/ Community hosptial
1984	Krober (52)	C?	E, P	0	8	0	United States/Pediatric surgical and medical wards
1984	Noble (22)	T	A	3	11	16 (15 more cases in another facility)	United States/NICU
1984	Klein (23)	N, T	A	4	9	6	United States/NICU, well-baby nurseries
1984	Reed (25)	C/N	E, P, U	3	20	4	United States/Children's hospital PICU, medical ward
1985	Skidmore (53)	International travel	E, P, U	1	12	0	United Kingdom/Medical ward
1985	Edgar (54)	Sewage	E, P, U	0	7	1+	United Kingdom/Medical ward
1987	Azimi (26)	T	A	0	15	1	United States/NICU
1987	Baptiste (56)	C?	E, P, U	0	1	0	United States/Endoscopy suite
1987	Drusin (57)	C (family)	E, I, U	0	7	3	United States/PICU
1989	Giacoia (27)	T (RBC + platelets)	A	4	5	14	United States/NICU
1991	Rosenblum (28)	T (RBC)	A, I	11	30	4	United States/NICU
1992	Lee (29)	T (FFP)	A, I	0	9	1	United States/NICU
1993	Watson (48)	V	A	3	10	0	United States/NICU
1993	Doebbeling (55)	C?	I, P	1	11	1	United States/Burn unit
1995	Burkholder (58)	International travel	A, E	1	19	4	United States/Pediatric hospital
1996	Hanna (59)	C/N	I, P	1	3	2	Australia/ICU
1998	Jensenius (60)	C	P, poor personal hygiene	4	8	2	Norway/Medical ward
2002	Petrosillo (61)	C	E, I, P	2	1	0	Italy, Pediatric ward

A, prolonged asymptomatic fecal shedding of HAV; C, community; E, fecal incontinence and/or gross environmental contamination; F, foodborne; FFP, fresh frozen plasma; I, infection control lapses; N, not specified/determined; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; P, hospitalization during hepatitis A prodrome; RBC, red blood cells; T, transfusion; U, hepatitis A diagnosis unsuspected; V, vertical transmission.

is introduced. The combination of frequent contact with soiled diapers, asymptomatic infection in neonates, and prolonged HAV excretion among preterm infants may facilitate HAV transmission.

Most patients hospitalized for symptomatic hepatitis A are admitted after onset of jaundice, when they are beyond the point of peak infectivity (1,*62*). Consequently, most source patients for outbreaks of hepatitis A outside of NICUs were usually admitted for diagnoses other than hepatitis A, were incubating hepatitis A, and developed subclinical or symptomatic hepatitis after hospitalization *(20,25,49–61)*. Patient-to-healthcare personnel and patient-to-patient transmission of HAV in such situations was usually associated with fecal incontinence and/or gross environmental contamination with feces *(20,25,49–54,56–58,61)*. One such outbreak involved an adult hospitalized for elective cholecystectomy who developed fever, abdominal pain, vomiting, and diarrhea postoperatively *(51)*. She had several episodes of fecal incontinence with gross contamination of her bed linen and floor. Despite developing jaundice, she was discharged without a specific diagnosis. However, on readmission for further diagnostic evaluation of her jaundice, she was confirmed to have acute hepatitis A. Five nurses who were exposed to the patient during her first admission became clinically ill with laboratory-confirmed hepatitis A. As part of a serologic survey of exposed personnel, a sixth nurse was found to have asymptomatic infection. The index patient's hospital roommate, who had assisted the index patient in the bathroom postoperatively, also developed clinical illness.

Other healthcare-associated outbreaks of hepatitis A had features similar to the outbreak just described *(25,50,52–61)*. In many of these outbreaks, the index patient was admitted for a condition other than hepatitis, for example, malaria, amebic hepatic abscess, burns, or cardiac surgery. When the index patient developed symptoms consistent with hepatitis A, the diagnosis was often not suspected until after his or her contacts, usually personnel, developed symptomatic hepatitis A.

Prevention of Healthcare-Related HAV Transmission

The primary means of preventing HAV transmission in healthcare settings is by observing Contact Precautions with patients with acute hepatitis A who are in diapers and/or incontinent and by avoiding fecal–oral contact (63). Continent patients can be managed with Standard Precautions alone (63). Meticulous hand hygiene after touching the patient, the patient's feces, or the environment around the patient (64) and not eating, drinking, or smoking in patient-care areas are essential to preventing HAV transmission in healthcare settings (63). In addition, cleaning and disinfection of all patient-care areas is important for frequently touched surfaces, especially those closest to the patient, which are most likely to be contaminated (e.g., bedrails, bedside tables, commodes, doorknobs, sinks, surfaces, and equipment in close proximity to the patient) (63). The frequency or intensity of cleaning may need to change based on the patient's level of hygiene and the degree of environmental contamination (63). An Environmental Protection Agency (EPA)—approved hospital disinfectant/detergent designed for general housekeeping surfaces is preferred (65).

Inactivated hepatitis A vaccines are available for prevention of hepatitis A (12,*66–68*). The vaccines containing HAV antigen that are currently licensed in the United States are the single-antigen vaccines HAVRIX (manufactured by GlaxoSmithKline, Rixensart, Belgium) and VAQTA (manufactured by Merck & Co., Inc., Whitehouse Station, NJ) and the combination vaccine TWINRIX (containing both HAV and HBV antigens; manufactured by GlaxoSmithKline). These vaccines are highly immunogenic as well as highly effective in the prevention of clinical hepatitis A *(67,68)*. With universal childhood immunization with hepatitis A vaccine, catch-up vaccination of older children in geographic regions with historically high incidence, and broader vaccination coverage of at-risk groups, the overall population level of immunity will continue to rise. Already, increased vaccination coverage for hepatitis A among children has led to the lowest rates of hepatitis A in the United States, consistent with herd immunity *(69)*. Healthcare-associated hepatitis A transmission is likely to remain a rare event.

Because serologic surveys among healthcare personnel have not shown greater prevalence of HAV infection than in control populations, healthcare personnel are not considered at increased risk for acquiring HAV infection, and routine administration of vaccine in healthcare personnel is not recommended (12,*70,71*). Vaccine is recommended for some persons because of occupational risk, including those who handle HAV-infected primates or are exposed to HAV in a research laboratory (12). Hepatitis A vaccine is also recommended for all children at age 1 year (12–23 months), for persons at increased risk of infection, such as those traveling or working in countries with high or intermediate endemicity of infection, men who have sex with men, injection and noninjection illicit-drug users, persons with clotting factor disorder, and for persons with chronic liver disease who are at increased risk for severe complications from hepatitis A (12).

Immune globulin (IG) is available for preexposure and postexposure prophylaxis (12,72). IG provides protection against hepatitis A through passive transfer of antibody, and is 80% to 90% effective in preventing clinical hepatitis A when administered before exposure or early in the incubation period after exposure, that is, within 14 days. The recommended dose of IG for hepatitis postexposure prophylaxis is a single dose of 0.02 mL/kg administered intramuscularly as soon as possible after exposure (12,72).

Hepatitis A vaccine administration was recommended as preferred over IG for postexposure prophylaxis by the Advisory Committee on Immunization Practices in 2007 (72). For healthy persons aged 12 months to 40 years, single antigen hepatitis A vaccine at the age-appropriate dose is preferred to IG because it offers long-term protection and is more easily administered. For persons aged >40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group; vaccine can be used if IG cannot be obtained. The magnitude of the risk for HAV transmission from the exposure should be considered in decisions to use IG or vaccine. IG should be used for children aged <12 months, immunocompromised persons, persons who have had chronic liver disease diagnosed, and persons for whom vaccine is contraindicated. Persons given IG, for whom hepatitis A vaccine is also

recommended for other reasons, should receive a dose of vaccine simultaneously with IG. For persons who receive vaccine, the second dose should be administered according to the licensed schedule to complete the series (72). The efficacy of IG or vaccine administered >2 weeks after exposure has not been established.

Hepatitis A postexposure prophylaxis is not routinely indicated when a single case occurs in an elementary or secondary school, an office, or in other work settings, and the source of infection is outside the school or work setting (12,72). Similarly, when a person who has hepatitis A is admitted to a hospital, staff should not routinely be administered hepatitis A postexposure prophylaxis; instead, Standard Precautions and careful hygienic practices should be emphasized. Hepatitis A postexposure prophylaxis should be administered to persons who have close contact with index patients if an epidemiologic investigation indicates that HAV transmission has occurred among students in a school or among patients or between patients and staff in a hospital. When outbreaks occur in hospitals, use of hepatitis A vaccine or IG for persons in close contact with infected patients is recommended (12,72).

HEPATITIS B

Epidemiology

HBV belongs to the family Hepadnaviridae, a group of DNA viruses. The only known hosts for HBV are humans, although some nonhuman primates can be infected under laboratory conditions (73). HBV infection can cause both acute disease and asymptomatic infection and may result in chronic infection. Worldwide, HBV is the most common cause of chronic viremia; there are an estimated 360 million chronic carriers worldwide who are at risk for HBV-related liver disease (73), and there are 500,000 to 700,000 deaths each year due to acute and chronic liver disease (73,*74*). In the United States, approximately 0.3% to 0.5% of the general population, or 800,000 to 1.4 million persons, are chronically infected with HBV; they provide a reservoir for infection in the population *(75,76)*.

HBV is transmitted by percutaneous or mucosal exposure to blood and other body fluids from infected persons. Blood contains the highest HBV titers of all body fluids and is the most important vehicle of transmission in the healthcare setting. Hepatitis B surface antigen (HBsAg) is also found in several other body fluids, including breast milk, bile, cerebrospinal fluid, feces, nasopharyngeal washings, saliva, semen, sweat, and synovial fluid *(77)*. However, the concentration of HBsAg in body fluids can be 100- to 1,000-fold higher than the concentration of infectious HBV particles. Therefore, most body fluids are not efficient vehicles of transmission, because they contain low quantities of infectious HBV, despite the presence of HBsAg.

Children born to infected mothers are at high risk for perinatally acquired HBV infection. Persons parenterally exposed to blood, particularly IDUs, are also at significant risk. Sexual contact with infected partners is another efficient mode of HBV spread. In most industrialized countries, adult infections usually are acquired sexually or by injection drug use (*10*,73,*78*).

HBV is a relatively hardy virus, resistant to drying, ambient temperatures, simple detergents, and alcohol. It has been found to remain viable and infectious on environmental surfaces for at least 7 days and can be present in high concentrations on inanimate objects, even in the absence of visible blood *(76,79,80)*. Thus, indirect contact transmission can occur through inanimate objects (e.g., contaminated medical equipment or environmental surfaces). Transmission in households is well documented, and, in part, may be attributable to contact with fomites or environmental surfaces contaminated with secretions or blood from infected persons. HBV has been shown to be inactivated by several intermediate-level disinfectants, including 0.1% glutaraldehyde and 500 parts per million (ppm) free chlorine from sodium hypochlorite (e.g., household bleach) *(81,82)*. Heating to 98°C for 2 minutes also inactivates HBV *(83,84)*.

Clinical Illness

The average incubation period (time from exposure to onset of jaundice) for acute HBV infection is 90 days with a range of 6 weeks to 6 months *(76)*. The period of infectivity precedes the development of jaundice by 2 to 7 weeks and correlates with the presence of HBsAg in the serum. Symptoms of acute hepatitis B include fatigue, poor appetite, nausea, vomiting, abdominal pain, low-grade fever, jaundice, dark urine, and light stool color. Clinical signs include jaundice, liver tenderness, and possibly hepatomegaly or splenomegaly. Fatigue and loss of appetite typically precede jaundice by 1 to 2 weeks. Acute illness typically lasts 2 to 4 months. Most newly infected infants, children aged <5 years, and immunosuppressed adults are typically asymptomatic, while 30% to 50% of children aged >5 years and adults will have initial clinical signs or symptoms. The case-fatality rate among persons with reported acute hepatitis B is approximately 1%, with the highest rates (~5%) occurring in adults aged >60 years *(10)*.

The risk of developing chronic HBV infection varies inversely with the age at infection. Chronic infection occurs in 90% of infants infected at birth, 25% to 50% of children infected at 1 to 5 years of age, and about 5% to 10% of people infected as older children and adults *(76,85)*. However, immunosuppressed persons (e.g., hemodialysis patients and persons with HIV infection), persons with diabetes, and the elderly are also at increased risk of developing chronic HBV infection (*86*,87). An estimated 15% to 25% of persons with chronic HBV infection will die prematurely of either cirrhosis or primary hepatocellular carcinoma (HCC) (73,*76*,*88*).

Diagnosis

Hepatitis B is differentiated from other causes of hepatitis by serologic assays. Several well-defined antigen–antibody systems are associated with HBV infection, including HBsAg and antibody to HBsAg (anti-HBs); hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Serologic assays are commercially available for all of these except HBcAg, because no free HBcAg circulates in blood. These markers of HBV infection change over time, with different patterns seen in patients with acute infection that resolves and patients with chronic infection (Table 46-2) *(76)*.

TABLE 46-2

Interpretation of Patterns of HBV Serologic Markers

Serologic Marker				
HBsAg[a]	*Total Anti-HBc*[b]	*IgM*[c] *Anti-HBc*	*Anti-HBs*[d]	*Interpretation*
–	–	–	–	Susceptible, never infected
+	–	–	–	Acute infection, early incubation[e]
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Recovered from past infection, and immune
+	+	–	–	Chronic infection
–	+	–	–	False positive (i.e., susceptible), past infection, or "low-level" chronic infection
–	–	–	+	Immune if titer is ≥10 mIU/mL

[a]HBsAg, hepatitis B surface antigen.
[b]Anti-HBc, antibody to hepatitis B core antigen. The total anti-HBc assay detects both IgM and IgG antibodies.
[c]IgM, immunoglobulin M.
[d]Anti-HBs, antibody to hepatitis B surface antigen.
[e]Transient HbsAg positivity (lasting ≤18 days) might be detected in some patients during vaccination.
+, positive; –, negative.
(Adapted from Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Morb Mortal Wkly Rep* 2009;57(RR-8):1–20, Table 2.)

The presence of HBsAg is indicative of active HBV infection and all HBsAg-positive persons should be considered infectious *(76)*. In newly infected persons, HBsAg is the first marker present in serum. The average time from exposure to HBsAg detection is 30 days (range 6–60 days) and persists for variable periods. Transient HBsAg positivity (usually lasting ≤18 days) can be detected in some patients after the receipt of hepatitis B vaccination and is clinically insignificant *(89,90)*. Anti-HBc develops in all HBV infections, appearing at onset of symptoms or liver test abnormalities in acute HBV infection, rising rapidly to high levels, and persisting for life *(76)*. Acute or recently acquired infection can be distinguished by presence of the IgM class of anti-HBc, which persists for approximately 6 months if the infection resolves. Persons with exacerbations of chronic HBV infection can test positive for IgM anti-HBc *(76)*. The positive predictive value of the IgM anti-HBc test is low in asymptomatic persons, and its use for diagnosis of acute hepatitis B should be limited to persons with evidence of acute hepatitis or epidemiologic link to a person with HBV infection *(76)*.

In persons who recover from HBV infection, HBsAg and HBV DNA are eliminated from the blood, usually in 3 to 4 months, and anti-HBs usually develops during convalescence. The presence of anti-HBs indicates immunity from HBV infection. After recovery from natural infection, most persons will be positive for both anti-HBs and anti-HBc, whereas only anti-HBs develops in persons who are successfully vaccinated against hepatitis B. Persons who do not recover from HBV infection and become chronically infected remain positive for HBsAg (and anti-HBc) and HBV DNA, although a small proportion of persons with chronic HBV infection (0.5%–2% per year) spontaneously resolve infection, clear HBsAg and HBV DNA, and develop anti-HBs *(76,91)*. The persistence of HBsAg for 6 months after the diagnosis of acute HBV is indicative of progression to chronic HBV infection.

HBeAg can be detected in serum of persons with acute or chronic HBV infection. The presence of HBeAg correlates with more active disease and high levels of HBV DNA (i.e., high infectivity), and the presence of anti-HBe correlates with lower HBV DNA levels. However, all HBsAg-positive persons should be considered infectious, regardless of their HBeAg or anti-HBe status.

Testing can be performed to assess the presence or concentration of circulating HBV DNA. HBV infection can be detected using qualitative or quantitative tests for HBV DNA. Highly sensitive single-sample nucleic acid tests can detect HBV DNA in the serum of an infected person 0 to 10 days before detection of HBsAg. A number of HBV DNA tests approved by the Food and Drug Administration (FDA) are available. HBV DNA tests are most commonly used for patients being managed with antiviral therapy *(88)*.

HEPATITIS C

Epidemiology

HCV is an RNA virus of the Flaviviridae family. Worldwide the estimated prevalence of HCV infection is 2%, representing 123 million people (92). HCV infection is the most common chronic blood-borne infection in the United States, affecting an estimated 1.3% of the US general population or 3.2 million persons *(93)*. There are six HCV genotypes and more than 50 subtypes. Genotype 1 accounts for 70% to 75% of all HCV infections in the United States; subtype 1a predominates over subtype 1b *(94–96)*. HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among US adults *(97)*. As with HBV, persons with chronic HCV infection provide a reservoir for new infection in the population.

The highest prevalence of HCV infection (70%–90%) is reported among persons with substantial or repeated direct percutaneous exposures to blood (e.g., IDUs,

recipients of blood from unscreened donors, and persons with hemophilia treated with clotting factor concentrates that did not undergo viral inactivation) (92,*93*). Risk factors associated with acquiring HCV infection in the United States have included transfusion of blood and blood products and transplantation of solid organs from infected donors, occupational exposure to blood (primarily contaminated needlesticks), birth to an infected mother, sex with an infected partner, and multiple heterosexual partners. The incidence of acute hepatitis C in the United States has declined by ≥90% since 1990, primarily as a result of a decrease in cases among IDUs; however, these declines have plateaued since 2003 *(10)*. Injection drug use remains the primary mode of HCV transmission in developed countries (92).

Degradation of HCV occurs when serum containing HCV is left at room temperature. Specific animal infectivity studies have shown survival up to 16 hours but not as long as 4 days *(98)*. The potential for environmental survival of HCV suggests that environmental contamination with blood containing HCV can pose a risk for transmission in the healthcare setting. The risk for transmission from exposure to fluids or tissues other than HCV-infected blood has not been quantified but is expected to be low. HCV is not known to be transmissible through the airborne route or through casual contact in the workplace.

Clinical Illness

The average incubation period for acute HCV infection is 6 to 7 weeks and ranges from 2 to 24 weeks. HCV infection produces a spectrum of clinical illness similar to that of HBV infection and is indistinguishable from other forms of viral hepatitis based on clinical symptoms alone. Most adults with acute HCV infection will be asymptomatic; about one-third of adults develop clinical symptoms and jaundice *(99)*. The course of acute hepatitis C is variable, although elevations in serum alanine aminotransferase (ALT) levels, often in a fluctuating pattern, are its most characteristic feature. Normalization of ALT levels might occur and suggests full recovery, but this is frequently followed by ALT elevations that indicate progression to chronic disease *(100)*. After acute infection, 15% to 25% of persons appear to resolve their infection without sequelae as defined by sustained absence of HCV RNA in serum and normalization of ALT levels *(101)*. Fulminant hepatic failure following acute hepatitis C is rare *(10,99)*.

The lack of a vigorous T-lymphocytic response and the high propensity of the virus to mutate appear to promote a high rate of chronic infection *(94,99)*. HCV preferentially replicates in hepatocytes but is not directly cytopathic, resulting in persistent infection. During chronic infection, HCV RNA reaches high levels, generally ranging from 10^5 to 10^7 international units per milliliter (IU/mL), but the levels can fluctuate widely. Within the same individual, however, RNA levels are generally relatively stable.

Chronic HCV infection develops in most (75%–85%) persons; 60% to 70% of these chronically infected persons have persistent or fluctuating ALT elevations, indicating active liver disease *(99)*. The course of chronic liver disease is usually insidious, progressing slowly without symptoms or physical signs in the majority of patients during the first 2 or more decades after infection. Chronic hepatitis C frequently is not recognized until asymptomatic persons are identified as HCV-positive during screening, or elevated ALT levels are detected during routine physical examinations. Most studies have reported that cirrhosis develops in 10% to 20% of persons with chronic hepatitis C over 20 to 30 years, and HCC in 1% to 5%, with striking geographic variations in rates of this disease *(102–106)*. However, when cirrhosis is established, the rate of development of HCC might be as high as 1% to 4% per year.

Diagnosis

As with other types of viral hepatitis, laboratory testing is necessary to establish a specific diagnosis of hepatitis C (107,*108*). The two major types of tests available for the laboratory diagnosis of HCV infection are serologic assays for anti-HCV and the nucleic acid test to detect HCV RNA *(109)*. Testing for anti-HCV is recommended for initially identifying persons with HCV infection, and includes initial screening with an immunoassay, and if positive, confirmation by an additional more specific assay or a high screening-test–positive signal-to-cutoff ratio (107). Assays for anti-HCV detect only IgG antibody; no IgM assays are available. With the third-generation enzyme immunoassays used at present, anti-HCV can be detected 4 to 10 weeks after infection *(110)*. Anti-HCV can be detected in 97% of persons by 6 months after exposure. False-negative results can occur in persons tested early in the course of acute infection due to the prolonged interval between exposure and seroconversion, and among immunosuppressed individuals (*111*,*112*,113).

There are several FDA–licensed diagnostic tests for qualitative and quantitative detection of HCV RNA *(109)*. HCV RNA can be detected in serum or plasma within 1 to 2 weeks after exposure to the virus and weeks before onset of liver enzyme abnormalities or appearance of anti-HCV. HCV RNA tests are commonly used in clinical practice in the early diagnosis of infection, for determining the presence of chronic infection, and for monitoring patients receiving antiviral therapy. However, false-positive and false-negative results can occur from improper handling, storage, and contamination of the test specimens. Viral RNA may be detected intermittently, and thus, a single negative assay result is not conclusive. Genotype determination is used in clinical management to determine the appropriate antiviral therapy regimen and also in epidemiologic studies.

TRANSMISSION OF HBV AND HCV IN HEALTHCARE SETTINGS

The delivery of healthcare has the potential to transmit both HBV and HCV to patients if infection control or disinfection procedures are inadequate and contaminated equipment is shared among patients. Settings in which HBV and HCV transmission from patient to patient has occurred include hospitals, outpatient medicine and surgery clinics, private physicians' offices, hemodialysis centers, and long-term care facilities (LTCFs) *(3,5,7,8)*. Incidents of HBV and HCV transmission can be grouped by their presumed mechanism of transmission.

Transmission Related to Blood Sampling

Multiple episodes of HBV, and one of HCV, transmission to patients through contamination of equipment used by

healthcare personnel or other staff during blood sampling have been reported, both internationally and in the United States (114). These episodes have occurred in hospitals, LTCFs, and in residential care or assisted living facilities. Almost all of the reported outbreaks have been associated with the use of reusable fingerstick devices and/or blood glucose testing meters; many have also involved the gloves or hands of personnel performing procedures being contaminated with blood. In two HBV infection outbreaks, a reusable spring-loaded fingerstick device was used for several patients, and the disposable platform used to stabilize the patient's finger during the procedure was either not changed or cleaned and disinfected between uses *(115–117)*. During the investigations, visible blood contamination was observed on the platform and was believed to be the probable mechanism of transmission. Failure to change the disposable platform of shared spring-loaded fingerstick devices for monitoring of capillary blood glucose between patients also led to HCV transmission in a ward for cystic fibrosis and diabetes *(118)*. During 1986 to 1988, 18 patients with cystic fibrosis and four with diabetes acquired HCV infection through this mechanism.

In two other HBV infection outbreaks, reusable pen-like fingerstick devices that included both disposable and reusable components were implicated in transmission *(119,120)*. In these outbreaks, the device used had a separate lancet and end cap that rested on the skin during the procedure and could have become contaminated after the lancet retracted. Both the lancets and end caps were disposable and should have been replaced after each use. However, only the lancet was routinely replaced, suggesting that exposure of subsequent patients to residual blood on the end cap contributed to transmission.

Numerous other HBV infection outbreaks in long-term care settings have been attributed to sharing of reusable pen-like fingerstick devices that were intended for individual patient use *(121–126)*. In these outbreaks, lancets were reported to have been changed between each patient; however, contamination of the reusable barrel and its use on multiple patients likely contributed to HBV transmission. In one outbreak investigation *(124)*, a multi-lancet pen-like fingerstick device, containing six lancets in a drum and obviously intended for individual patient use, was used on multiple patients for blood glucose monitoring by 16 of 38 nursing home staff. Although it was not known if the lancets were reused, contamination of the reusable barrel component between patients most likely contributed to HBV transmission.

In four other outbreaks in long-term care settings, HBV transmission between patients occurred in facilities where reusable fingerstick devices were not present (i.e., single-use safety lancets were used exclusively) (*121*,*127*,128). Implicated factors for transmission in these outbreaks were blood contamination of shared blood glucose meters that were not cleaned and disinfected between each patient use, and failure to routinely change gloves or perform hand hygiene between each patient. In one outbreak facility, the staff in a nursing home reported they were discouraged from wearing gloves in order to decrease the sense of a clinical environment *(121)*.

Contamination of unused blood glucose monitoring equipment and supplies when stored with used items has also played a role in HBV transmission. In one outbreak, 17 nursing home patients, all undergoing blood glucose monitoring by the same general practitioner, were found to have acute HBV infection *(129)*. During blood glucose monitoring procedures, both clean and used supplies were stored on a common tray and carried between patients' rooms, and gloves were not routinely changed between patients. The same opportunities for cross-contamination were found during the investigation of an outbreak in a drug trials unit where visible blood contamination of hands or gloves and lack of hand hygiene between individual blood sampling procedures were recalled by staff and volunteers *(130)*.

Transmission Related to Improperly Cleaned, Disinfected, or Sterilized Equipment

Lapses in reprocessing of endoscopy equipment have previously been described as contributing to both HBV and HCV transmission *(131,132)*. However, in an investigation of HBV transmission linked to endoscopy equipment, other factors such as anesthesia administration and the potential for shared medications were not explored *(131)*. In an investigation of HCV transmission that led to infections in two patients undergoing endoscopy following a known HCV-infected patient, the same colonoscope was noted to be used for all three patients. Lapses in endoscope reprocessing included failure to clean the biopsy-suction channel with a brush and failure to autoclave biopsy equipment after use *(132)*. However, the source patient shared biopsy equipment with only one of the index patients. Additionally, evaluation of anesthesia practices revealed that the anesthetist routinely used the same syringe to administer anesthetic to multiple patients. The anesthetist stated that he discarded syringes only after they were used on a patient known to be infected and that he used a check valve to avoid backflow of blood into the syringe. The source patient in this outbreak was known to have HCV infection and the anesthetist reported discarding that patient's syringes. However, the possibility exists that this did not occur and syringes were reused on the index patients or that the vials of medication became contaminated and served as a potential reservoir of infection.

HCV transmission has been described in six patients receiving computed tomography (CT) scanning with contrast at three separate facilities in Spain *(133)*. These patients' procedures had followed CT scans of HCV carriers. The exact mechanism of transmission was not determined. However, one piece of equipment shared by patients was an injector that was loaded automatically from a 500-mL bottle containing contrast solution. Furthermore, the bottle of contrast solution was shared by four or more patients and the injector was used from 8 hours to several days before being replaced. An extension tube from the injector to the patient's intravenous (IV) line was fitted with a nonreturn valve and was supposed to be changed for each patient. Observations made during the investigation identified potential for blood contamination of the equipment when the extension tube was changed. Two sets of control measures were introduced at all facilities and included use of a separate contrast injection syringe for each patient and introduction of written protocols for performing the procedure to avoid transmission of infectious diseases.

HBV transmission has previously been reported in association with improper sterilization of acupuncture needles *(134–136)* and with use of a jet injection gun for administering daily injections in a weight reduction clinic in the United States *(137)*.

Transmission Related to Medication Administration

Episodes of HBV and HCV transmission related to medication administration have resulted when providers have failed to use aseptic technique and/or to adhere to the principles of Standard Precautions when preparing and administering injections to patients. Circumstances documented to have led to HBV and/or HCV transmission include using the same syringe to administer medications to more than one patient (i.e., direct syringe reuse), contaminating medication vials that were used for more than one patient by reusing syringes to access and administer medications, and preparing injections in blood-contaminated environments or near contaminated medical equipment.

Direct Syringe Reuse One of the largest healthcare-associated viral hepatitis outbreaks in the United States was identified during an investigation at a pain remediation clinic (*138*,139). In total, 31 HBV and 71 HCV infections were identified among patients attending the clinic. Patient-to-patient transmission resulted from direct reuse of needles and syringes by a certified registered nurse anesthetist. The nurse anesthetist prepared a single needle and syringe at the beginning of each clinic session for each of the three sedation medications: Versed (midazolam HCl), fentanyl, and propofol. These same three syringes and needles were then used to administer these medications to as many as 24 consecutively treated patients at each clinic session. These medications were administered through heparin locks that were connected directly to IV cannulae. This was a long-standing practice by the nurse anesthetist, who reported believing that the heparin lock provided a sterile field.

Additional outbreaks of HCV transmission through direct syringe reuse have also been described in patients undergoing sclerotherapy of varicose veins by a physician in France *(140)* and in research study participants in Canada and Sweden *(141,142)*. In the research study in Sweden, blood sampling of study participants was performed on several occasions from an indwelling IV catheter during a 24-hour period *(142)*. Syringes for flushing the IV catheter were labeled only with the patient's study number and were used repeatedly instead of being discarded after each flushing. It was theorized that syringes could have gotten mixed up during the flushing process, particularly since the study participants overlapped in the same room on multiple occasions.

Contamination of Medications through Syringe Reuse Reuse of syringes for withdrawal and administration of medications can lead to contamination of both single-use and multidose medication vials used for more than one patient. This mechanism of infection transmission has led to several recent large outbreaks of HBV and HCV transmission. A recent US investigation of acute HCV infections among patients who attended the same endoscopy center in Nevada identified seven patients with newly diagnosed HCV infection; their infections were associated by epidemiologic data and viral sequencing to unsafe injection practices at the facility (143,*144*,*145*). Nurse anesthetists at the endoscopy center routinely reused syringes on the same patient, after changing the needle, to obtain additional doses of the anesthetic propofol when further sedation was required. The needle and syringe were discarded at the end of each procedure and not used for subsequent patients. However, any medication remaining in the single-dose vial of propofol was then, contrary to labeling, used as a source of anesthetic for subsequent patients (Fig. 46-1). The investigation at the endoscopy center identified these long-standing infection control breaches, resulting in a large public health response. Approximately 50,000 patients who had received

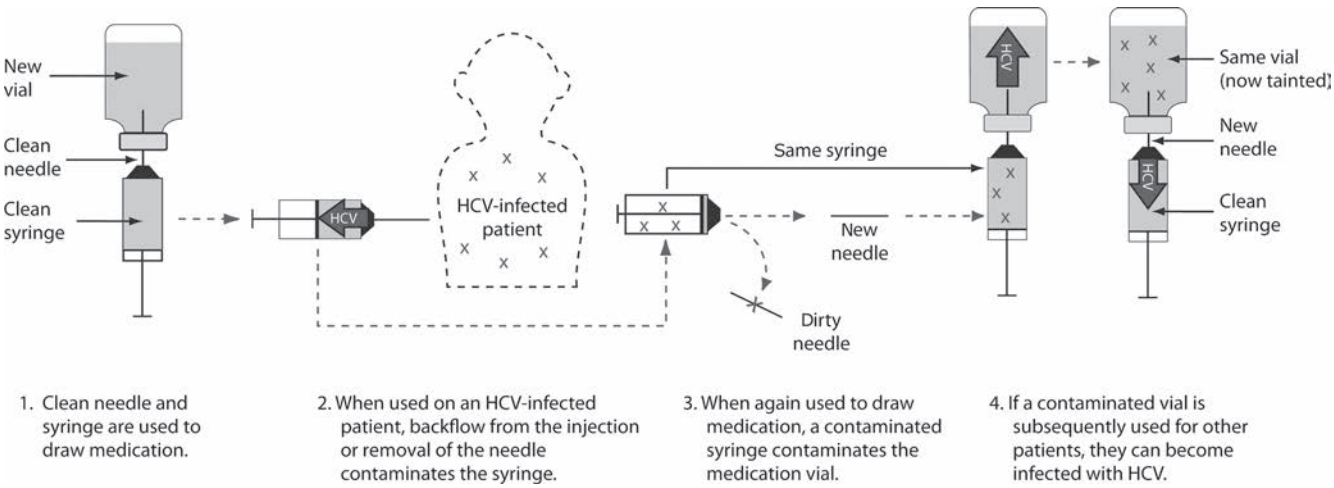

FIGURE 46-1 Unsafe injection practices that likely resulted in HCV transmission during endoscopy. (From Centers for Disease Control and Prevention. Acute hepatitis C virus infections attributed to unsafe injection practices at an endoscopy clinic—Nevada, 2007. *MMWR Morb Mortal Wkly Rep* 2008;57:513–517.)

sedation at the center were notified and recommended to undergo blood-borne pathogen testing. As a result of this testing as well as further investigation, an additional 101 patients with HCV infection were potentially linked to the receipt of healthcare at this center (143,*144*,*145*).

In another US example, a large HCV infection outbreak occurred among patients receiving treatment in a hematology/oncology clinic (113,*138*). Through this investigation, 99 patients were found to be infected with HCV. Among the 95 patients for whom HCV genotype was available, all were genotype 3a. An assessment of practices at the clinic found that a nurse would use the same syringe to draw blood from a patient's central venous catheter and then draw catheter-flushing solution from a single 500-mL saline bag used for multiple patients. A patient known to have chronic infection with HCV genotype 3a began attending the clinic at the beginning of the 22-month period investigated. After dismissal of the implicated nurse and introduction of prefilled syringes of saline flush, no further HCV transmission was identified.

Multiple other instances of HBV and HCV transmission clearly linking reuse of syringes to access medication vials used for more than one patient have been described. They include HBV transmission at a primary care office in Belgium where needles and syringes were reused to access a vial of local anesthetic that was used as a common source for multiple patients *(146)* and also in Sweden where syringes were reused to withdraw multiple doses of local anesthetic for the same patient from a shared multidose vial in which a permanent aspiration needle was left in place *(147)*. Syringe reuse to withdraw medication through a needle permanently left in the vial for aspiration was also described as one of the lapses contributing to HBV transmission at a dermatology practice in the United States *(148)*. Other lapses potentially contributing to this outbreak included failure of the provider to wear gloves or wash his hands between patients and the reuse of electrocautery tips that were neither changed nor cleaned between patients. HCV transmission due to contamination of shared medications through syringe reuse has also been described in patients at a surgery clinic in France *(149)*, in patients undergoing arthroscopy procedures in Australia *(150)*, and in patients receiving chemical stress tests at a cardiology clinic in the United States *(151)*.

Similar infection control breaches and subsequent HBV and HCV transmission have also been reported at alternative medicine practices where autohemotherapy and ozone enrichment have been performed *(152–155)*. At a clinic in the United Kingdom, the procedure involved drawing blood from the patient, mixing the blood with saline, and reinjecting the autologous blood mixture *(152)*. Here, saline was drawn directly after venipuncture with a syringe containing the patient's blood from a bottle used for multiple patients.

Environmental or Other Sources of Medication Contamination HBV transmission has been documented at a private physician's office in the United States when medication vials used for more than one patient were stored and injections were prepared on the same work surface where syringes were dismantled and injection equipment was discarded after use (*138*,156). Similar practices were described as part of an outbreak investigation in a pediatric hematology and oncology ward in Denmark where medication vials used for more than one patient were placed next to the disposal container for used infusion bags and lines, syringes, needles, and blood samples *(157)*. The outbreak ended when infection control staff dedicated vials to a single patient and established a separate disposal area.

In three outbreaks of HBV infections associated with endomyocardial biopsy (EMB), environmental contamination was felt to be the most likely mechanism of HBV transmission *(158–162)*. Simulation of EMB in one of the investigations demonstrated the plausibility of viral contamination of instruments or solutions placed up to 1 to 2 m from the EMB table through droplets of blood generated when inserting and withdrawing biopsy forceps *(158)*.

An outbreak of acute HCV infection was identified among patients undergoing myocardial perfusion studies at three separate outpatient cardiology clinics in the United States *(163)*. An epidemiologic investigation traced the source of transmission back to a common lot of radiopharmaceutical prepared at a nuclear pharmacy. Blood from a patient with chronic HCV and HIV infections was processed for a radiolabeled white blood cell study approximately 12 hours before the lot of radiopharmaceutical was prepared for the cardiac patients. Sixteen doses were prepared and administered from the first lot of radiopharmaceutical prepared at this pharmacy. All 16 patients who received doses from this lot became infected with HCV. The HCV quasispecies sequences from the presumptive source patient and the case-patients were nearly identical. The exact mechanism of contamination was not identified, but opportunities for cross-contamination included reuse of syringes and needles during dilutions and use of common medication preparation hoods for some steps in the preparation of sterile and blood-derived products.

At least 12 additional outbreaks of HBV and HCV infections have been attributed by investigators to contamination of medication vials, primarily of local anesthetic and flush solutions that were used for more than one patient. Settings have included an endoscopy clinic *(138)*, pain clinic *(164)*, emergency department *(165)*, and both adult *(166–172)* and pediatric *(173,174)* wards in hospitals. Syringe reuse was not reported and the exact mechanism of contamination in these outbreaks was not identified by investigators. However, in some instances, other lapses such as failure to change gloves after each patient may have contributed to medication contamination *(173)*.

A further seven outbreaks of HCV infection in inpatient and outpatient settings, including a fertility clinic, had no clear lapse or route contributing to HCV transmission identified *(3,175–180)*. Although the outbreaks, unlike those mentioned above, were not clearly attributed to contamination of shared medications, the presence of vials used for multiple patients was described in all but one of these settings.

Transmission Related to Other or Unknown Mechanism

Hepatitis transmission has also been described through single case-reports of acute infection in individuals who lacked traditional risk factors and had discrete healthcare encounters during the exposure period. HCV transmission was identified in a routine blood donor who

lacked traditional risk factors and whose only healthcare exposure was at an outpatient IV clinic that provided antibiotic therapy to patients *(181)*. Standard practice at the clinic involved labeling and storing patient-specific IV solution bags and tubing in a cupboard in the clinic, using the same equipment each time the patient returned for a dose of antibiotics, and only changing that equipment at 72-hour intervals. Multidose vials were not used at the facility. The index patient's clinic visits overlapped with visits to the same clinic by an HCV-infected patient, whose HCV isolate demonstrated a high degree of relatedness to the index patient. The exact mechanism of transmission was not identified. However, investigators postulated that the IV bag and tubing previously used by the source patient could have been connected to the index patient in error.

HBV transmission was identified at an outpatient oral surgery clinic when a patient without other risk factors developed acute HBV infection after undergoing oral surgery following an HBV-infected patient *(182)*. An infection control assessment identified no breakdowns in procedures, including those related to handling of medications and processing of shared patient equipment. The source patient was HBeAg positive with a high viral load and cross-contamination from an environmental surface was postulated as one possible mechanism for transmission.

Prevention of Healthcare-Related HBV and HCV Transmission

Because HBV and HCV have similar modes of transmission in healthcare settings, the same infection control principles apply to preventing their transmission. In all of the outbreaks described above, it was not the medical or surgical procedures themselves that led to hepatitis transmission, but rather lapses in infection control by the healthcare providers *(7)*. The outbreaks described above could have been prevented through adherence to basic infection control practices (63–65).

Patient-to-patient transmission of HBV and HCV during blood glucose monitoring can be prevented by consistent adherence to recommended practices, which include the following: use of single-use auto-disable lancets for fingersticks; assignment of blood glucose meters to individual patients; cleaning and disinfecting monitors between each use; preventing blood contamination of clean equipment and supplies; and changing gloves and performing hand hygiene between patients (Table 46-3) (114,*121*,*183*).

Prevention of outbreaks linked to unsafe injection practices and medication handling must focus on adherence to Standard Precautions and ensuring that healthcare personnel understand and use aseptic technique when preparing injectables for patient administration (Table 46-3). Needles and syringes are single-use devices that should never be used for more than one patient nor reused to access medication vials. Providers have attempted to justify syringe reuse through the incorrect belief that changing the needle on the syringe or injecting through IV catheters, intervening lengths of tubing, or use of a check valve eliminates any risk of transmission. However, decades-old experiments have demonstrated blood contamination of syringes even after the needle has been changed *(184–186)*. One of these studies also demonstrated contamination of IV tubing, only a third of which was visible by direct observation, and determined that the presence of a check valve made no difference in the incidence of contamination *(186)*.

Providers should limit the use of shared medication vials for multiple patients. Single-use medications, which were inappropriately used for multiple patients in some of the described outbreaks, should not be used for more than one patient. Multidose vials should be dedicated to a single patient whenever possible. If they are used for multiple patients, they should be stored according to manufacturer's instructions and kept outside of the patient-care environment in a centralized medication area that is separate from used or contaminated equipment. The need for adherence to these infection control practices is not negated by the presence of preservative, which offers no protection against viruses such as HBV and HCV.

Standard sterilization and disinfection procedures recommended for patient-care equipment are adequate to sterilize or disinfect items contaminated with blood or other body fluids from people infected with bloodborne pathogens, including HBV and HCV *(187)*. Because organic material, salts, and visible soils can interfere with the sterilization or disinfection procedure, devices must first be adequately cleaned *(188)*. This is particularly important for devices such as endoscopes that may become heavily soiled and may not tolerate heat sterilization *(189,190)*.

HBV and HCV have been demonstrated to remain infectious in dried blood on environmental surfaces for at least 7 days and 16 hours, respectively *(80,98)*. Therefore, all spills of blood and bloody body fluids should be cleaned promptly by a person wearing gloves and using an EPA–registered disinfectant (65). (Visibly bloody material should first be removed with disposable towels or other means to prevent direct contact with blood. The area should then be decontaminated with an appropriate disinfectant (65,*187*).

HBV infection is largely preventable through vaccination. Hepatitis B vaccine provides both preexposure and postexposure protection against HBV infection (87). The currently available vaccines in the United States are produced by recombinant DNA technology. There are two single-antigen vaccines available in the United States—Recombivax HB (Merck & Co., Inc., Whitehouse Station, NJ) and Engerix-B (GlaxoSmithKline Biologicals, Rixensart, Belgium)—and three licensed combination vaccines—one (Twinrix [GlaxoSmithKline Biologicals]) is used for vaccination of adults and two (Comvax [Merck & Co., Inc.] and Pediarix [GlaxoSmithKline Biologicals]) are used for vaccination of infants and young children (87). Three intramuscular doses of hepatitis B vaccine induce a protective antibody response in >90% of healthy recipients. Adults who develop a protective antibody response are protected from clinical disease and chronic infection. The duration of vaccine protection is under investigation. Most data suggest that protection persists even when anti-HBs concentrations fall below the level of detection, and routine screening and boosting are not currently recommended (87).

There is currently no vaccine against HCV, and postexposure prophylaxis is not recommended for exposures to HCV *(187)*.

TABLE 46-3

Recommended Infection Control, Safe Injection and Blood Glucose Monitoring Practices to Prevent Patient-to-Patient Transmission of Blood-Borne Pathogens

1. Hand hygiene and glove use
   a. Perform hand hygiene (i.e., handwashing with soap and water or use of an alcohol-based handrub) before preparing and administering an injection, before and after donning gloves for obtaining blood samples, after inadvertent blood contamination, and between patients.
   b. Wear gloves for procedures that may involve contact with blood and change gloves between patients.
2. Injection safety
   a. Use a sterile, single-use, disposable needle and syringe for each injection and dispose intact in an appropriate sharps container after use. Syringes and needles should not be used for more than one patient or reused to draw up additional medication.
   b. Use single-dose medication vials, prefilled syringes, and ampoules when possible. Do not administer medications from single-dose vials to multiple patients or combine leftover contents for later use.
   c. If multidose vials are used, restrict them to a centralized medication area or for single patient use. Store vials in accordance with manufacturer's recommendations and discard if sterility is compromised.
   d. Do not use bags or bottles of intravenous solution as a common source of supply for multiple patients.
   e. Use aseptic technique to avoid contamination of sterile injection equipment and medications.
3. Blood glucose monitoring and other patient-care equipment
   a. Restrict the use of fingerstick devices for blood sampling to individual patients. Select auto-disabling single-use fingerstick devices that permanently retract upon puncture.
   b. Handle all patient-care equipment that may be contaminated with blood in a way that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of microorganisms to other patients and surfaces.
   c. Evaluate equipment and devices (e.g., blood glucose testing meters) for potential cross-contamination of blood. Establish procedures for safe handling during and after use, including cleaning and disinfection or sterilization as indicated.
4. Work environment
   a. Dispose of used lancets, needles, and syringes at the point of use in a sharps container that is puncture-resistant and leakproof and that can be sealed before completely full.
   b. Maintain physical separation between clean and contaminated equipment and supplies.
   c. Prepare medications in areas physically separate from those with potential blood contamination.
   d. Use barriers to protect surfaces from blood contamination during blood sampling.
   e. Clean and disinfect blood-contaminated equipment and surfaces in accordance with recommended guidelines.
5. Administrative
   a. Infection control measures should be tailored to the individual practices setting.
   b. Responsibility for oversight and monitoring should be clearly designated.
   c. Periodic reviews of staff practices should be conducted.
   d. Procedures and responsibilities should be established for reporting and investigating breaches in infection control policy.

(Adapted from Williams IT, Perz JF, Bell BP. Viral hepatitis transmission in ambulatory health care settings. *Clin Infect Dis* 2004;38:1592–1598.)

Identification of Healthcare-Associated Viral Hepatitis Transmission or Infection Control Breaches

Healthcare professionals can play a key role in the identification and containment of healthcare-associated HBV and HCV infections by reporting potential clusters or newly diagnosed cases to their local or state public health officals. When diagnosing new HBV and HCV infections, physicans should consider the role of healthcare exposures in transmission, especially among older adult populations or others who do not report traditional risk factors (e.g., injection-drug use, high-risk sexual behaviors) for infection (191). Potential clusters involving two or more patients with a common healthcare exposure during the likely exposure period should immediately be reported to public health authories. Single cases of acute hepatitis B or C (or documented seroconversion) occurring in a cancer, dialysis, or transplant patient, a long-term care resident, or a routine blood donor represent a "red flag" for medical transmission that deserves thorough investigation (192). In addition, the identification of infection control breaches in the absence of disease transmission requires futher assessment to determine whether patient notification and testing for blood-borne pathogens is required (193).

CONCLUSION

HAV, HBV, and HCV have different routes of transmission; yet all have been involved in healthcare-related transmissions, primarily due to breaches in basic infection control practices. Transmissions of HBV and HCV have frequently involved unsafe injection or blood glucose monitoring practices.

Preventing transmission of these viruses in healthcare settings requires careful attention to aseptic technique and consistent adherence to infection control practices, including hand hygiene and appropriate use of gloves.

Since a large proportion of patients with acute HAV, HBV, or HCV infection are asymptomatic, newly acquired infections may not come to the attention of healthcare providers, and clusters of infected patients with common risk factors may not be recognized and reported to public health authorities. In addition, when cases do occur, they may not be reported or adequately investigated. Healthcare-related transmission should be suspected when cases without traditional risk factors for infection are detected.

In many of the HBV and HCV outbreaks reported above, healthcare workers violated fundamental principles related to safe injection practices, which suggests that they failed to understand the potential of their actions to lead to disease transmission. In some of these outbreaks (113,*138*,139,*145*,156), the relevant healthcare worker reported performing the implicated practices routinely over a period of years.

Awareness of fundamental infection control principles, aseptic techniques, and safe injection practices is essential to prevent healthcare-related transmission of hepatitis viruses. These principles, techniques, and practices need to be reinforced in training programs; added to institutional policies and in-service education for healthcare staff, including those in outpatient settings; and monitored as part of the oversight process (191,192). Episodes of such transmission should be viewed as sentinel events for the detection of breaches in infection control practice. They are reminders that such lapses have important public health and patient safety implications.

DISCLAIMER

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

The findings and conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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PART E. Other Pathogens

CHAPTER 47

Uncommon Causes of Healthcare-Associated Infections

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Some community-acquired infections are seen infrequently in hospitals either because they are rare (e.g., rabies) or because they are not endemic to the United States (e.g., hemorrhagic fever virus infections). Some of these infections are potentially lethal and have been transmitted in hospitals. Thus, the diagnosis of these infections can cause great concern and even panic among healthcare workers and infection control personnel. This chapter discusses such uncommon healthcare-associated infections.

RABIES

Etiology and Pathogenesis

Rabies is a severe encephalitis caused by the rabies virus, a rhabdovirus, that infects mammals, including humans. In most areas of the world, rabies is almost always transmitted by the bite of an infected mammal. In the United States, most cases are now cryptic; that is, they occur without a clear exposure to the rabies virus *(1–4)*. Of the 39 human cases reported in the United States since 1995, only 12 had reported bites *(5)*. Many of these are believed to result from inapparent bites from bats or from rabies virus that comes into contact with a break in the skin or mucous membranes *(2,4)*. The virus is believed to multiply at the inoculation site and then spread via peripheral nerves to the spinal cord and the central nervous system. By the time systemic symptoms develop, the virus has traveled peripherally down efferent nerves to nearly every organ and tissue including, most importantly for the life cycle of the virus, the salivary glands *(1)*. The incubation period is usually 20 to 90 days but has varied from 5 days to many years *(3,4)*. Antigenic and genetic analyses have demonstrated different viral strains that are endemic to different areas of the world and even to different animal species *(3,4)*.

Epidemiology

Human rabies has been acquired on all continents except the Antarctic. The epidemiology of rabies reflects that of local animal rabies. Dogs are the most important rabies reservoir for humans in underdeveloped countries. In the United States, wild carnivorous animals such as skunks, raccoons, bats, coyotes, and foxes are the most important reservoirs for rabies *(3)*. Hawaii is the only state that remains rabies-free.

In the United States, rabies in humans has decreased from an average of 22 cases per year in 1946 to 1950 to 0 to 5 cases per year since 1960. The number of rabies cases among domestic animals has decreased similarly. However, approximately 16,000 to 39,000 persons receive rabies prophylaxis every year because of animal exposures, about half of which are nonbite exposures *(6)*. The risk of rabies from nonbite exposures is extremely low. Scratches, abrasions, open wounds, or mucous membranes contaminated with saliva or other potentially infectious material (such as brain tissue) from a rabid animal are the usual nonbite exposures requiring prophylaxis. If the material containing the virus is dry, the virus can be considered noninfectious. Since 1980, an increasing number of human rabies cases have been associated with rabies variants that circulate in bats *(2–4)*. The nonbite exposures of highest risk appear to be exposures to large amounts of aerosolized rabies virus or to organs or tissues (i.e., corneas) transplanted from patients who died of rabies and to scratches from rabid animals (7). Two cases of rabies have been attributed to airborne exposures in laboratories, and two cases of rabies have been attributed to probable airborne exposures in a bat-infested cave in Texas (7).

Human-to-human transmission of rabies has occurred among 16 transplant recipients from corneas ($n = 8$), solid organs ($n = 7$), and vascular tissue ($n = 1$). Each donor died from rabies or a rabies-compatible illness (7). Two patients who received corneal tissue and one patient who received a liver from a rabies-infected donor did not develop clinical rabies *(8)*.

The risk for rabies transmission to healthcare workers is low *(9,10)*. Apart from organ and tissue transplants, bite and nonbite exposures inflicted by infected humans could theoretically transmit rabies, but no laboratory-diagnosed cases occurring under such situations have been documented *(11)*. Two human-to-human transmissions of rabies by saliva (a bite and a kiss) are not laboratory confirmed (7).

Clinical Manifestations

The early manifestations of rabies are usually nonspecific and can be difficult to differentiate from other encephalitic diseases. These consist of malaise, fatigue, headache, anorexia, and fever. Rabies progresses to one of two distinct presentations: the most common is the furious form characterized by hydrophobia, aerophobia, or episodic agitation and anxiety; the least common is the paralytic form. Rabies should be considered in any patient with rapidly progressive encephalitis of unknown etiology, particularly in patients who have lived in an area with enzootic canine rabies. Only one human with documented rabies infection is known to have survived the illness *(12)*.

Diagnosis

In the United States, the rapid fluorescent focus inhibition test is the standard test for measuring rabies-neutralizing antibody. The results from this *in vitro* cell culture neutralization test are available within 24 hours. In one study of antibody titers of rabies patients who did not receive postexposure treatment, 50% had serum antibodies by the 8th day and 100% by the 15th day of illness *(13)*. Rabies virus may be demonstrated by immunofluorescent antibody staining of brain and skin tissue. The most reliable and reproducible of the direct immunofluorescent studies that can aid in patient diagnosis is that performed on neck skin obtained by biopsy *(1)*. In this test, a 6- to 8-mm full-thickness wedge or punch biopsy specimen containing as many hair follicles as possible is obtained from the posterior aspect of the neck above the hairline. Histologic examination of brain tissue from human rabies cases typically shows perivascular inflammation of the gray matter, various amounts of neuronal degeneration, and, in many cases, characteristic cytoplasmic inclusion bodies (Negri bodies). A reverse transcriptase-polymerase chain reaction (PCR) test may be the diagnostic procedure of choice for suspected rabies *(4)*.

Prevention and Control

Patients who have suspected rabies should be placed on Contact Precautions (see Chapter 89) to minimize the number of possible healthcare worker exposures and to minimize anxiety, although Standard Precautions are adequate (14). Possible cases should be reported to public health officials immediately, so that they can assist with an epidemiologic and diagnostic workup. Healthcare workers who have had a significant exposure should receive postexposure prophylaxis (15). Casual contact with a person with rabies (i.e., touching the patient) or contact with noninfectious fluid or tissue (e.g., blood or feces) does not constitute an exposure and is not an indication for prophylaxis (7). Postexposure prophylaxis is recommended after contact with human rabies only if a bite or nonbite exposure (e.g., contamination of abraded skin or mucous membranes with saliva, nerve tissue, urine sediments, or other potentially infectious material) can be documented. Because postexposure prophylaxis after the onset of disease is of no known benefit, such treatment for patients after onset of clinical rabies is not recommended.

CREUTZFELDT–JAKOB DISEASE/ TRANSMISSIBLE SPONGIFORM ENCEPHALOPATHIES

Etiology

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are rare, progressive, invariably fatal neurodegenerative disorders (16). This family of diseases includes classic or sporadic Creutzfeldt–Jakob disease (CJD) and variant CJD (vCJD) in humans. The purported unconventional causative agents are prions, which induce abnormal folding of cellular prion protein through a mechanism that remains debatable *(17)*. The extremely small prions exhibit great resistance to chemical and physical agents (e.g., sterilization procedures), fail to induce either an inflammatory or an immune response, and lack demonstrable nucleic acid or nonhost protein *(18)*. Although CJD is clearly transmissible to animals and humans *(19,20)*, most cases of CJD occur sporadically and are of unknown cause (16), but CJD is also a genetic disorder inherited as a familial dominant trait *(21)*.

A new form of CJD in humans, called vCJD, emerged in the 1990s and may be related to bovine spongiform encephalopathy (BSE) *(20,22,23)*. BSE is also known as "mad cow disease" and may be transmitted to humans by consumption of beef products contaminated by central nervous system tissue. An outbreak of BSE in cattle in the United Kingdom occurred from the early 1980s to the late 1990s *(20)*. As of March 2010, a total of 216 cases of vCJD have occurred in humans, most of them in the United Kingdom *(24)*. Strong laboratory and epidemiologic evidence indicates that vCJD is linked causally with BSE. The epidemics of BSE and vCJD in the United Kingdom have prompted blood-collection agencies in the United States to refuse donors who have lived or traveled in Europe for an extended period of time. vCJD occurs at an unusually young age compared with classic CJD (median age 26 years vs. 68 years) *(22)*.

Pathogenesis

Infection by prions causes central nervous system degeneration with spongiform degeneration of gray matter, severe loss of neurons, vacuolization of neuronal cytoplasm, marked proliferation of astrocytes, and little inflammation. The actual mechanisms by which prions cause neurologic disease are unknown, but they appear to induce an abnormal irreversible folding of normal prion protein. There is no significant humoral or cell-mediated immune response to any known infectious agent. However, a characteristic brain protein can sometimes be detected in spinal fluid and used for diagnosis *(25,26)*. Prions have been found in lymph nodes, liver, kidney, spleen, lung, cornea, and cerebrospinal fluid, although less regularly and in far lower titers than in the brain and spinal cord. The brain may contain at least 10^8 infectious units per gram *(27)*.

Epidemiology

The incidence of CJD in the United States is about one case per million persons per year (16). This incidence appears to have become stable since 1979. The age-specific incidence peaks at 65 to 69 years, but occasional cases occur as early

as the second decade and as late as the ninth decade of life. vCJD cases occur at a younger age *(22)*.

More than 250 iatrogenic cases of CJD have been reported worldwide *(28)*. Most of these have been associated with the use of cadaveric dura mater grafts, growth hormone, and corneal grafts. Six cases are linked to contaminated invasive equipment, four with neurosurgical instruments, and two with stereotactic electroencephalographic depth electrodes. All of these equipment-related cases occurred before the routine implementation of sterilization procedures currently used in healthcare facilities. No such cases have been reported since 1976. There is no evidence of occupational transmission to healthcare workers *(28)*.

Clinical Manifestations

Patients with CJD usually present with progressive mental deterioration. In about half the patients, cerebellar or visual signs dominate the clinical presentation with only moderate to minimal mental deterioration. Abnormal movements, usually including myoclonus, are found late in the illness. The progression of disease is usually relentless. Most patients die within 6 months. There are no verified recoveries.

Diagnosis

Diagnosis can often be inferred by clinical features of the illness and by an immunoassay for protein 14-3-3 in the cerebrospinal fluid of patients with rapidly progressive dementias accompanied by myoclonus or ataxia *(25)*. A magnetic resonance imaging study may show characteristic findings for vCJD *(22)*. However, a brain biopsy or autopsy may be needed to confirm the diagnosis *(18,23)*.

Prevention and Control

Any program to prevent transmission of CJD and TSEs from patients in hospitals should first seek to detect all such patients before brain or other high-risk tissues (dura mater, spinal cord, and eyes) are biopsied. Such patients can be identified by screening patients for "unexplained dementia without a detectable brain mass." Any patient meeting this description should be considered to have CJD until proven otherwise even if another diagnosis such as vasculitis is being considered. The neurosurgeons, pathologists, and others in the operating room, the pathology department, and the infection control department should be alerted about such a patient if a biopsy of high-risk tissue is being considered. Some neurosurgeons may elect not to biopsy potential CJD patients unless an alternate, treatable diagnosis is also under consideration. Hospitals should develop a CJD protocol for nervous system tissue biopsies done on such patients (*28*–*30*,31). Disposable surgical instruments should be used when possible. Reusable instruments should be discarded or sterilized according to a CJD protocol or the instruments should be quarantined until another diagnosis is made. Powered instruments, such as drills and saws, should be avoided or covered by a disposable protective shield. Brain and other high-risk tissues should be labeled as "suspected CJD" before being sent to pathology. The pathology department should have a plan to track such tissue and quarantine and disinfect instruments, such as microtomes, that contact CJD tissue. It is important to note that formalin- and glutaraldehyde-fixed tissues may be infectious indefinitely *(29)*. Confirmed CJD tissue can be managed as regulated medical waste per state regulations. No one suspected of having CJD should serve as a blood or tissue donor even though transmission of classic CJD has never been linked to blood, but vCJD has been transmitted via blood transfusion *(32,33)*. Blood or blood products from such patients should be disposed of per state regulations for regulated medical waste.

CJD patients should be cared for using Standard Precautions (14). Sharps injuries involving spinal fluid or high-risk tissues can be cleansed using 0.5% sodium hypochlorite or 1 N sodium hydroxide *(28,29)*. During an operation or autopsy, disposable surgical caps, water-repellant gowns, aprons, double gloves, and face visors (covering eyes, nose, and mouth) should be worn *(29)*. Autopsies should be done only if the pathologist is aware of the potential diagnosis of CJD and uses the Precautions mentioned previously for the autopsy suite and pathology laboratory *(29)*. When the patient dies, the morgue and funeral home should be notified that the patient had suspected or confirmed CJD.

VIRAL HEMORRHAGIC FEVER

The term *viral hemorrhagic fever* (VHF) refers to the illness associated with a number of geographically restricted viruses. This illness is characterized by fever and, in the most severe cases, shock and hemorrhage *(34)*. Although a number of other febrile viral infections may produce hemorrhage, only the agents of Lassa, Marburg, Ebola, and Crimean–Congo hemorrhagic fevers (CCHFs) are known to have caused significant outbreaks of diseases with person-to-person transmission.

None of these viruses are endemic to the United States. However, increasing levels of international travel result in rare cases of VHF imported into the United States, and there is concern that these viruses may be used for bioterrorism (*34*,35,*36*–*39*). When cases are hospitalized, there is often concern about the potential for healthcare-associated transmission. However, evidence shows that transmission of these viruses does not occur through casual contact and is rare in hospitals if adequate Standard Precautions are used *(34,36,40)*. Hantaviruses can cause hemorrhagic fever and are endemic in the United States but are not spread person-to-person or in hospitals *(41)*.

Lassa Fever Virus

Lassa fever virus is spread in Africa by a rodent not present in the United States. Person-to-person spread requires close personal contact or contact with blood or excreta. Careful follow-up of household and other close contacts of cases imported into Western Europe and North America has shown no evidence of secondary transmission from casual contact, in stark contrast to earlier reports from African hospitals *(34,36)*. The clinical spectrum of Lassa fever is wide, and the likelihood ratio of illness to infection is 9% to 26% *(42)*. After an incubation period of 1 to 3 weeks, illness begins insidiously with fever, sore throat, weakness, and malaise. The long incubation period increases the likelihood that asymptomatic cases will be imported into the

United States. The infection often progresses over several days to a generalized toxic syndrome with pharyngitis (often severe and exudative); retrosternal pain; vomiting; abdominal tenderness; and signs of vascular instability and capillary leakage including hypotension, bleeding, and edema of tissues. High levels of viremia and aminotransferase concentrations are associated with mortality and probably infectiousness of body fluids. The virus is present in blood and, sporadically, in the throat and urine of patients *(40)*. Overall, the case-fatality rate is about 1% to 2% *(42)*. Diagnosis can be made by viral isolation or by demonstrating immunoglobulin M (IgM) antibodies to Lassa fever virus or a fourfold rise in titer of IgG antibody between acute- and convalescent-phase serum specimens *(34,43)*. Treatment with ribavirin effectively reduces mortality *(44)*.

Marburg and Ebola Viruses

Marburg and Ebola hemorrhagic fever viruses are closely related, as is their endemic geographic area. The mode of acquiring natural infection is unknown. Secondary person-to-person transmission results from close personal contact. Healthcare-associated transmission has occurred with both viruses and appears to depend on contact with blood, secretions, and excretions *(34,45)*. There is no evidence of spread by casual contact or aerosol. The onset of illness is abrupt, and clinical manifestations include fever, headache, general malaise, myalgia, arthralgia, and sore throat. These symptoms are often followed by diarrhea, abdominal pain, a desquamating morbilliform rash, and hemorrhagic manifestations including petechiae and frank bleeding. Diagnosis requires isolating the virus from blood, detection of nucleic acids using PCRs, or demonstrating IgM or rising IgG antibodies *(46,47)*. Treatment is supportive. In one epidemic of Marburg hemorrhagic fever in Europe related to an imported African green monkey, the case-fatality rate was 23% for primary cases, but no deaths were reported among the six secondary cases *(48)*. The incubation period ranges from 3 to 10 days for Marburg hemorrhagic fever. For Ebola hemorrhagic fever, the case-fatality rate is even higher, generally greater than 50% in reported epidemics. The incubation period ranges from 2 to 21 days and averages about 7 days *(34)*.

Crimean–Congo Hemorrhagic Fever Virus

The CCHF virus is present in many wild and domestic animals in the endemic areas. Ticks act both as a reservoir and a vector for CCHF; ground-feeding birds may disseminate infected ticks *(34)*. Humans become infected by being bitten by ticks or crushing them. Contact with blood, secretions, or excretions of infected animals or humans may also transmit infection. Healthcare-associated transmission is well described *(34)*. Evidence suggests that blood and other body fluids are highly infectious and that airborne transmission is unlikely. Initial symptoms include fever, headache, myalgia, arthralgia, abdominal pain, and vomiting. Sore throat, conjunctivitis, jaundice, photophobia, and various sensory and mood alterations may develop. A petechial rash is common and may precede a hemorrhagic diathesis including hemorrhage from multiple sites. The case-fatality rate is estimated to range from 15% to 70%, but more than 15% of cases may be asymptomatic. The incubation period is 2 to 9 days. Diagnosis requires isolating the virus from blood or detecting rising IgG antibody or nucleic acids using PCR *(49)*. Treatment is supportive.

Diagnosis

The patient's travel history, symptoms, and physical signs provide the most important clues to the diagnosis of any of the causes of VHF. Travel exclusively to urban zones in endemic areas or an interval of greater than 3 weeks from travel in an endemic area to onset of symptoms make VHF unlikely *(34)*. Other patients at risk for VHF include those who, within 3 weeks before onset of fever, have had direct contact with blood or other body fluids, secretions, or excretions of a person or animal with VHF or who worked in a laboratory or animal facility that handles hemorrhagic fever viruses. A single case of any VHF in the United States should suggest bioterrorism unless there is an appropriate travel history *(45)*.

Initial symptoms are flu-like and nonspecific. The differential diagnosis includes influenza, arboviral, and other viral infections; bacterial infections such as typhoid fever, toxic shock, streptococcal pharyngitis, and rickettsial diseases; and parasitic infections such as malaria. Symptoms and signs supporting the diagnosis of VHF are pharyngitis, conjunctivitis, a skin rash, and, later, hemorrhage and shock.

Prevention and Control

If clinicians feel that VHF is likely, they should take two immediate steps: (a) notify local and state health departments and the Centers for Disease Control and Prevention (CDC) and (b) institute special precautions, including the use of a private room and use of gloves for all patient and specimen contact. The CDC in 1988 recommended precautions for VHF that were updated in 1995 and 2005 (*34*,35,*50*). Blood, urine, feces, vomitus, and respiratory droplets should be considered infectious. Gloves, gowns, face shields, and goggles should be used as necessary to prevent exposures to these body fluids. Patients should be placed on Contact Precautions (see Chapter 95) (14). In addition, the following measures should be implemented: (a) eye covering (goggles or shields) for all contact within 3 ft, (b) a negative pressure room and use of a high-efficiency particulate air respirator (mask) if aerosolization of virus is likely (e.g., patients who have a prominent cough), (c) use of class II biologic safety cabinet following biosafety level 3 practices for laboratory specimens, and (d) pretreatment of serum specimens with polyethylene glycol *p-tert*-octylphenyl ether (10 μL of 10% Triton X-100 per mL of serum) for 1 hour *(50)*. All specimens should be marked with the biohazard symbol, so that all persons handling these specimens will be alerted to use proper precautions, including gloves. If a patient with any VHF dies, all unnecessary handling of the body, including embalming and autopsy, should be avoided. The corpse should be placed in an airtight bag and cremated or buried immediately.

Patients who likely have Lassa fever should be treated with ribavirin, as should all individuals who have had unprotected contact with the patient's body fluids or excretions *(44)*. Examples of unprotected contact include sexual intercourse, shared use of eating or drinking utensils, and failure to use gloves to handle items known to be contaminated with the patient's blood or secretions.

MENINGOCOCCAL INFECTIONS, INCLUDING PNEUMONIA

Infections caused by *Neisseria meningitidis* are endemic throughout the world, but also occur in epidemics. Among civilians in the United States, meningococcal disease occurs primarily as single isolated cases or, infrequently, in small localized clusters. One third of all cases of meningococcal disease occur among patients 20 years of age or older. Healthcare-associated spread of the meningococcus is rare, but hospitalization of a case of invasive meningococcal disease is often associated with severe anxiety among healthcare workers caring for the patient.

Etiology

N. meningitidis is a gram-negative diplococcus that produces a polysaccharide capsule that forms the basis for the serogroup typing system. There are at least 13 serogroups, but serogroups B and C cause most cases of meningococcal disease in the United States, with serogroup Y increasingly seen and serogroup W135 accounting for most of the rest *(51)*.

Epidemiology

Carriage of meningococci in the pharynx is common. One study found a 4.9% to 10.6% prevalence of carriage in a nonepidemic situation involving crowded living conditions *(52)*. No disease was noted in this population. The median duration of carriage was 9.6 months, and a 5.7% to 12.5% yearly incidence of acquisition was noted. Crowding appears to be one important factor influencing the prevalence of meningococcal carriage. The risk of acquisition of carriage is also increased if the index carrier is ill rather than asymptomatic *(53,54)*. Acquisition of a new meningococcal serotype can result in asymptomatic colonization (the carrier state), local infection, or, rarely, invasive disease. The recent acquisition of carriage, rather than chronic carriage, may be the factor associated with the greatest risk of disease, because carriage longer than 2 weeks results in the development of apparently protective type-specific antibody *(55)*. Transmission is believed to occur by direct contact, including contact with large droplets from the nose and throat of infected or colonized carriers. Generally, close live-in or intimate contact (e.g., mouth-to-mouth contact) is required to transmit meningococci effectively, especially if the index carrier is asymptomatic *(52)*.

Risk to hospital personnel and patients from casual contact with an infected patient appears to be small. Epidemics of disease and colonization related to meningococcal pneumonia have been reported *(56)*. However, most *N. meningitidis* pulmonary infections apparently are not associated with serious illness or transmission. Transmission from patients who have meningococcemia or meningitis to hospital personnel is rare but can occur to personnel who have intimate contact with respiratory secretions from infected patients *(57–60)*. Laboratory workers are also at risk for meningococcal disease *(61)*. Laboratory workers should follow biosafety procedures and consider meningococcal vaccination (*61*,62) (see also Chapter 77). It is not clear why transmission of meningococcal disease in hospitals is so rare compared with community transmission. Perhaps, transmission is limited because of the rapid institution of barrier precautions, treatment of the patient, and prophylaxis of exposed persons. The incubation period for disease varies from 2 to 14 days and is commonly 3 to 4 days.

Clinical Manifestations and Diagnosis

Meningococcal disease includes bacteremia without sepsis, meningococcemia without meningitis, meningitis with or without meningococcemia, and the meningoencephalitic presentation. A petechial rash is often present in invasive disease. Diagnosis is made by appropriate cultures and detection of antigen in spinal fluid, blood, or urine *(63)*.

Prevention and Control

Droplet Precautions should be used to minimize transmission from patients with invasive meningococcal disease (see Chapter 90). Confirmed cases should be promptly reported to public health authorities to limit illness in prehospital contacts.

In addition, antibiotic prophylaxis should be considered for those with intimate contact with an untreated patient. This group potentially includes (a) community contacts, including family; (b) rarely, hospital personnel; and (c) possibly, hospitalized patients who are close contacts of a patient with untreated meningococcal pneumonia. When prophylaxis is necessary, it is important to begin it immediately, often before results of antimicrobial susceptibility testing are available (*63*,64). Ceftriaxone can be used for pregnant women. In the absence of a known exposure to meningococcal illness, personnel found to be colonized with meningococci should not be treated or removed from patient care activities.

Laboratory scientists with percutaneous exposure to an invasive *N. meningitidis* isolate from a sterile site should receive treatment with penicillin; those with known mucosal exposure should receive antimicrobial chemoprophylaxis (*61*,64). Microbiologists who manipulate invasive *N. meningitidis* isolates in a manner that could induce aerosolization or droplet formation (including plating, subculturing, and serogrouping) on an open benchtop and in the absence of effective protection from droplets or aerosols should also consider meningococcal vaccination and antimicrobial chemoprophylaxis when indicated (see also Chapter 77) (62).

PLAGUE

Etiology

Plague is a zoonotic infection caused by *Yersinia pestis (65). Y. pestis* is a gram-negative, facultatively anaerobic, asporogenous bacillus that belongs to the bacterial family Enterobacteriaceae. It grows aerobically on most culture media, including blood agar and MacConkey's agar *(65). Y. pestis* produces numerous virulence factors, including V and W antigens and endotoxin *(65–67)*.

Pathogenesis

Plague bacteria are inoculated by the bite of an infected flea and migrate by cutaneous lymphatics to the regional lymph nodes. *Y. pestis* resists destruction within mononuclear phagocytes and multiplies intracellularly. Acute

necrotizing suppurative lymphadenitis develops in the involved lymph nodes (the bubo) *(66)*. Transient bacteremia is common in bubonic plague and may result in metastatic lesions (liver, spleen, meninges) and endotoxemia with hypotension, oliguria, altered mental status, and subclinical disseminated intravascular coagulation.

Epidemiology

Plague is an ancient disease. Epidemics of plague brought devastation to many societies, including medieval Europe, with a massive loss of population. Humans, however, are an accidental host and have no role in the maintenance or propagation of plague in nature. Rats, which were the reservoir of epidemic plague, no longer are subject to epizootics of plague as they were in the past. Now, infected sylvatic rodents are the primary reservoir in the southwestern United States and have become entrenched in rural areas of many countries *(65,66)*. Plague occurs worldwide, with most of the human cases reported from developing countries of Asia, Africa, and South America. Several hundred cases are reported annually to the World Health Organization (WHO) *(65–67)*. From 1989 through 2003, 38,310 cases of plague and 2,845 deaths (7%) were reported to the WHO by 25 countries in Africa, the Americas, and Asia *(68)*.

In the United States, most of the human plague (except for rare laboratory accidents and imported cases) is contracted in nonurban sylvatic foci in the states of New Mexico, Arizona, Colorado, Utah, and California. Each year, 10 to 40 cases are reported in the United States *(65–67,69,70)*. From 1970 through 2007, 415 cases of plague were reported in the United States (a mean of 11 cases per year), with 59 deaths (14%) *(65)*. Cases in travelers, acquired in endemic areas but manifested elsewhere, have been reported *(71)*. A delay in diagnosis and poor outcome may result if travel history is not ascertained. Most of the cases are diagnosed during the months of May to October. A disproportionately large number of cases occur in American Indians *(72)*.

Plague is primarily a zoonotic infection. It is perpetuated in the natural animal reservoirs of urban and sylvatic rodents by flea bites or by ingestion of infected animal tissues. Worldwide, rats are the most important reservoirs of plague bacillus. In sylvatic foci of plague, such as in the southwestern United States, the important reservoirs are the ground squirrel, rock squirrel, and prairie dog. Humans become infected when bitten by rodent fleas and occasionally by handling of contaminated animal tissues *(73)*. Transmission from domestic cats has been reported in the United States *(74–76)*. Direct person-to-person spread of plague is rare and occurs during epidemics of pneumonic plague.

Clinical Manifestations

Bubonic plague is the most common clinical presentation. The incubation period is 2 to 7 days following the bite of an infected flea. Patients present with a sudden onset of high fever, chills, weakness, headache, and, at the same time or shortly thereafter, a swollen and intensely painful regional group of lymph nodes (the bubo) usually in the groin, axilla, or neck *(65–67)*. Hematogenous spread may result in secondary pneumonia characterized by a rapid course and high mortality. The sputum is purulent and contains plague bacilli. Plague pneumonia is highly contagious by droplet transmission. Primary inhalation pneumonia is rare, but it is always a potential threat following exposure to a patient or a cat with plague pneumonia *(74,75)*. Any patient with plague and cough should be suspected of having pneumonia until proven otherwise.

Other clinical syndromes include septicemia, meningitis, pharyngitis, and cutaneous plague. Gastrointestinal symptoms (nausea, vomiting, and diarrhea) may dominate the clinical picture and lead to diagnostic confusion.

Diagnosis

Diagnosis of plague should be suspected in febrile patients with a history of exposure to rodents or to other mammals in endemic areas. The aspirate from the bubo should be stained with Gram and Wayson (or Giemsa or Wright) stains and also cultured. Several blood cultures should be obtained. Blood smears may be positive in patients with septicemia. Smears and cultures of the sputum, cerebrospinal fluid, and skin lesions should be done when appropriate. Rapid diagnostic tests, such as F1 antigen detection, IgM enzyme immunoassay, immunostaining, PCR, and serological testing of specimens of acute and convalescent phases of illness, are available only at some state health departments, the CDC, and military laboratories *(65,67)*. Chest radiography should be done in every patient with suspected plague. Testing of clinical specimens and isolates from suspected plague patients should be coordinated through state health departments and sent to CDC's Diagnostic and Reference Laboratory Section, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases (telephone: 1-800-232-4636). The CDC, Plague Branch (telephone: 1-800-232-4636), can perform the fluorescent antibody stain, PCR testing, the definitive culture identification, and serologic testing on acute- and convalescent-phase sera (*http://www.cdc.gov/ncidod/dvbid/plague/diagnosis.htm* [cited January 7, 2010]).

Prevention and Control

No healthcare-associated transmission of plague has occurred in the United States in modern times, but the potential danger demands prompt institution of infection control measures any time the disease is suspected. Plague is an internationally quarantinable disease. All patients with suspected plague must be immediately reported to the health department.

All patients with plague must be placed on Droplet Precautions for the first 72 hours after start of effective treatment because of the possibility that pneumonia may supervene (14,77). Standard Precautions are then adequate for the duration of hospitalization. In patients with pharyngitis or a positive throat culture, Droplet Precautions should continue until a negative throat culture is obtained for *Y. pestis*. For patients who have plague and have a cough or pneumonia, Droplet Precautions plus eye protection should be continued for at least 72 hours after the initiation of effective antimicrobial therapy. Respiratory isolation is not necessary as the droplet nuclei do not play a significant role in transmission of plague pneumonia *(78)*. All contacts of plague pneumonia patients should be rapidly identified. Individuals with a direct face-to-face contact (<2 m) with a person with plague pneumonia who has not

had antibiotic treatment for at least 48 hours should be given prophylactic or abortive treatment *(79)*. Doxycycline 200 mg/day for 5 to 10 days is recommended in nonpregnant adults. Streptomycin, gentamicin, chloramphenicol, ciprofloxacin, or, in pregnant women, trimethoprim-sulfamethoxazole may also be used for abortive therapy (*79*,*80*,81). All contacts should be instructed to have their temperature taken twice daily and to report fever, cough, or other symptoms. Surveillance may terminate 7 days after the last contact with the case–patient. Isolation of asymptomatic close contacts is not recommended. All laboratory specimens should be handled with gloves. Laboratory personnel should be alerted to the possibility of plague to avoid skin contact with and aerosolization of cultures. A previously used formalin-killed vaccine was discontinued in 1999 by its manufacturers and is no longer available.

Bioterrorism Potential

Plague outbreaks following use of an aerosolized plague bacillus as a biologic weapon are a plausible threat (see Chapter 102) *(79)*. The occurrence of cases and clusters of cases of primary pneumonic plague in locations not known to have enzootic infection or in persons without risk factors should lead to a suspicion of bioterrorism. Recommendations on the management of bioterrorism-related plague outbreaks have been published *(79)* (see also Chapter 102).

PSITTACOSIS

Etiology

Psittacosis (ornithosis) is a disease of birds caused by *Chlamydophila* (*Chlamydia) psittaci* and is transmissible to humans. *C. psittaci* is an obligate intracellular parasite and is considered a specialized bacterium *(82)*.

Pathogenesis

C. psittaci enters the body via the upper respiratory tract after the inhalation of infectious material. The microorganism spreads to the reticuloendothelial cells of the liver and spleen and, after replication, invades the lungs and other organs by hematogenous dissemination *(82)*. Psittacosis is a systemic illness with predominantly pulmonary involvement.

Epidemiology

Dried excreta of birds is the main source of infection. Human-to-human transmission is rarely reported but may result in more severe disease. Human-to-human transmission has also been reported with the related species *Chlamydophila pneumoniae (82–84)*. Clusters of possible healthcare-associated transmission of *C. psittaci* have been reported, but possible serologic cross-reactivity with *C. pneumoniae* complicates the evaluation of these reports *(85–87)*.

Psittacosis is reported worldwide and is associated with exposure to infected birds and other animals *(82–88)*. There has been a recent decline in psittacosis cases in the United States associated with effective control of the disease in domestic and imported birds, but 100 to 250 cases are reported annually, and small outbreaks continue to occur (*82*,89,*90*). Psittacosis is an occupational hazard for people working with birds, including veterinarians, and poultry-processing plant employees and bird fanciers are also at risk of infection *(91,92)*. A minority of patients have no history of bird contact and may have had only an exposure to a contaminated environment or to an infected human *(93)*.

Clinical Manifestations

The incubation period is 6 to 20 days. The severity of illness ranges from a mild flu-like illness to an overwhelming lethal infection. In the preantibiotic era, the mortality rate was 20%. Chills, fever, headache (often severe), malaise, anorexia, myalgias, and persistent cough are the usual symptoms *(94–96)*. Pneumonia is the major clinical manifestation. Hepatosplenomegaly is common and should lead to a consideration of psittacosis in a patient with pneumonia. Asymptomatic seroconversion can occur.

Diagnosis

A compatible clinical illness in a patient with a history of exposure to birds should lead to a suspicion of psittacosis. Chest radiography usually shows a pulmonary infiltrate but is nonspecific. A fourfold rise in titer of complement-fixing antibodies to *Chlamydia* antigen to at least 1:32 between acute and convalescent specimens is diagnostic. A single titer of 1:32 in a compatible clinical setting is presumptive evidence of psittacosis *(82)*. Effective antibiotic therapy may blunt the antibody response. The isolation of *C. psittaci* by culture of respiratory secretions is possible but not routinely available except in reference laboratories *(82)*. PCR analysis of human and bird clinical specimens for *C. psittaci* has been successfully used in the management of outbreaks of psittacosis, but the assay is not commercially available *(97,98)*. Laboratory diagnostic criteria and commercially available laboratory tests for psittacosis in humans have been summarized in a recent publication (99).

Prevention and Control

Prevention of psittacosis consists of control of avian infection and prevention of bird-to-human transmission (99). Human respiratory secretions may be infectious, but human-to-human transmission is very rare, and healthcare-associated psittacosis is only a remote possibility. CDC guidelines do not recommend isolation of hospitalized patients with psittacosis or the use of a private room, masks, gowns, or gloves (14). Pet-assisted therapy in healthcare facilities is gaining in popularity in the United States. The introduction of birds as pets into hospitals is undesirable *(100)* (see Chapter 93). Psittacosis is a notifiable disease, and cases should be reported to the local health department *(83)*. The mortality rate in treated patients is low (<1%) *(82)*.

TETANUS

Tetanus (lockjaw) is a disease caused by a neurotoxin tetanospasmin produced by *Clostridium tetani*. Tetanus is manifested by uncontrolled muscle spasms, results in high mortality, and is preventable by immunization. It is more common in developing countries but continues to occur in the United States, especially in unimmunized or inadequately immunized elderly persons *(101)*.

Etiology

C. tetani is a motile, gram-positive, strictly anaerobic, nonencapsulated, spore-forming rod. The drumstick-shaped spores are highly resistant to chemical disinfection and heat but are destroyed by autoclaving. *C. tetani* can be found in human and animal feces, and the spores can survive in dry soil for years. *C. tetani* is a noninvasive microorganism and depends on the introduction of its spores into damaged or devitalized tissue to provide the anaerobic conditions favorable for its growth.

Pathogenesis

The potent neurotoxin tetanospasmin is produced by vegetative *C. tetani* in a localized site of infection and enters the nervous system at myoneural junctions of motor neurons either locally or after hematogenous and/or lymphatic spread. Tetanospasmin is carried by retrograde axonal transport to the neuraxis, where it binds to the presynaptic terminals of the inhibitory synapses, preventing transmitter release. The absence of inhibition results in increased muscle tone, rigidity, and simultaneous spasms of both agonist and antagonist muscles *(101)*.

Epidemiology

C. tetani resides harmlessly in the intestines of horses and other animals, including humans. Soil or fomites contaminated with human or animal feces serve as a source of infection. *C. tetani* spores are ubiquitous, and essentially any wound or infected area with an anaerobic environment can serve as a nidus for the disease *(101)*. The incidence of tetanus in a population is related to the prevalence of immunity and the frequency of trauma. In the United States, the incidence of tetanus has been 0.16 cases per 1,000,000 population in recent years *(102)*. A total of 40 to 50 cases are reported annually *(101–108)*. The disease in the United States occurs predominantly in older adults who are either unimmunized or inadequately immunized. Serologic analysis of the US population suggests that tetanus immunity wanes with age *(109)*. Women, Mexican-Americans, and immigrants from underdeveloped countries have a significantly lower rate of immunity than do non-Hispanic white males *(110)*. Neonatal tetanus is very rare in the United States. Tetanus is a major problem in developing countries, where the prevalence of immunity is low. Common predisposing factors in developing countries include wounds, contamination of umbilical stumps in neonates, postpartum manipulation of the placenta, chronic ear infections, nonsterile injections, unskilled abortions, ear piercing, scarification rituals, and female circumcision *(101,103)*.

Most of the cases are secondary to acute wounds. Other predisposing conditions include chronic wounds, skin ulcers, abscesses, burns, gangrene, parenteral drug abuse, body piercing, and surgery *(107)*. Tetanus occasionally follows surgical procedures, with gastrointestinal surgical procedures most often reported *(101,108,111,112)*. Several small outbreaks of postoperative tetanus have been reported. Both exogenous surgical site contamination in the operating room and endogenous sources (intestinal flora of the patient) of *C. tetani* have been implicated. Standard surgical instrument sterilization techniques are effective against *C. tetani* spores *(101)*. Rarely, the patient has no recognizable tetanus-prone wound.

Clinical Manifestations

The incubation period is usually within 2 weeks but may range from 2 days to months. Early manifestations include localized or generalized weakness, stiffness or cramping, difficulty in chewing and swallowing food, and trismus resulting from increased masseter muscle tone (lockjaw). The disease progresses to generalized muscle rigidity and reflex spasms. Tonic contractions of muscles may result in painful opisthotonos, abdominal rigidity, and the characteristic facial expression called risus sardonicus. Laryngospasm and/or respiratory muscle involvement may interfere with ventilation. Aspiration may result from difficulty in swallowing. Reflex tetanic spasms may be precipitated by stimuli such as noise, light, or touch and may result in opisthotonos, apnea, fractures, tendon separations, and rhabdomyolysis. The autonomic dysfunction with excessive catecholamine release is common and may result in labile hypertension, tachycardia, cardiac arrhythmias, peripheral vasoconstriction, sweating, elevated temperature, toxic myocarditis, and cardiac arrest *(101,104)*. The mortality rate is high in severe tetanus, especially in infants and the elderly, and may exceed 40% *(101,106)*.

Diagnosis

The diagnosis of tetanus is primarily clinical and is based on history and examination. *C. tetani* is rarely seen in Gram stains from a wound or recovered on culture. A definite history of having received a complete immunization series and/or a serum antitoxin level of 0.01 units/mL or higher makes the diagnosis very unlikely *(101)*. The differential diagnosis of tetanus includes meningitis, dental abscess, peritonitis, rabies, hypocalcemic tetany, epilepsy, decerebrate posturing, alcohol and drug withdrawal, dystonic reactions to antipsychotic drugs, and strychnine poisoning.

Prevention and Control

Antibody to tetanospasmin is protective. Serum antitoxin levels of 0.01 units/mL or above are considered protective, although mild tetanus cases have been reported in patients with titers in the range of 0.01 to 1.0 units/mL *(101,104)*. Tetanus is a disease with no naturally acquired immunity but is preventable with appropriate immunization and wound care. Tetanus toxoid is an effective immunizing agent and is administered via intramuscular injections. Current recommendations for active immunization have recently been updated and include the use of Tdap (tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine) (113–115). Completion of the primary series confers immunity to tetanus for at least 10 years in 95% or more of vaccinees. Booster vaccinations are recommended every 10 years to maintain protective antitoxin levels. Healthcare employees can be immunized or given booster injections as part of the preemployment screening process.

Appropriate management of wounds is very important in preventing tetanus. Tetanus-prone wounds include those contaminated with dirt, feces, or saliva; puncture wounds (including accidental needle punctures); avulsions; and wounds resulting from missiles, crushing, burns, and frostbite. However, any wound can result in tetanus, including surgical sites and decubitus ulcers. Careful cleansing, drainage, and debridement of the wound and removal of foreign

bodies and necrotic tissue can reduce the likelihood of tetanus. Recommendations for specific immunoprophylaxis depend on the patient's prior immunization history and the nature of the wound (115). Patients who have received a full immunization series but who have not received a dose for more than 10 years should be given a booster vaccination with (or without) any type of wound. This is especially important in preoperative patients, pregnant women (to protect both mother and child), nursing home residents and paraplegics (risk of decubitus ulcer), patients with chronic foot ulcers, intravenous drug abusers, and healthcare personnel sustaining accidental needle punctures. If the patient is uncertain about prior vaccinations or knows that the full tetanus series has not been received, tetanus vaccine should be given for any type of wound (with arrangements made to complete the series), and additional passive immunization with tetanus immune globulin (TIG) should be given for tetanus-prone wounds. When vaccine and TIG are given concurrently, separate syringes and separate sites of administration should be used. One study demonstrated that the antitetanus prophylaxis given in hospital emergency rooms is often inadequate *(116)*.

Tetanus is not directly transmissible from person to person, and no isolation precautions are indicated for the management of a patient with tetanus. Cases of tetanus must be reported to the health department. Hospitalization or a visit to an emergency room may be the only contact of an unimmunized or inadequately immunized individual with the healthcare system, and routine review of tetanus immunity status should be considered for all hospitalized patients but especially for the elderly, children, pregnant women, preoperative patients, patients with wounds (including burns and decubitus ulcers), and parenteral drug abusers.

BOTULISM

Etiology

Botulism is a disease caused by *Clostridium botulinum* exotoxin. *C. botulinum* is a gram-positive spore-forming anaerobic bacillus. The neurotoxin produced by the microorganism causes a paralytic illness.

Pathogenesis

The toxin can cause the disease by (a) being preformed in the food (botulism food poisoning), (b) being produced in a traumatic wound contaminated by *C. botulinum* (wound botulism), and (c) being produced by *C. botulinum* in the gastrointestinal tract of infants (infant botulism) *(117–119)*. A potent neurotoxin is released after spores germinate and bacterial growth and autolysis occur under appropriate conditions. These conditions include an appropriate pH (>4.6), a temperature generally >10°C, sufficient availability of water, and a relatively anaerobic environment *(118)*. Seven toxin types have been described (A, B, C, D, E, F, and G). Types A, B, and E are the most common causes of disease in humans. Botulinum neurotoxins are the most potent known poison. The toxins interfere with neurotransmission at peripheral cholinergic synapses by binding tightly to the presynaptic membrane and preventing the release of the neurotransmitter acetylcholine.

Epidemiology

From 1990 to 2000, 17 to 43 cases of foodborne botulism have occurred annually in the United States *(120)*. The toxin, when ingested with food, is absorbed from the stomach, the small intestine, and, slowly, the colon. Food items contaminated by botulinum toxin may have a completely normal appearance and taste. If *C. botulinum* microorganisms or spores are ingested and reach the colon, toxin production and absorption can occur in the human gastrointestinal tract as in infant botulism *(117,121)*. The spores of *C. botulinum* are heat-resistant, but the toxins are heat-labile and are destroyed by boiling for 10 minutes or by heating at 80°C for 30 minutes. Thus, terminal heating of toxin-containing food can prevent botulism *(117)*.

Wound botulism occurs when *C. botulinum* contaminates a traumatic wound and produces toxin *in situ (122–124)*. The toxin is then absorbed systemically. The incubation period is 4 to 14 days from the time of injury. The wound may appear clean, but antibiotic therapy may not prevent intoxication. The clinical picture is similar to foodborne botulism but without gastrointestinal symptoms; fever may occur secondary to wound infection. Wound botulism is rare, with only a few cases reported annually *(117)*. Compound fractures and crush injuries to the extremity are the major types of associated wounds *(122)*. Postoperative cases have been reported *(124)*. Parenteral and/or intranasal illicit drug use has been reported as a risk factor for wound botulism *(125,126)*. The use of "black-tar" heroin has emerged as the main cause of wound botulism *(127)*.

Infant botulism is the most common form of botulism in the United States, with 2,419 cases identified in the United States from 1992 to 2006 (average: 2.1 cases per 100,000 live births) *(119,128,129)*. The infant gastrointestinal tract becomes colonized with *C. botulinum* (often from honey contaminated with spores), and toxin is produced *in vivo*. Infants younger than 1 year are usually affected. The illness typically begins with constipation followed by lethargy, listlessness, poor feeding, ptosis, difficulty in swallowing, loss of head control, hypotonia and generalized weakness (the floppy baby), and, in some cases, respiratory arrest. Occasionally, infant-type botulism can occur in adults with altered gastrointestinal anatomy or microbial flora that permits the proliferation of ingested *C. botulinum* and production of toxin *in vivo (130)*. With the availability of botulinum toxins A and B for therapeutic use in muscle spasm disorders, the possibility of inadvertent, surreptitious, or criminal misuse of the toxin should be considered in patients with an otherwise unexplained clinical syndrome consistent with botulism *(131)*. Iatrogenic botulism cases have been reported with therapeutic and unlicensed cosmetic use *(132–134)*.

C. botulinum spores are found in soil and marine sediment worldwide and, therefore, may easily contaminate food products. In the United States, type A spores predominate west of the Mississippi River and type B spores predominate in the eastern states. Type E disease is usually associated with fish products *(117,118)*.

Most cases of botulism food poisoning occur singly or in small clusters and are due to home-canned or home-prepared foods; commercial products and restaurant-prepared foods are implicated in some instances *(135,136)*.

Clinical Manifestations

The incubation period is 12 to 36 hours, with a range of 6 hours to 8 days. Early symptoms include weakness and dizziness. Nausea and vomiting are uncommon. The picture of cholinergic inhibition is manifested by diminished salivation, extreme dryness of the mouth and throat, ileus, constipation, and urinary retention. Cranial nerve involvement is manifested by diplopia, blurred vision, photophobia, dysphonia, dysarthria, and dysphagia. Symmetric descending weakness of the extremities and respiratory muscle weakness occur. The patient characteristically is alert, oriented, and afebrile. Orthostatic hypotension may be present. Ptosis, extraocular muscle palsies, and dilated fixed pupils usually (but not always) are present on eye examination. Oral mucous membranes are dry. Variable degrees of muscle weakness and deep tendon reflex abnormalities are observed. Sensory examination is normal. Respiratory failure may develop secondary to respiratory muscle weakness. The clinical course is often prolonged, and the recovery is gradual *(137,138)*.

Diagnosis

A characteristic clinical picture and history of exposure should lead to suspicion of botulism. Characteristic abnormalities are observed in electromyographic studies in patients with botulism *(117)*. The diagnosis is confirmed by detecting *C. botulinum* toxin (by bioassay in mice) in the blood, stool, gastric contents, or suspected food or by culturing *C. botulinum* from the food, stool, gastric contents, or wounds (in patients with wound botulism) *(139,140)*. These tests are usually performed by reference laboratories.

Prevention and Control

The health department should be promptly notified of all suspected cases of botulism. The source food should be identified, and all potentially exposed individuals should be informed. The disease is not communicable, and isolation is not indicated. The mortality rate for adult botulism is 10% to 25% with modern supportive care and is as low as 2% in infant botulism.

Bioterrorism Potential

An aerosolized or foodborne botulinum toxin weapon potential exists (Chapter 102). Botulinum toxin has been weaponized, and terrorists have tried to use botulinum toxin as a weapon *(141)*. Hospital personnel should be alert to a possibility of a deliberate attack with botulinum toxin when an outbreak of flaccid paralysis is detected.

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SECTION VI

Epidemiology and Prevention of Healthcare-Associated Infections in Pediatric Patients

CHAPTER 48

Healthcare-Associated Viral Respiratory Infections in Pediatric Patients

Ronald B. Turner

Healthcare-associated viral respiratory infection has historically been an important cause of morbidity in pediatric patients. Studies based on virus isolation reported that viral pathogens caused 23% to 35% of all healthcare-associated infections in children and the incidence of healthcare-associated viral infections in this population ranged from 0.59 to 0.72 per 100 patients *(1,2)*. There have been no comprehensive studies of hospital-acquired viral respiratory infection using modern diagnostic techniques, but available data suggest that the apparent incidence has changed little in recent years (*3*,4). Whether these data truly reflect no improvement in healthcare-associated infection rates over the last 20 years or whether improvements in infection control are obscured by the increased sensitivity of polymerase chain reaction (PCR) for detection of viral pathogens is not clear.

The viral pathogens that have been most commonly associated with healthcare-associated respiratory infections in pediatric patients include respiratory syncytial virus (RSV), parainfluenza virus, adenovirus, rhinovirus, and influenza virus. Viruses that are spread via the respiratory tract but that produce more prominent symptoms in other organ systems (i.e., measles, varicella-zoster, and parvovirus B19) are not considered in this chapter (see Chapters 42 and 51). Bocavirus has recently been detected from the respiratory tract of children with respiratory symptoms in a number of studies. The role of this virus as a respiratory pathogen, however, is obscured by the frequent detection of this virus from asymptomatic individuals and the frequent codetection of other established respiratory pathogens in symptomatic individuals *(5)*. This virus will not be considered further in this chapter.

VIRAL PATHOGENS

Respiratory Syncytial Virus and Metapneumovirus

RSV is an enveloped virus with a genome composed of a single negative strand of RNA. The virion has a diameter of 150 to 300 nm. The nucleocapsid, 12 to 15 nm in diameter, is smaller than that of the other members of the paramyxovirus family; thus, the virus has been placed in the separate genus *Pneumovirus*. Human metapneumovirus (HMPV) was described in 2001 *(6)*. The virologic, epidemiologic, and clinical characteristics of this virus are similar to those of RSV *(6–12)*.

RSV is relatively quickly inactivated after exposure to different environmental conditions. In studies using partially purified virus, virus survival decreased as the temperature at which the virus was stored was increased over the range from 55°C to 65°C *(13)*. Virus survival was best at a pH of 7.5 with decreasing infectivity as pH was raised or lowered. RSV is rapidly inactivated by ether, chloroform, and detergents *(14,15)*. Studies of virus survival using nasal secretions from infected infants revealed that infectious virus could be recovered for approximately 0.5 hours on skin, 1 hour on porous surfaces, and 7 hours on nonporous surfaces *(16)*.

Both RSV and HMPV have a single serotype based on neutralization with human sera but have two subgroups *(17)*. The clinical and immunologic significance of these antigenic differences has not been clarified; however, the detection of different viral strains by monoclonal antibody testing and/or nucleic acid analysis is useful in epidemiologic studies *(18–20)*.

RSV infection is the most common cause of lower respiratory infection in young infants. Fifty percent to seventy percent of all infants are infected during the first year of life, and by the age of 4 virtually all infants have had at least one infection *(21,22)*. Reinfection with RSV is common and, despite the nearly universal experience with this infection, the attack rate is approximately 40% for exposed individuals in all age groups *(21,23)*. HMPV infection is also very common with most individuals infected in early childhood.

The seasonal occurrence of RSV infections is well defined. Epidemics of RSV occur annually in the winter or spring *(24)*. These epidemics are consistently associated with increased hospital admissions for pediatric respiratory infection, although the severity of the epidemic varies from year to year. RSV is transmitted by contact with infected respiratory secretions. A study of RSV transmission found that close contact with an infected infant, when virus may be transmitted directly or by large-particle aerosols, or contact with virus-contaminated fomites could transmit infectious RSV to volunteer recipients *(25)*. Transmission of virus by small-particle aerosols was not detected in this study. The role of environmental contamination in the transmission of RSV is not clear, although RSV can survive on environmental surfaces for hours *(16)* and can be recovered from the environment of infected infants *(25)*. Infection with RSV requires that the virus reach the respiratory mucosa. Inoculation of infectious virus into either the nose or the eye is equally efficient for initiation of infection and much more efficient than oral inoculation *(26)*. The incubation period of RSV infection is 2 to 8 days with an average of about 5 days *(27–29)*. Once virus infects the upper respiratory mucosa, it may spread to the lower respiratory tract. RSV infection is limited to the respiratory tract, and respiratory secretions are the only body fluids that contain infectious virus. Shedding of RSV can be detected for a few days before onset of symptoms and generally continues for approximately 1 week *(30)*. Shedding is detected for >2 weeks in approximately 10% of patients.

Immunoprotection against RSV appears to be conferred by serum and secretory antibody *(21,31,32)*. A role for cell-mediated immune responses in the termination of RSV infection is suggested by the observation that children with deficiencies of T-cell immunity have unusually severe infections and prolonged shedding of virus *(33)*.

RSV infection may result in clinical illness involving any level of the respiratory tract. The most severe manifestations of RSV infection are bronchiolitis or pneumonia. The incidence of lower respiratory symptoms is greatest during primary infections in young infants *(21,22)*. Both increasing age and recurrences of infection are associated with an increasing proportion of infections that are asymptomatic or limited to the upper respiratory tract. Hospitalization for RSV infection is generally due to lower respiratory tract infection or apnea. However, during the RSV season, many infants admitted to the hospital have an incidental, community-acquired, RSV infection. HMPV has a similar clinical presentation but generally produces milder illnesses than RSV *(34,35)*.

Parainfluenza Virus

The parainfluenza viruses are enveloped RNA viruses that are members of the genus *Paramyxovirus* in the family Paramyxoviridae. These viruses are susceptible to a variety of chemical disinfectants *(36,37)*. There are four different serotypes of parainfluenza, types 1 to 4, which can be differentiated by antibody to complement-fixing and hemagglutinating antigens. No antigenic variation in these serotypes has been recognized over many years of observation.

Early studies of the parainfluenza viruses reported that both parainfluenza type 1 and type 3 were endemic with infections reported in virtually all months of the year *(38)*. More recent data suggest that infection with parainfluenza type 1 occurs as a fall epidemic in 2-year cycles (39). Parainfluenza, type 2, is much less common and the epidemic peak is more variable. Infections with parainfluenza virus types 1 and 2 are most common in children between 6 months and 6 years of age. By 5 years of age, most children have been infected with both serotypes of virus *(38)*.

In contrast to the behavior of serotypes 1 and 2, infection with serotype 3 occurs in biennial peaks that may be moderated somewhat in the years of high parainfluenza type 1 activity (39). Parainfluenza virus type 3 is a common cause of infection in young infants. A serologic survey reported that 60% of infants were seropositive by 1 year of age and 80% were positive by the time they were 4 years old *(38)*. The actual incidence of infection may be somewhat higher because reinfection, which would not be detected by serology, occurs often in young infants *(40)*. Parainfluenza type 3 often produces illness in the first 6 months of life despite the presence of maternal antibody. The peak incidence of illness is in the second year of life. Primary infections occurring in the second year of life are more likely to be associated with lower respiratory tract infection than those that occur earlier or later. Reinfections with parainfluenza type 3 occur commonly but are generally associated with mild upper respiratory illness.

The parainfluenza viruses have an apparent incubation period of 2 to 8 days *(41,42)*. Viral shedding from the upper respiratory tract occurs 1 to 4 days before the onset of symptoms and continues for 7 to 10 days in most patients with primary infection *(30)*. Some patients with primary infection continue to have intermittent shedding of virus for 3 to 4 weeks. The duration of shedding following reinfection is generally shorter than that after primary infection; however, reinfected patients occasionally shed virus for longer than 2 weeks *(30)*. The mechanism of transmission of the parainfluenza viruses is not known; however, the route of spread is presumed to be by large droplets or direct person-to-person contact.

The serotype of the virus and the presence of preexisting homotypic antibody appear to affect the clinical manifestations of parainfluenza virus infection. Infection with parainfluenza type 1 is most commonly associated with a febrile upper respiratory infection. The most common lower respiratory tract manifestation of type 1 infection is croup. Parainfluenza type 2 is associated with similar clinical manifestations, although the illnesses are generally less severe. Preexisting nasal secretory antibody appears to offer some protection against infection *(42)*. Parainfluenza virus type 3 is associated with disease at all levels of the respiratory tract and is not associated with a predominant clinical syndrome (39). This virus is second only to RSV as a cause of bronchiolitis and pneumonia in young infants.

Adenovirus

The adenoviruses are nonenveloped viruses with a genome of double-stranded DNA. These viruses are not inactivated by ether or chloroform and are stable at temperatures of 4°C to 36°C and pH of 5 to 9. Adenovirus is inactivated by sodium dodecylsulfate, chlorine, ultraviolet (UV) radiation, or formalin. There are >40 distinct serotypes of adenovirus; types 1 to 7 are the most important in pediatric respiratory disease. Adenovirus type 14 has recently emerged as a cause of respiratory disease especially in military recruits but is not yet a significant threat for hospital-acquired infection (43).

Adenovirus infections are an important cause of illness in childhood *(44)*. Antibody to serotypes 1 and 2 is detected in the serum of 60% to 80% of children by 5 years of age, and approximately 40% also have antibody to serotypes 3 and 5 *(45,46)*. About one-half of the adenovirus infections in these infants are associated with illness. The peak incidence of adenovirus-related illness occurs between 6 months and 2 years of age *(47)*, and adenovirus causes 5% to 10% of all febrile respiratory illnesses in children younger than 7 years *(46,47)*. Adenovirus is a much less common cause of respiratory illness in older children or adults. Adenovirus infections are endemic and cause illness in all months of the year *(24)*; an increased incidence of infection has been noted between December and July in some studies *(45,46)*.

The fecal–oral route may be the most likely route of transmission of adenovirus between young children although transmission by aerosol can also occur. Transmission of infection has been documented in families following experimentally induced fecal excretion of adenovirus type 4 *(48)*. During adenovirus infections, fecal excretion of virus occurs in >75% of children *(46)*. Transmission of infection is relatively efficient; 46% to 67% of susceptible household and day care contacts were infected after exposure to adenovirus *(46,47)*. The incubation period of adenovirus in children is not known. However, in adults challenged by the aerosol route, the incubation period was 6 to 13 days *(49)*, and, in a hospital outbreak, the apparent incubation period was 2 to 18 days *(50)*. A unique feature of adenovirus among the pediatric respiratory viruses is that intermittent shedding of the virus may continue for years after infection. Approximately one-half of adenovirus infections are associated with only a single day of virus shedding. One-fourth of the infections, however, result in intermittent shedding of virus for >3 months, and almost 10% continue to shed virus for >1 year *(46)*. Homotypic antibody, whether actively acquired by previous infection or passively acquired by maternal transmission, is partially protective for both infection and illness.

The most common respiratory manifestation of adenovirus infection in young infants is a febrile upper respiratory syndrome *(44,47,51,52)*. Although conjunctivitis is widely recognized as a manifestation of adenovirus infection, only 12% of outpatients *(47)* and 4% of hospitalized patients i have this finding. Hospitalized patients with adenovirus infection often have high and prolonged fevers (*51*,*52*).

Rhinovirus

The rhinoviruses are small, nonenveloped, single-stranded RNA viruses in the picornavirus family. The human rhinoviruses are stable at a pH of 6 to 8 and are not inactivated by chloroform, ether, or detergents (*53–55*). These viruses are rapidly inactivated at a pH of 3 and by UV irradiation. Rhinovirus survives well under environmental conditions. Virus was recovered after 1 hour on porous surfaces, 3 hours on nonporous surfaces, and 3 hours on human skin *(56)*. Other reports have suggested that virus may remain viable in the environment for several days *(57)*. There are >100 distinct rhinovirus serotypes that all appear to have similar epidemiologic characteristics and produce a similar clinical syndrome.

In contrast to other viral respiratory pathogens of childhood, the incidence of rhinovirus infection varies little with age. Approximately two-thirds of children experience a rhinovirus infection each year *(58,59)*; about 60% of these infections are associated with illness. Rhinoviruses cause illness in all months of the year, but there are distinct epidemic peaks of illness in the early fall and in the late spring *(58–61)*.

The mechanism of transmission of rhinovirus has been studied extensively. In experimental models, rhinovirus is transmitted most efficiently by direct person-to-person contact *(62)*, although transmission by large-particle aerosols has also been documented *(62,63)*. A study of natural colds found that treatment of the hands with a virucidal compound prevented transmission of rhinovirus infection, suggesting that hand-to-hand transmission may be important in a natural setting *(57)*. Once virus is transmitted, the incubation period is generally short, with onset of symptoms in 2 to 3 days, although, in a family setting, rhinovirus was cultured from 15% of specimens collected 7 to 10 days before the onset of symptoms *(58)*. Rhinovirus is shed exclusively from the upper respiratory tract. Shedding is most efficient from nasal secretions, although lower titers of virus can be detected in saliva and pharyngeal secretions *(64)*. Virus can also be recovered from the hands of a high proportion of infected volunteers *(56)*. Shedding of virus from infected individuals continues for 2 to 3 weeks after the onset of illness *(58,65)*. Homotypic serum neutralizing antibody correlates with resistance to rhinovirus infection *(59,66,67)*. The characteristic clinical syndrome associated with rhinovirus infection is the common cold but rhinovirus is also an important cause of exacerbations of asthma. These infections are generally not associated with fever.

Influenza

The influenza viruses are discussed in detail in Chapter 42. These viruses are enveloped RNA viruses classified in the family Orthomyxovirus. The virus is classified as type A, B, or C based on antigenic differences in the nucleoprotein and the matrix protein. Heat (56°C), lipid solvents, acid, formaldehyde, and UV irradiation all inactivate influenza viruses. Influenza is capable of prolonged survival on fomites. On nonporous surfaces, the virus was detectable for >48 hours, and, on porous surfaces, virus was detectable for 8 to 12 hours *(68)*. The amount of virus present on hands decreases rapidly with drying but residual virus can be detected for at least 1 hour when the hands are contaminated with large quantities of virus (69). The protective immune response to the viruses is directed at the hemagglutinin and neuraminidase antigens on the surface of the virion. The epidemic behavior of influenza viruses

is a result of variation in the antigenicity of these surface antigens.

The incidence of influenza infections is highest in preschool and school-aged children, with infection rates of 20% to 50% per year *(70–72)*; 60% to 80% of influenza infections in the pediatric age group are associated with illness *(70,72)*. The seasonal epidemiology of influenza virus infection is well established, with annual midwinter and spring epidemics *(70,71)*. Transmission of influenza may occur by small-particle aerosols, by large-particle aerosols (droplets), or by direct contact. The role of small-particle aerosols in transmission has been controversial and resolution of this question has important implications for hospital infection control recommendations (73,74). The incubation period for influenza is 24 to 48 hours. Virus shedding is primarily from the respiratory tract, and most patients shed virus for <1 week after the onset of illness, although shedding may last somewhat longer in young children *(75,76)*. Influenza virus is present in the stool of some infected children *(77,78)*, but the significance of this observation for pathogenesis and transmission of the virus is not known. The clinical manifestations of influenza in children differ from adult infections in that children are less likely to have lower respiratory infection, more likely to have associated gastrointestinal symptoms, and tend to have higher fevers *(71,72)*.

HEALTHCARE-ASSOCIATED VIRAL RESPIRATORY INFECTION

Healthcare-associated viral respiratory infections have important implications for the patient. These infections are associated with an average increase of 5 to 6 days in the length of hospitalization *(1,79)*. The increased length of stay may be somewhat greater when only influenza and RSV are considered (*80*,*81*). In addition to the increased length of stay, many patients with healthcare-associated infection are subjected to additional diagnostic studies or administration of unnecessary antibiotics. Healthcare-associated respiratory infection frequently involves children with chronic underlying medical conditions, presumably because of their frequent and prolonged hospitalizations (4,*82*).

Patients with uncorrected congenital heart disease, chronic lung disease, compromised immune function, and premature infants are at increased risk from healthcare-associated viral infections. In 1982, MacDonald et al. *(83)* reported that healthcare-associated RSV infection was associated with a mortality rate of 44% in patients with congenital heart disease. More recent studies have reported much lower mortality rates in these patients *(84,85)*. Improvements in intensive care management and pediatric cardiac surgery may account for the reductions in the mortality in these populations. A high mortality rate has been associated with healthcare-associated adenovirus infections in patients with underlying pulmonary or cardiac disease in two studies *(86,87)*.

Immunosuppressed patients who acquire a viral lower respiratory infection have a mortality rate of 25% to 45% *(88)*. Infections with RSV and adenovirus are particularly dangerous in this population. The magnitude of the risk of severe illness associated with viral respiratory infections appears to be related to the intensity of the immunosuppressive therapy.

The impact of healthcare-associated viral respiratory infections in neonatal intensive care nurseries is inconsistent from study to study. RSV and adenovirus infections in these patients have been associated with a high (18–29%) mortality rate in some reports *(89–91)*. In contrast, other studies of neonatal healthcare-associated viral infection have reported low or no mortality *(92–100)*, and, in many of these studies, a large proportion of patients were asymptomatic. Most studies, however, have reported significant morbidity associated with healthcare-associated viral infections in neonates (see also Chapter 52 for additional information on healthcare-associated viral respiratory infections in neonates).

Healthcare-associated respiratory infections with a particular virus are temporally related to the presence of the virus in the community *(75,76,101–103)*. Thus, the incidence of hospital-acquired viral respiratory disease is seasonal and the risk of infection is greatest during community epidemics. Virtually all patients, visitors, and hospital personnel are at risk for infection with healthcare-associated viral respiratory pathogens and may serve as a source of infection in the hospital. A respiratory viral pathogen or *Mycoplasma* was detected in 61% of symptomatic pediatric patients admitted to the hospital during the respiratory virus season *(79)*. Furthermore, in this study, a viral pathogen was detected in almost 50% of patients who were asymptomatic or in whom respiratory symptoms were initially overlooked. The incidence of RSV infection in hospital personnel during community outbreaks has been reported to range from 5% to 61% depending on the personal protection measures used *(104,105)*. In one study, 18% of the infections were asymptomatic, and an additional 36% were associated only with mild illness *(106)*. Consistent with the multiple potential sources of virus, detailed studies of healthcare-associated outbreaks of viral respiratory pathogens have found that these outbreaks are usually caused by different strains of virus and are not true point-source outbreaks *(18,20,50,107–109)*.

Young children with underlying chronic medical conditions are most likely to be affected by healthcare-associated viral respiratory infections (4). Specific risk factors, such as intravascular lines or immunosuppression, appear to be less important but a few risk factors have been identified. Children with immunosuppression resulting from cancer have been found to have a higher incidence of influenza infection than children with normal immunity *(110)*. This increased incidence appeared to be related to a failure of preexisting antibody to protect from disease in immunocompromised patients. Specific procedures and devices such as orotracheal and orogastric intubation have both been associated with an increased risk of acquisition of infection *(93,98,111)*. Despite these reports, targeting high-risk patients for specific preventive measures would have little impact on the overall incidence of healthcare-associated viral respiratory infection.

DIAGNOSIS

Epidemiologic and clinical information can provide important clues to the specific etiology of viral respiratory infections. The occurrence of viral respiratory disease in a

community is the result of sequential and relatively discrete epidemics of individual pathogens *(112,113)*. The etiologic diagnosis of an individual patient is aided by knowledge of which viruses are prevalent in the community at a given time. Furthermore, although any of the viral respiratory syndromes may be caused by any of the pathogens, specific pathogens are often associated with particular clinical syndromes as described previously. The presence of a clinical syndrome characteristic of a virus known to be present in the community provides a reasonably reliable prediction of the etiologic diagnosis.

Laboratory Tests for Diagnosis

Laboratory confirmation of the etiologic diagnosis is usually not necessary for management of viral respiratory infections or for the institution of appropriate infection control measures. Specific identification of a pathogen is useful for cohorting of patients and for directing specific antiviral therapy. A specific viral diagnosis may be established by PCR, virus isolation, viral antigen detection in respiratory secretions, or detection of specific antiviral antibodies in acute and convalescent sera.

PCR assays for the detection of the parainfluenza viruses, RSV, and the influenza viruses are commercially available and have become the preferred method for detection of these pathogens. Assays for metapneumovirus, coronavirus, adenovirus, and rhinovirus/enterovirus are also available in some laboratories. These assays require only hours to perform and permit a sensitive and specific diagnosis. Nasal wash specimens appear to be most sensitive for detection of viral pathogens by PCR (114).

Virus isolation in cell cultures remains the standard method for diagnosis of the respiratory pathogens. Isolation of these viruses in cell culture, however, generally requires several days and, in some cases, may take >2 weeks. Recent studies of RSV, influenza, and rhinovirus have found that virus isolation has a sensitivity of 75% to 85% compared with detection of virus by PCR *(115–117)*. The time of collection in relation to the onset of symptoms, the method of specimen collection, and the handling of the specimen before inoculation into cell culture all affect the recovery of virus from infected individuals. Specimens for virus isolation should be obtained as early as possible in the course of the patient's illness. Although some individuals may shed virus for weeks *(30,65)*, virus is most consistently recovered in the first few days after the onset of symptoms. Nasal wash specimens are better than swab specimens for detection of respiratory pathogens *(118–120)*.

Detection of viral antigen in respiratory secretions has been reported for many of the respiratory viruses. Enzyme-linked immunosorbent assay reagents are commercially available as kit technologies for RSV and influenza. These assays provide rapid results but are less sensitive than cell culture or PCR. Many laboratories also offer antigen detection by fluorescent antibody methods; however, the accuracy of these techniques depends on the technical expertise of the laboratory and the quality of the specimen submitted for testing.

Serologic assays are available for most of the respiratory pathogens; however, the need for a convalescent serum limits the usefulness of the serologic tests in the clinical setting. Acute serum specimens should be obtained as soon as possible after onset of symptoms, and convalescent sera should be collected 2 to 3 weeks later. Sera may be stored at 4°C for short periods and may be stored at –20°C indefinitely.

Interpretation of Laboratory Results

Virus Isolation The isolation of a viral pathogen from the upper respiratory tract of a patient with respiratory symptoms is generally considered diagnostic. Virus isolation is absolutely specific if the laboratory confirms the identity of the virus by immunologic methods.

Viral Antigen Detection and PCR Detection of viral antigen in respiratory secretions allows rapid diagnosis of viral infection. The commercially available reagents for detection of RSV infection generally have a sensitivity and specificity of 85% to 95% compared with virus isolation, although individual studies have reported markedly lower sensitivities *(121,122)*. When antigen detection methods are compared with PCR, the sensitivity of antigen detection appears to be 65% to 75% *(116,123)*.

PCR is more sensitive than other methods for detection of viral respiratory pathogens. The sensitivity of PCR relative to virus isolation and antigen detection is consistently >90% *(115–117,124)*. The exquisite sensitivity of PCR can lead to false-positive results if meticulous care is not taken to prevent contamination of the assay.

Viral Serology Interpretation of serologic results depends on comparison of antibody levels in acute and convalescent sera. Antibody levels in a single serum specimen are generally not helpful for diagnosis of viral infection. A fourfold increase in antibody titer in a convalescent serum specimen compared with the titer in an acute serum specimen drawn early in the illness is evidence of infection with the virus.

PREVENTION AND CONTROL OF HEALTHCARE-ASSOCIATED INFECTIONS

Active Immunization

The influenza vaccine is the only vaccine available for the prevention of infection by the respiratory viruses. The influenza vaccine usually contains two type A strains and one type B strain selected to provide immunity to the virus expected in the following influenza season. The strains of virus in the vaccine are changed, as necessary, in response to the changing epidemiology of the influenza viruses. The vaccines available in the United States are trivalent inactivated vaccines and live-attenuated influenza vaccine. All children 6 months to 18 years of age, all adults ≥50 years of age, adults 19 to 49 years of age with underlying medical conditions, and anyone (e.g., healthcare workers and household contacts) who has contact with individuals at high risk for influenza-related complications should be immunized each year *(125)*. Immunization is not effective for intervention in healthcare-associated outbreaks of influenza *(126)* unless antiviral therapy is given for 2 weeks following vaccination to prevent infection while one waits for antibody titers to rise to a protective level (see also Chapter 42).

Passive Immunization

Palivizumab, a humanized monoclonal antibody to RSV, reduces the severity of illness in premature infants, but has no effect on the incidence of infection *(127)*. The role of this preparation for the prevention of healthcare-associated infection has not been studied. Because of the lack of effect on RSV infection, it is unlikely that passive immunization will be useful for prevention of transmission of virus. The use of palivizumab to protect appropriate high-risk patients during healthcare-associated outbreaks of RSV infection has been reported and appears to be effective *(128)*.

Antivirals

Effective antiviral therapy is available for the treatment or prevention of influenza infection (129). Amantadine and rimantadine are useful for prophylaxis of influenza A infections in children older than 1 year. Oseltamivir and zanamivir may be used for prevention of both influenza A and B infections. Oseltamivir is approved for in children over 1 year of age and zanamivir is approved for children 5 years of age or older. The drug resistance patterns of circulating influenza isolates will influence the appropriate choice for prophylaxis. These drugs are not a substitute for immunization but can be used in patients who cannot be immunized or who are immunized after influenza is already present in the community to prevent infection before development of a protective antibody response. These agents may also be used to prevent infections in patients who may have an impaired antibody response to the vaccine. Patients who are at high risk from influenza infections should be immunized or treated prophylactically before hospitalization when feasible; the cost–benefit ratio of prophylaxis for low-risk patients has not been established. Prophylaxis with antivirals in the setting of a healthcare-associated outbreak may be of use; however, detection of the outbreak in time to institute effective prophylaxis may be difficult *(126)* (see also Chapter 42).

Isolation

Respiratory viruses can be transmitted from person to person by aerosols or by hand contact with the virus followed by self-inoculation. Aerosols are readily produced by coughing, sneezing, and nose blowing *(130,131)*. Some aerosolized particles have also been detected during normal speech *(130)*.

Small-particle aerosols, composed of droplet nuclei 2 to 3 μm in diameter, account for approximately 95% of the total number of particles and 25% of the total volume of coughs and sneezes *(130)*. The small-particle aerosol fraction is slightly higher for coughs than for sneezes. These particles remain suspended in the air and can be transmitted over extended distances. Once a virus suspended in a small-particle aerosol contaminates an air space, only the circulation of the air and the ability of the virus to survive in the environment limit the time during which infection can be transmitted. Small-particle aerosols are not filtered by the nose and are inhaled into the lungs.

Large-particle aerosols are composed of particles larger than 10 μm in diameter. These particles settle quickly and are transmitted only a few feet. For this reason, transmission of infection by a large-particle aerosol requires relatively close contact between infected and susceptible individuals. Large-particle aerosols are effectively filtered in the nose and do not reach the lower respiratory tract.

Transmission of viral respiratory infections by direct contact requires that susceptible individuals contaminate their hands with virus by contact with either an infected individual or contaminated objects in the environment. The virus is then inoculated onto the mucous membranes by hand-to-nose or hand-to-eye contact. Respiratory viruses can conceivably be spread from infected to susceptible individuals by an uninfected intermediate person, but this has not been demonstrated. Spread of infection by direct contact is limited only by the ability of viruses to survive on skin and environmental surfaces.

Information about the mechanisms of spread of different viral pathogens under natural conditions is limited. Although it is likely that any of the different mechanisms of transmission may be involved in the spread of respiratory infection, studies in controlled settings suggest that for some viruses one route may be more efficient than another.

The viruses associated with healthcare-associated respiratory infections in children, with the possible exception of influenza, appear to require relatively close contact for transmission from person to person (*25*,*57*,73,74). Given the role of direct person-to-person contact in the transmission of these pathogens, strict compliance with good hand hygiene should theoretically be sufficient to control healthcare-associated spread. The alcohol-based hand cleaners recommended in recent guidelines *(132)* rapidly inactivate viral respiratory pathogens *(133–136)*, but the effectiveness of these preparations for prevention of healthcare-associated viral respiratory infections has not been studied. The efficacy of various other interventions for prevention of transmission of respiratory viruses, particularly RSV, in the hospital setting has been examined in a number of studies. The intensity of the interventions studied has ranged from the use of gloves to cohorting of patients based on universal preadmission testing for viral antigen. The use of gowns and masks does not appear to effectively interrupt transmission of RSV *(137,138)*. Cohorting of symptomatic infants also appears to contribute little to the control of healthcare-associated RSV *(105,106,139)*. Demonstration of self-inoculation of personnel by transfer of RSV from contaminated hands to the eyes *(25)* suggested the potential for the use of face shields as a control measure for prevention of these infections. Two studies have reported a significant reduction in infections in personnel when goggles were used *(104,105)*, and in one study this was associated with a decrease in healthcare-associated infections in patients *(105)*. Gloves might also be expected to reduce hand-to-face contact, and in one study strict enforcement of gloving effectively prevented healthcare-associated transmission of RSV *(140)*. A more recent study found that gloves were ineffective *(139)*; however, the mechanism by which compliance with glove use was enforced was not described. Two studies have shown that diagnostic viral testing of infants at the time of admission with subsequent cohorting to infected and uninfected cohorts effectively controls healthcare-associated RSV *(139,141)*, but this is not feasible as a routine infection control measure.

Several issues specific to the respiratory viruses present obstacles to the success of interventions for the prevention of healthcare-associated infections: (a) healthcare-associated

infections with these agents occur when there are large numbers of infected individuals in the community providing an opportunity for new introductions of the virus not only by patients but also by personnel and visitors; (b) a large proportion of the patient population is susceptible to infection; (c) many infected individuals will be asymptomatic; and (d) diagnostic testing for most of the viral pathogens of concern is either not sufficiently rapid or not sufficiently accurate to guide decisions for isolation. With these limitations in mind, all patients with symptoms consistent with viral respiratory illness should be placed on Contact Precautions. Patients with likely influenza or adenovirus infection should also be managed with Droplet Precautions. If a healthcare-associated outbreak of viral respiratory disease occurs, cohorting of infected infants (based on diagnostic testing if possible), cohorting of uninfected high-risk patients, and heightened surveillance of staff and visitors for symptomatic infections should be instituted.

Isolation for Prevention of Influenza The mechanism of transmission of influenza has been controversial, but there is some suggestion that small-particle aerosols may play a role (73,74). Transmission by small-particle aerosol has implications for both the type of mask (surgical vs. respirator) and the type of isolation that might be required. Contact and Droplet Precautions are currently recommended for patients with known or suspected influenza when healthcare personnel can be immunized and high-risk patients either immunized or treated with prophylactic antiviral therapy. UV radiation has been reported to reduce the incidence of influenza infections in the hospital setting *(142)*. However, carefully controlled studies of UV radiation for disinfection in the general hospital setting have not been done, and it is likely that this modality would be effective only under very limited conditions *(143)* (see also Chapter 90).

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CHAPTER 49

Healthcare-Associated Bacterial Infections of the Central Nervous System, Upper and Lower Respiratory Tracts, and Skin in Pediatric Patients

W. Matthew Linam and Terry Yamauchi

Clinicians involved in the care of children must be alert for signs or symptoms of healthcare-associated infections in their pediatric patients. Infections involving the central nervous system, respiratory tract, and skin can occur even under optimal conditions. Clinicians must be aware of the potential infecting microorganisms and should understand the pathogenesis of these illnesses. An understanding of these factors allows for appropriate therapy and infection-control measures.

CENTRAL NERVOUS SYSTEM INFECTIONS

Healthcare-associated infections of the central nervous system include intracranial infections, meningitis or ventriculitis, and shunt infections. Central nervous system infections account for 2% to 17% of all healthcare-associated infections in infants in intensive care units (*1,2*,3,*4,5*,6,*7*). Most of these infections involve surgical procedures and/or manipulation/trauma within the central nervous system. Information concerning pediatric intensive care units is less readily available; although some investigators have demonstrated a central nervous system infection rate of 25% in their pediatric intensive care units, others have had no occurrences *(8,9)*.

Intracranial Infections

Pathogenesis Intracranial infections, such as brain abscesses, are not commonly encountered and should meet the criteria from the Centers for Disease Control and Prevention (CDC) in Table 49-1 for diagnosis (10). Brain abscesses commonly form via direct spread from a contiguous source or via hematogenous spread from a distant source. In approximately one-third of situations, however, no predisposing factors are identified. Respiratory diseases such as chronic sinusitis, otitis media, and mastoiditis account for the majority of sites from which microorganisms can extend directly into the brain *(11,12)*. Patients who develop abscesses resulting from contiguous spread usually have a single abscess in the proximity of the infected region. Abscesses acquired through the hematogenous route tend to follow the course of the middle cerebral artery and cause abscesses in the frontal and parietal regions. Cyanotic congenital heart disease with right-to-left shunts or pulmonary arteriovenous fistulas predisposes patients to brain abscess formation *(13,14)*. The most common lesion encountered in such patients is tetralogy of Fallot *(15)*. A healthcare-associated brain abscess is particularly likely in patients who have suffered head trauma or who have undergone neurosurgical procedures. Approximately 6% to 11% of abscesses are in patients with head trauma or neurosurgical procedures, and their symptoms usually develop within 10 days to 2 months following the inciting episode *(13,14,16,17)*.

Etiology Brain abscesses are often polymicrobial in origin, but when they occur in patients who have had head injuries or neurosurgical procedures, *Staphylococcus aureus*—including methicillin-resistant *S. aureus* (MRSA)—followed by the viridans streptococci and *Streptococcus pneumoniae* are the most common microorganisms isolated *(13–17)*. Abscesses in patients with complex congenital heart disease include anaerobes, viridans streptococci, microaerophilic streptococci, enterococci, and *Haemophilus* species. The etiologic agents in patients with a history of chronic sinusitis or otitis media are anaerobes, gram-negative rods (*Proteus*, *Pseudomonas*, *Haemophilus*), and *S. aureus*.

Clinical Manifestations Symptoms associated with a brain abscess include fever (68%), headache (66%), vomiting (59%), focal neurologic deficits (46%), seizures (44%), papilledema (39%), and meningeal signs (36%) *(18)*. Papilledema and meningeal signs may not be present in patients younger than 2 years *(13,14)*. The classic triad of symptoms—headache, fever, and focal neurologic deficits—is demonstrated in <30% of patients *(14)*.

TABLE 49-1

Definitions for Central Nervous System Infections in Pediatric Patients

Intracranial Infection

- Microorganism must be cultured from the brain tissue or dura
- Patient shows evidence of infection at surgery or by histopathologic examination
- Patient indicates two or more of the following without another recognizable cause: headache, dizziness, fever (>38°C), localizing neurologic signs, change in mental status; these symptoms must be followed by institution of appropriate antimicrobial therapy with the microorganism seen on microscopic examination, or there must be a positive antigen test, radiographic evidence of infection, or a diagnostic antibody test
- Criteria are similar for patients younger than 12 mo with the inclusion of hypothermia (<37°C), apnea, or bradycardia

Meningitis/Ventriculitis

- Microorganism is isolated from the cerebrospinal fluid
- Appropriate antimicrobial therapy is instituted, and the patient has one or more of the following: fever (>38°C), headache, stiff neck, meningeal signs, cranial nerve signs, irritability; *and* one of the following laboratory abnormalities: increased white cells, elevated protein, and/or decreased glucose in the cerebrospinal fluid; positive gram stain; positive blood culture; positive antigen detection; or a diagnostic antibody test
- Criteria are similar for patients <12 mo with the inclusion of hypothermia (<37°C), apnea, and bradycardia

(Adapted from Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.)

Diagnosis The diagnosis of a brain abscess can be established by cerebral imaging using cranial ultrasonography, computed tomography, or magnetic resonance imaging.

Prevention Prophylactic antimicrobial agents may prevent the development of brain abscesses in certain situations. Antimicrobial prophylaxis to prevent infective endocarditis is currently only recommended for patients with cardiac conditions that place them at the highest risk for complications from infective endocarditis (Table 49-2) (*19,*20). Antimicrobial prophylaxis is indicated in patients before dental procedures that involve the manipulation of the periapical region of the teeth or the gingival mucosa or the perforation of the oral mucosa. Prophylaxis should also be considered for invasive respiratory procedures that involve incision or biopsy of the respiratory mucosa and infected skin, skin structure, or musculoskeletal tissue *(19)*. Recommended prophylaxis regimens are outlined in Table 49-3.

Antimicrobial prophylaxis for neurosurgical procedures has been demonstrated to be effective for clean and clean–contaminated procedures *(21–26)*. Antibiotics should be started within 60 minutes of the skin incision with the exception of vancomycin and fluoroquinolones, which should be started 60 to 120 minutes before the skin incision. For procedures lasting longer than 4 hours, antibiotic redosing should be based on the half-life of the antibiotic, but antibiotics should be discontinued within 24 hours after surgery (27). Multiple regimens have been used involving vancomycin *(21)*, vancomycin/gentamicin *(24)*, cefazolin/gentamicin *(26)*, piperacillin *(22)*, cloxacillin *(25)*, and cefuroxime *(28)*. Despite the multiple combinations that have been used, all the regimens should include activity against staphylococci. It is recommended that patients undergoing clean or clean–contaminated neurosurgical procedures receive antimicrobial prophylaxis with cefazolin or vancomycin as the drugs of choice (*23,*29). Patients known to be colonized with MRSA should receive vancomycin for prophylaxis (27). In hospitals with high rates of healthcare-associated gram-negative infections, consideration should be given to including antimicrobial agents in the regimen that are active against the prominent gram-negative microorganisms as well.

TABLE 49-2

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for which Prophylaxis with Dental Procedures is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair

Previous IE

Congenital heart disease (CHD)[a]

- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure[b]
- Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)

Cardiac transplantation recipients who develop cardiac valvulopathy

[a]Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
[b]Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 mo after the procedure.
(Reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation* 2007;116:1736–1754 ©2007, American Heart Association, Inc.)

TABLE 49-3

Regimens for a Dental Procedure

		Regimen: Single Dose 30–60 min before Procedure	
Situation	***Agent***	***Adults***	***Children***
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b]	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg/kg IM or IV	20 mg/kg IM or IV

[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM, intramuscular; IV, intravenous.
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Meningitis and Ventriculitis

Pathogenesis Meningitis or ventriculitis is usually the result of a bacteremia. The bacteria gain access to the central nervous system from the blood in the region of the choroid plexus. Meningitis less commonly develops as a complication of endocarditis, pneumonia, or thrombophlebitis. There may also be a direct extension from a chronic respiratory source (i.e., mastoiditis) or as a complication of trauma (i.e., basilar skull fracture), an anatomic defect of the cribriform plate, or a direct communication between the skin and meninges (meningomyelocele) *(30)*. Some degree of ventriculitis can be demonstrated in most cases of bacterial meningitis, but ventriculitis is more common as an infectious complication of ventricular shunting. The predominant microorganisms involved in healthcare-associated meningitis or ventriculitis are different from those involved in community-acquired disease. Contributing factors include the age, immune status, and antibiotic history of the patient. The diagnostic criteria for healthcare-associated meningitis or ventriculitis are outlined in Table 49-1.

Etiology In children older than 3 months, the common pathogens causing meningitis have traditionally included *Haemophilus influenzae* type B, *S. pneumoniae,* and *Neisseria meningitidis*. Because of the efficiency of the *Haemophilus* vaccines, however, this microorganism is no longer the predominant pathogen *(31)*. For children younger than 3 months, group B β-hemolytic streptococci (GBS), *Escherichia coli,* and *Listeria monocytogenes* are the most frequent causes of meningitis *(32)*. Newborns become colonized with these microorganisms from passage through the birth canal and may develop illness within hours after birth. If illness occurs within the first 6 days of life, it is considered an early-onset illness. Infections that develop after 6 days of life are considered late-onset illnesses. Early-onset illnesses are due to microorganisms harbored in the mother's birth canal. Microorganisms that cause late-onset disease may have been transmitted from the mother or may have been acquired from caregivers or the environment.

Most healthcare-associated cases of meningitis in children older than 3 months are due to the staphylococci, although enterococcal and gram-negative enteric (*E. coli*, *Klebsiella*, *Enterobacter*, *Proteus*) infections do occur *(2,33)*. When staphylococcal meningitis occurs, there is an associated defect in the central nervous system resulting from surgery or trauma in approximately 75% of cases *(34,35)*. Therefore, most cases are due to direct extension of the microorganism instead of hematogenous spread. Spread of the more traditional microorganisms such as *N. meningitidis* and *H. influenzae* occurs via the respiratory route, and therefore, respiratory spread is a potential hazard for healthcare-associated transmission. These microorganisms are responsible for secondary diseases in family members but only rarely have been associated with healthcare-associated infections of the central nervous system *(36)*.

Early-onset GBS disease usually manifests itself as respiratory distress with bacteremia. Most early-onset disease, regardless of the microorganism, usually lacks meningeal involvement. Meningeal involvement is a common manifestation in late-onset disease *(37)* (see Chapter 32). Most

newborns who develop meningitis while hospitalized are in neonatal intensive care units. Therefore, clinicians should be concerned about the bacteria that are known to be present in each nursery. Outbreaks of meningitis in neonatal intensive care units have been attributed to several microorganisms, both gram-positive and gram-negative, including *S. aureus*, *Staphylococcus epidermidis*, *Serratia*, *Klebsiella*, and *Citrobacter (7,38–40)* (see Chapter 52).

Clinical Manifestations Children with meningitis usually have signs and symptoms relating to their central nervous system, whereas infants may not. The diagnosis of meningitis must be considered in any patient with fever, altered mental status, and meningismus.

Diagnosis A lumbar puncture is the method of choice for establishing this diagnosis. An increased number of white blood cells with a polymorphonuclear predominance, elevated cerebrospinal fluid (CSF) protein levels, and decreased glucose levels are typically found with bacterial meningitis. The CSF should be sent for gram staining, and CSF and blood should be cultured for bacteria to aid in finding the etiologic agent. Bacterial antigens are less helpful because the more common healthcare-associated pathogens are not included in such panels. Recently, polymerase chain reaction (PCR) has become more readily available for the detection of bacterial meningitis. Broad-range PCRs targeting the 16S rRNA gene and specific PCRs for the detection of pathogens such as *S. pneumoniae* and *Neisseria meningitides* can assist in diagnosing bacterial meningitis, particularly in situations in which the patient has received antibiotics prior to the collection of spinal fluid *(41–44)*.

Prevention To aid in the prevention of healthcare-associated disease, patients admitted to the hospital with meningitis resulting from *N. meningitidis* or *S. pneumoniae* should be placed on Droplet Precautions for the first 24 hours of hospitalization, and all contacts of the patient should observe strict hand washing *(45)*. Antibiotic prophylaxis may be indicated for household or day-care contacts who have had direct exposure to the oral secretions of patients who have an *N. meningitidis* infection. Only hospital personnel with exposure to a patient's respiratory secretions through situations such as unprotected mouth-to-mouth resuscitation, intubation, or airway suctioning should receive prophylaxis (see Chapter 76). Rifampin, 10 mg/kg (maximum of 600 mg), every 12 hours for 2 days is indicated for persons aged 1 month or older. Contacts who are younger than 1 month should receive 5 mg/kg every 12 hours for 2 days. Affected individuals should be alerted to the potential side effects of the medication: urine and other secretions are discolored (orange or red), contact lenses can become permanently discolored, and rifampin may alter the activity of birth control pills.

Pregnant women should be excluded from rifampin prophylaxis *(46)*. Options for individuals unable to take rifampin include ceftriaxone or ciprofloxacin (47). Ceftriaxone given in a single intramuscular injection at a dose of 125 mg for children younger than 15 years and 250 mg for others has been demonstrated to effectively eradicate the meningococcal carrier state with group A *N. meningitidis (48)*. A single oral dose of ciprofloxacin, 20 mg/kg (maximum dose 500 mg), has been demonstrated to be effective in adults but cannot be used in children or in pregnant or lactating women *(49)*. Ceftriaxone should be used in pregnant women. These options should only be considered in circumstances in which rifampin cannot be used.

Meningococcal vaccine can be used as an adjunct to chemoprophylaxis in outbreaks caused by serogroups that are included in the vaccine (A, C, Y, and W-135). For adults and children older than 2 years, the preferred vaccine is the tetravalent meningococcal (A, C, Y, and W-135) conjugate vaccine, but the tetravalent meningococcal (A, C, Y, and W-135) polysaccharide vaccine may also be used. Serogroup B is not contained in the vaccine. The tetravalent meningococcal (A, C, Y, and W-135) polysaccharide vaccine has been used in children younger than 18 months. This is given as 2 doses 3 months apart to control outbreaks *(50)*.

For trauma patients with basilar skull fractures, antimicrobial prophylaxis for the prevention of meningitis is controversial *(51)*. Currently, antimicrobial prophylaxis does not appear to decrease the incidence of meningitis after a basilar skull fracture *(51)*. Surgical intervention should be performed when there is no evidence of healing and/or repeated infection occurs. For open skull fractures, antibiotic prophylaxis is generally recommended *(52)*.

The prevention of early-onset meningitis in neonates begins with good prenatal care and intervention strategies to prevent the transmission of potentially harmful microorganisms to the newborn infant *(53)*. To prevent early-onset neonatal GBS disease, all pregnant women should have vaginal and rectal cultures for GBS at 35 to 37 weeks of gestation. Women identified as carriers during the current pregnancy should receive intrapartum antibiotic prophylaxis at the onset of labor or rupture of membranes. Intrapartum prophylaxis should be administered to all women who have had a previous infant with invasive GBS disease or who are found to have GBS bacteriuria during the current pregnancy. If the results of the GBS screen are not known at the onset of labor or rupture of membranes, intrapartum antimicrobial prophylaxis should be administered if any of the following risk factors are present: gestation of <37 weeks, prolonged rupture of membranes ≥18 hours, or intrapartum temperature ≥38°C. The antimicrobial agent of choice is penicillin G (5 million U initially and then 2.5 million U every 4 hours) given intravenously until delivery. Intravenous ampicillin (2 g initially, followed by 1 g every 4 hours until delivery) can be used, but penicillin is preferred because of its narrow spectrum. Intravenous cefazolin or vancomycin can be used for penicillin-allergic patients. Because of the increasing prevalence of resistance, clindamycin and erythromycin should not be used for antibiotic prophylaxis for GBS. The management of infants born to mothers who have received chemoprophylaxis should be based on the gestational age of the infant, the number of doses of the prophylactic agent received, and the clinical findings of the infant *(54)*.

Shunt Infections

Pathogenesis Approximately 4.5% to 25% of patients who have undergone CSF shunting procedures develop infectious complications *(55–59)*. Risk factors for infection include young age of the patient (<3 months), inexperienced surgeons, prolonged shunting procedures,

and distal catheter tip location *(60–63)*. Shunt infections usually occur within 2 months after placement; most of these infections are caused by transient or permanent bacterial inhabitants of the skin. The latter observations suggest that direct inoculation in the perioperative period is probably the pathogenesis of this infection *(64)*.

Etiology Staphylococci are responsible for approximately 75% of infections; *S. epidermidis* is the primary agent in 50% and *S. aureus* in 25% *(55,56,58)*. Infections with gram-negative enteric microorganisms (*E. coli*, *Klebsiella*, *Proteus*) and *Pseudomonas* account for approximately 20%; the remainder of infections are caused by less-common microorganisms such as *Enterococcus*, viridans streptococci, *N. meningitidis*, micrococcus, *H. influenzae*, diphtheroids, *Propionibacterium*, and *Corynebacterium (56,58,65–68)*.

Clinical Manifestations The most common symptoms of shunt infections are usually symptoms of shunt malfunction. Headache, irritability, lethargy, nausea, and change of mental status are common. Although fever is usually present, approximately 10% to 20% of children are afebrile *(56,58)*. In most shunt infections, signs of meningeal irritation are absent because there is no communication between the infected ventricle and the CSF.

Diagnosis Shunt infections should be suspected in any patient who has a ventricular shunt with complaints of malfunction. Fluid from the shunt or ventricle is needed to secure the diagnosis, and the fluid usually displays an increase in the white blood cell count (>10 cells/mm^3). CSF should be cultured aerobically and anaerobically and also plated on media for the isolation of fungi. Extreme care should be used when obtaining a CSF specimen from a ventricular shunt bubble. Neurosurgical consultation should be considered before attempting to violate the shunt. The area should be cleaned before penetration with a needle to avoid contaminating the shunt. If patients have concomitant complaints of abdominal distention, peritonitis, shunt wound infection, erythema, or swelling along the shunt tract or if they appear toxic, the shunt should be assumed to be infected.

Prevention The role of prophylactic antimicrobial agents for the prevention of shunt infections has been controversial with the protective efficacy demonstrated to vary widely (5–84%) *(23)*. A meta-analysis performed by Langley et al. *(69)* showed that antibiotic prophylaxis resulted in a 50% reduction in postoperative infections after cerebrospinal shunt insertion. In a recent systematic review, perioperative antibiotic prophylaxis was associated with a significant reduction in shunt infections (*70*). Based on current data, the use of antibiotic prophylaxis with an antistaphylococcal agent (i.e., nafcillin, cefazolin, vancomycin) beginning before the procedure and continuing for up to 24 hours after the procedure is recommended *(70)*. Recently, silicone catheters impregnated with rifampin and clindamycin have been developed to help reduce the incidence of shunt infections. Initial experience reveals that antibiotic-impregnated catheters appear to be well tolerated and can reduce the incidence of shunt infection in children and adults *(71–73)*.

Occasionally, patients require external ventricular drains. These drains may be placed for limited periods after surgery or trauma or when the release of ventricular fluid is required to combat increased intracranial pressure. Catheters are placed directly into the ventricle and drain into an external receptacle. Patients who require these drains are at an increased risk for infectious complications; therefore, CSF specimens should be carefully extracted when these devices are entered. Regular catheter exchange does not prevent infections associated with external ventricular drains *(74)*.

RESPIRATORY TRACT INFECTIONS

Upper Respiratory Tract Infections

Most healthcare-associated upper respiratory tract infections are nonbacterial and appear approximately 2 weeks after admission (*2*,6). Respiratory syncytial virus, adenovirus, and influenza virus account for most of these infections *(75)* (see Chapter 48). The role of bacteria in healthcare-associated upper respiratory tract infections is manifested predominantly in sinusitis and otitis media. Less commonly encountered problems include pharyngitis, bacterial tracheitis, and diphtheria.

Pharyngitis Group A *Streptococcus* is a common cause of community-acquired pharyngitis but not of healthcare-associated disease. Patients are rarely admitted to the hospital for a streptococcal throat infection but may be admitted for complications of this infection, such as a peritonsillar or retropharyngeal abscesses. When such complications occur, cultures often reveal multiple microorganisms including *S. aureus*, gram-negative microorganisms, and anaerobic microorganisms *(76,77)*. Secondary cases of disease resulting from *Streptococcus pyogenes* are higher among siblings than among adult contacts. Rates of infection may be as high as 50% for sibling contacts compared with 20% for adult contacts. Asymptomatic, culture-positive individuals (children and adults) are well documented and may be the source for some infections *(78)*. The most important means of controlling group A streptococcal infections, therefore, is early identification and treatment of the disease. Although many contacts develop illness, asymptomatic contacts should not be cultured or treated. Symptomatic contacts should undergo a throat culture and be treated if group A *Streptococcus* is isolated *(78)*.

Bacterial Tracheitis Bacterial tracheitis is a bacterial infection thought to be secondary to a primary viral respiratory infection, usually parainfluenza or influenza viruses *(79,80)*. The viral infection may cause local mucosal damage, alter the patient's immune response, or both, thus leading to a secondary bacterial infection *(81,82)*. The most common microorganism involved is *S. aureus*. Other implicated microorganisms include *S. pneumoniae, H. influenza,* and *S. pyogenes (79,80)*. Before the availability of *H. influenzae* conjugate vaccines, this disorder was as common as epiglottitis, but because of a dramatic decrease in the incidence of invasive *H. influenzae* disease, bacterial tracheitis may now be more common *(79)*. The patient with

bacterial tracheitis usually has a waning viral respiratory illness when the fever rises and stridor begins or worsens. Patients assume any position that maximizes their airflow, not just the sniffing position as demonstrated with epiglottitis. Patients can deteriorate quickly and frequently require intubation to maintain patency of the airway and facilitate frequent suctioning. Endoscopic examination, which should be performed in an operating room, reveals copious, tenacious, purulent secretions above the subcricoid trachea. No isolation is required. Early recognition and treatment is the only method to prevent life-threatening illness.

Diphtheria Diphtheria is a disease that usually manifests itself as a membranous nasopharyngitis and/or an obstructive laryngotracheitis resulting from *Corynebacterium diphtheriae*. This disease has been uncommon since the advent of the diphtheria vaccine. Specimens for culture should be obtained from the nose and throat; the culture requires special media from the clinical laboratory. Once the culture has been obtained, the laboratory should be alerted to facilitate the evaluation. Patients with pharyngeal diphtheria should be placed on Droplet Precautions until two cultures from both the nose and the throat are negative. Communicability is usually <4 days once effective antimicrobial treatment has started. Patients with cutaneous forms of diphtheria should be placed on Contact Precautions until two cultures of the skin are negative *(83)*. Close contacts of the patient should be cultured irrespective of their immunization status and should be given antimicrobial prophylaxis with orally administered erythromycin or intramuscularly administered penicillin. The efficacy of antimicrobial prophylaxis is presumed but not proven; therefore, these patients should be kept under surveillance for 7 days. Asymptomatic contacts should receive a booster of diphtheria toxoid if they have not received a booster in the preceding 5 years. The vaccine series should be started for unimmunized individuals. Diphtheria antitoxin for unimmunized close contacts is not generally recommended *(83)*. However, in the rapidly deteriorating patient with the presumptive diagnosis of diphtheria, a dose of equine antitoxin administered intravenously may be needed. Tests for sensitivity to horse serum should be performed before the antitoxin is given.

Sinusitis Most cases of acute sinusitis in children are due to *S. pneumoniae*, *H. influenzae*, and *Moraxella catarrhalis* (84). These agents are also recovered from patients with chronic sinusitis, but *S. aureus* and anaerobic bacteria (*Peptococcus*, *Peptostreptococcus*, and *Bacteroides*) are recovered more often from children with sinus symptoms that have lasted longer than 1 year *(85–87)*. Healthcare-associated sinusitis may be due to the major agents of acute or chronic sinusitis but also include pathogens endemic to the hospital, such as *Pseudomonas aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter*, and *Proteus* (88). *Aspergillus* species have also been recovered from hospitalized patients with sinusitis, in which the most likely source of the fungus was hospital construction or a faulty ventilation system (see the section on Lower Respiratory Tract Infections in this chapter).

The major predisposing factor for the development of healthcare-associated sinusitis is the use of obstructive devices in the nasal cavity. The paranasal sinuses are inflamed or infected because of the trapping of sinus secretions in closed spaces. Nasogastric and nasotracheal tubes are the most common instruments noted to predispose patients to sinusitis (88,*89–92*). This may occur in up to 40% of patients who have undergone nasotracheal intubation *(93)*. Other forms of instrumentation of the oropharynx, such as oropharyngeal intubation and tracheostomy, also contribute to this disease process. Other risk factors include nasal packing, high-dose corticosteroid therapy, prior antimicrobial treatment, and facial or cranial fractures.

The symptoms are nonspecific. Most patients develop illness during the first 2 weeks of intubation. Fever is usually the only complaint, although purulent rhinitis may be demonstrated *(90)*. Radiographic studies are usually needed to establish a diagnosis. The demonstration of mucosal thickening, opacification, or air-fluid levels of the sinuses is consistent with an inflammatory process. Computed tomography is superior to plain radiographs for the evaluation for sinusitis *(94)*. The diagnosis of sinusitis should be based on a combination of clinical, radiographic, and microbiologic findings.

Prevention of sinusitis includes maintaining good oral hygiene while patients are intubated. Proper hand hygiene of healthcare workers is also necessary to prevent the transmission of microorganisms to the patient. Patients should be regularly assessed for the continued need of nasal or oral tubes, and all tubes—particularly nasogastric and nasotracheal tubes—should be promptly removed when they are no longer indicated. Sinusitis occurs more frequently in patients with nasotracheal intubation compared to patients with oropharyngeal intubation; therefore, unless contraindicated, oropharyngeal intubation is preferred *(89,95)* (see also Chapter 23).

Otitis Media Otitis media is one of the most common illnesses of infants and children. Predisposing factors include lower socioeconomic groups, secondhand smoke exposure, bottle-feeding, day-care attendance, craniofacial abnormalities, gastroesophageal reflux, and atopy *(96–98)*. The most common microorganisms involved in acute otitis media are *S. pneumoniae, M. catarrhalis*, and *H. influenzae (99)*. Microorganisms that have been associated with chronic suppurative otitis media include coagulase-negative staphylococci, *P. aeruginosa,* and *S. aureus* (including MRSA) *(100,101)*. Healthcare-associated otitis media is a common entity, particularly in intensive care units. The bacteriology usually reflects that of the hospital environment and not that of the community *(102)*.

Healthcare-associated otitis media is usually due to prolonged dysfunction of the eustachian tubes. Like sinusitis, it is most commonly demonstrated with the use of devices that occlude the airways *(102)*. This dysfunction of the eustachian tube leads to the stasis of fluid and bacteria in the middle ear and allows infection. Fever is the most common symptom associated with otitis media. Older children may be able to verbalize a complaint of ear pain, and occasionally, there may be purulent otorrhea. The diagnosis can be established by physical examination. An absent light reflex, decreased tympanic motility, a retracted or bulging tympanic membrane, or purulence behind the tympanic

membrane can be demonstrated by otoscopy. In severely ill or immunocompromised patients, a diagnostic myringotomy may be indicated to direct therapy.

Many children who are admitted to the hospital have a recent history of antimicrobial therapy for otitis media. If the child develops this complication while hospitalized, there is always a question of whether this represents disease that was resistant to initial therapy or a new infection. Children presenting with symptoms of otitis media within 1 month after therapy may have an infection caused by a new microorganism *(103)*. The bacteria that cause most recurrences are also sensitive to the antimicrobial agent just completed *(104)*. Therefore, children who develop otitis media while hospitalized usually have a healthcare-associated infection rather than a relapse from a previously treated case of otitis media.

Since the risk factors for healthcare-associated otitis media are similar to those that cause healthcare-associated sinusitis, the same prevention strategies apply. Using devices that obstruct the nasopharynx and oropharynx, such as nasogastric, nasotracheal, or orotracheal tubes, for as short a time as possible may aid in the prevention of healthcare-associated otitis media.

Lower Respiratory Tract Infections

Healthcare-associated lower respiratory tract infections (LRTIs) account for approximately 15% to 22% of healthcare-associated infections of infants and children (*2*,6,*7*,105). These infections constitute a common but potentially life-threatening complication of hospitalization. Mortality rates associated with healthcare-associated LRTIs are estimated to range from 20% to 50%, and 15% of all deaths occurring in hospitalized patients of all ages are directly related to these infections (106). The increased risk of poor outcome with a healthcare-associated LRTI has become more obvious because of modern intensive care facilities. Intensive care units can support critically ill patients for prolonged periods with invasive life-support techniques. Healthcare-associated LRTIs that occur in intubated, mechanically ventilated patients are called ventilator-associated pneumonias (VAPs). Many of the patients undergoing prolonged support are very low birth weight infants, premature infants, or immunocompromised patients; these conditions enhance the risk of healthcare-associated LRTIs with subsequent increased morbidity and mortality. A recent study in children who developed VAP showed a mortality rate of 19% (107).

Pathophysiology The pathophysiology of healthcare-associated LRTIs is thought to involve the altered or circumvented pulmonary antimicrobial defenses of the upper and lower respiratory tract *(108)*. Although a few infections represent hematogenous seeding of the lungs from a distant suppurative focus (i.e., endocarditis, meningitis), most patients suffer from subclinical aspiration of oropharyngeal secretions containing bacteria that have colonized the upper airway of the patient. This flora includes aerobic gram-positive and gram-negative microorganisms commonly identified in the hospital where the patient is located *(109)*. Flora commonly found in the oropharynx of children admitted to the hospital include both gram-positive (i.e., staphylococci, streptococci) and gram-negative microorganisms (i.e., *Neisseria* species). In colder months, many healthy infants and children are commonly colonized with microorganisms considered to be pathogens (i.e., *S. pneumoniae, S. pyogenes)* (106). The flora commonly demonstrated on admission changes within 4 days to those microorganisms commonly found in the hospital (110). The risk factors for colonization include acidosis, endotracheal intubation, hypotension, breaks in the aseptic technique, and broad-spectrum antimicrobial therapy *(109,111)*. Turbulence in the nasal airways normally prevents the deposition of large particles in the lower respiratory tract. Nasotracheal, orotracheal, or tracheostomy tubes bypass this defense mechanism and allow colonization of the upper respiratory tract with healthcare-associated microorganisms. Without colonization of the upper airways, only a few patients develop healthcare-associated LRTIs as compared with colonized patients (3% vs. 23%) *(112)*.

Most healthcare-associated LRTIs are caused by gram-negative microorganisms (*2,8*,106,107). A fecal–oral route for bacterial contamination of the upper airways has been suspected but has never explained the frequency of colonization with microorganisms such as *P. aeruginosa* or the *Acinetobacter* species. These microorganisms are not the usual inhabitants of the human gastrointestinal tract. In studies addressing this, members of the Enterobacteriaceae family (i.e., *E. coli, Klebsiella*) were isolated from the hypopharynx and rectum before they were isolated from the trachea in patients undergoing prolonged intubation in whom daily cultures were monitored from rectal, hypopharyngeal, and tracheal sites. In contrast, non-Enterobacteriaceae (i.e., *P. aeruginosa*, *Acinetobacter*) were rarely demonstrated before their appearance in the trachea (106). This suggests that non-Enterobacteriaceae microorganisms have environmental sources and that colonization with Enterobacteriaceae occurs from the patient's endogenous flora. The hands of the healthcare worker and certain components of the respiratory therapy equipment, therefore, may be important factors in the transmission of microorganisms.

A healthcare-associated LRTI results when the colonizing microorganisms evade the mucociliary and cellular defenses of the lower respiratory tract. Microorganisms can then attack the respiratory epithelium and possibly disseminate disease. The most important factor predisposing infants and children to the development of a healthcare-associated LRTI is endotracheal intubation (105). Healthcare-associated LRTIs have been shown to occur 4 times more often in intubated patients than in nonintubated patients (106). Rates for patients with tracheostomy tubes appear to be even higher *(113)*. Although the critically ill patient requiring prolonged hospitalization in intensive care units is at increased risk for healthcare-associated infections, the endotracheal tube eliminates the most effective natural host defense mechanism of the upper airway. The filtration system of the upper airway and the mucociliary system of the large airways is bypassed during intubation. The loss of the mucociliary transport system is accentuated by mechanical irritation and damage to the respiratory epithelium, which predisposes the patient to colonization with potential pathogens. Other risk factors for healthcare-associated LRTIs in infants and children are premature and low birth weight infants, poor nutrition, underlying

pulmonary disease, length of hospitalization, general anesthesia, respiratory therapy, tracheal reintubation, transportation of intubated patients out of the PICU, and the use of total parenteral nutrition (107).

Any infant or child admitted to the hospital should be considered at risk for healthcare-associated LRTIs. However, patients who have problems with acidosis, hypotension, hypoperfusion, altered mental status, or who have tubes (nasotracheal, orotracheal, or nasogastric) are at increased risk for these infections *(112,114)*. Infants and children with symptomatic or asymptomatic aspiration are also at risk (106). Patients with tracheoesophageal fistulae, swallowing dyscoordination, gastroesophageal reflux, facial burns, cardiac disease (i.e., shunt lesions with pulmonary hypertension), pulmonary disease, malnutrition, immunodeficiencies, or who have undergone surgery with unprotected airways also risk aspirating the resident flora in the hypopharynx.

Etiology Healthcare-associated LRTIs can be categorized by time of onset. Early-onset LRTIs occur within the first days of hospitalization. Causative microorganisms are similar to those causing community-acquired pneumonia, *S. pneumoniae*, *M. catarrhalis*, and *H. influenza*. Late-onset LRTIs are typically caused by gram-negative bacilli and *S. aureus* (110). The specific etiologic microorganisms for healthcare-associated LRTIs vary from institution to institution. Clinicians, therefore, must be familiar with the common microorganisms and antimicrobial susceptibility of these microorganisms at their institutions. Gram-negative rods are the most common bacterial cause of a healthcare-associated LRTI in infants and children *(115)* (Table 49-4). Among gram-negative organisms, *P. aeruginosa* is the most common microorganism causing VAP (107). Among gram-positive microorganisms, staphylococci are the predominant microorganisms encountered, with MRSA increasing in occurrence. Less-common microorganisms include *Legionella* spp. *(116,117)*. In pediatric hospitals, community-acquired microorganisms such as *S. pneumoniae* and *N. meningitidis* may also be encountered. If these microorganisms are identified, however, a septic metastasis or direct respiratory tract spread should be considered, because these microorganisms are an uncommon cause of healthcare-associated LRTIs.

TABLE 49-4

Common Etiologic Agents Causing Lower Respiratory Tract Infections in Hospitalized Children

E. coli
K. pneumoniae
P. aeruginosa
M. catarrhalis
S. aureus
S. epidermidis
Enterococcus species
Other gram-negative bacilli

Pertussis is caused by the microorganism *Bordetella pertussis* and has been an important respiratory pathogen with high infectivity in children, which can result in death. More recently, the disease has had an increased incidence in older patients, specifically adolescents and adults *(118)*. Outbreaks of pertussis in the hospital setting have also been reported *(119)*. Because of decreasing immunity, the incidence of clinical disease has increased in certain populations, particularly in medical personnel. Adults are more effective disseminators and, therefore, serve as major reservoirs for disease. Even when pertussis is present in a community in epidemic proportions, it is rarely transmitted within the hospital if proper precautions are taken *(120)* (see also Chapter 76).

Children with pulmonary infections resulting from *Mycobacterium tuberculosis* (TB) rarely transmit this microorganism to other individuals. Children are generally ineffective coughers, and in most cases, pulmonary involvement in infants and children is manifested by closed caseous lesions that have lower numbers of acid-fast bacilli compared with the cavitary lesions commonly demonstrated in adults with pulmonary disease *(121)*. Although children with active TB infections are infrequently contagious, adult caregivers, including healthcare workers with unrecognized active TB, can be sources for spread within the healthcare setting *(122)*.

In neonatal intensive care units, coagulase-negative staphylococci (i.e., *S. epidermidis*) have emerged as a major cause of healthcare-associated infections, and patients infected with this microorganism should be treated aggressively (3,*123*). In hospitals undergoing renovation or nearby construction or ventilation changes, *Aspergillus* may cause LRTIs in the hospitalized patient. Other agents that can present a problem for premature infants include *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis (124–126)*.

Diagnosis Diagnosing healthcare-associated LRTIs remains difficult. Historically, clinical presentation, chest radiographs, Gram stains, and cultures of respiratory secretions have established the diagnosis. Unfortunately, this method of detection has probably overestimated the true incidence of disease, because other entities can be easily confused with LRTIs in critically ill patients. Entities such as chemical aspiration, respiratory distress syndrome, pulmonary hemorrhage, lung contusion, atelectasis, congestive heart failure, pulmonary edema, pleural effusion, pulmonary emboli, or tumor may be confused with an LRTI *(127)*. Other conditions that can be confused with LRTIs in infants and children include congenital heart disease, bronchopulmonary dysplasia, and cancer chemotherapy effects (106). Because of such difficulties in diagnosis, the CDC has provided clinicians with guidelines for the definition for healthcare-associated LRTIs and for VAP (10,110) (Table 49-5).

A change in clinical status that is unexplained by other events is helpful in diagnosing healthcare-associated LRTIs. Patients in intensive care units generally have abnormal chest radiographs regardless of whether infection is present (Fig. 49-1). Likewise, fever and leukocytosis are often present irrespective of the presence of an LRTI. Cough and sputum production are infrequently diagnostic of LRTIs in intubated infants and children. If tracheal secretions are

TABLE 49-5

Algorithms for Clinically Defined Pneumonia (Pnui)

Radiology	*Signs/Symptoms*
Two or more serial chest radiographs with at least one of the following: • New or progressive and persistent infiltrate • Consolidation • Cavitation • Pneumatoceles, in infants ≤1 y old Note: In patients without underlying pulmonary or cardiac disease, one definitive chest radiograph is acceptable.	For any patient, at least one of the following: • Fever • Leukopenia or leukocytosis *And* at least two of the following: • New onset of purulent sputum or change of sputum or increased respiratory secretions or increased suctioning requirements • New or worsening cough, dyspnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange Alternate criteria, for infants ≤1 y old: Worsening gas exchange *And* at least three of the following: • Temperature instability • Leukopenia or leukocytosis • New onset of purulent sputum, change in sputum, increased respiratory secretions, or increased suctioning requirements • Apnea, tachypnea, nasal flaring with retraction of chest wall or grunting • Wheezing, rales, or rhonchi • Cough • Bradycardia or tachycardia Alternate criteria, for child >1 y old or ≤12 y old, at least three of the following: • Fever or hypothermia • Leukopenia or leukocytosis • New onset of purulent sputum, change in sputum, increased respiratory secretions, or increased suctioning requirements • New onset worsening cough, dyspnea, apnea, or tachypnea • Rales or bronchial breath sounds • Worsening gas exchange

(Adapted from Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332, with permission.)

purulent, the differentiation between tracheobronchitis and LRTIs may be difficult. Clinical suspicion, therefore, is needed to diagnose healthcare-associated LRTIs. The diagnosis of VAP is made based on a combination of clinical and radiographic findings. Changes such as a drop in oxygenation, increased oxygen requirements, or increasing ventilator requirements in combination with fever, leukocytosis/leukopenia, changes in respiratory secretions, wheezing, rales, or rhonchi should alert clinicians to a possible VAP. These factors, combined with a new or progressive infiltrate on a chest radiograph, are required to meet the clinical definition of a VAP. Although these criteria may lack sensitivity and specificity, they may be the only available parameters for clinicians (10,110).

Once a healthcare-associated LRTI is suspected, an attempt should be made to identify the specific etiologic agent. Microscopic examination of a gram-stained smear of upper airway secretions may reveal the presence of polymorphonuclear cells and bacteria. However, tracheal aspirations and endotracheal cultures are unreliable and do not help to identify the etiologic agent. Although rarely positive, blood cultures may help in identifying the etiologic microorganism. A culture of pleural fluid may also yield the etiologic agent (10). Culture results from specimens obtained from endotracheal tubes correlate poorly with those obtained from sterile sites such as the lung, blood, or pleural fluid. Qualitative culture of specimens obtained from endotracheal tubes has failed to predict the causative agent of respiratory deterioration in infants and children *(128)*. A positive quantitative culture from minimally contaminated lower respiratory tract specimen, such as protected specimen brushing (PSB) or bronchoalveolar lavage (BAL), may also be used to identify the causative microorganism(s). In adults, these specimens are often obtained via bronchoscopy (10,*129,130*). Unfortunately, bronchoscopic equipment for protected specimen collection cannot be used in infants and small children because of the small size of the airways. Therefore, the use of such

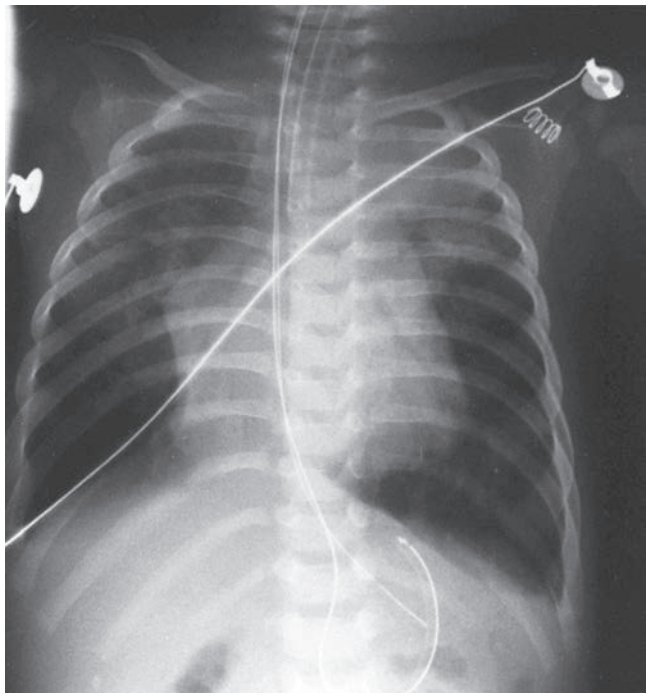

FIGURE 49-1 A chest radiograph demonstrating the difficulty in diagnosing a healthcare-associated lower respiratory tract infection in a child with respiratory distress syndrome.

techniques is severely limited in infants and children *(130)*. Nonbronchoscopically obtained PSB or BAL has been used with some success in ventilated children *(129,130)*. Thresholds used have been 10^3 colony-forming units (CFU)/mL for PSB and 10^4 CFU/mL for BAL *(130)*. *Legionella* can be diagnosed using special respiratory cultures, direct immunofluorescence of respiratory secretions, indirect immunofluorescent antibody assay, or urine antigen. Pertussis can be suspected in the unimmunized patient with a history of coughing to the point of vomiting, exposure to a known case, and lymphocytosis. Culture of *B. pertussis* is the "gold standard" and requires the inoculation of nasopharyngeal mucus onto special media (Regan–Lowe or Bordet–Gengou). Pertussis can also be diagnosed by PCR.

Prevention The prevention of healthcare-associated LRTIs and VAP should focus on two critical processes: the reduction of colonization of the upper airway by potential pathogens and the prevention of aspiration of microorganisms into the lower respiratory tract. The most important factor is strict compliance by healthcare workers with hand hygiene before and after contact with the patient or the patient's ventilator circuit. Physicians and nurses fail to perform hand hygiene before and after patient contact approximately 50% of time *(131)*. Effective hand hygiene can prevent healthcare-associated LRTIs, particularly in areas such as intensive care units. Despite this knowledge, the hand hygiene practices of healthcare workers have been difficult to improve *(132,133)*. Multimodal improvement interventions have shown success in a number of healthcare settings (see also Chapter 91). Healthcare workers should also wear a gown and gloves if they anticipate their hands or clothing becoming soiled with respiratory secretions. In addition to hand hygiene, employees should strictly comply with healthcare infection control policies and isolation techniques. Patients infected or colonized with antibiotic-resistant microorganisms, such as MRSA or extended-spectrum β-lactamase producing gram-negative bacilli, should be placed on Contact Precautions. In addition, patients should be placed in private rooms, if possible, or cohorted with other patients who are colonized or infected with the same microorganisms.

Intervention bundles that address both the reduction of airway colonization and the prevention of aspiration have successfully reduced VAP rates in both adult and pediatric institutions (107,*134*). There are a number of interventions recommended to reduce colonization of the upper airway (135). Comprehensive age-appropriate mouth care can help reduce the bacterial load in a patient's mouth. For children over 2 months old, institutions should consider using a chlorhexidine mouth care product. Condensate should be drained from the ventilator circuit every 2 to 4 hours. In addition, the use of heated ventilator circuits may reduce the amount of condensation that develops. Circuits should only be changed when they are visibly soiled or malfunctioning to prevent further contamination. In-line suction catheters should only be changed when visibly soiled, and open catheter systems should be considered single use. The next group of components is aimed at preventing the aspiration of microorganisms that are colonizing the upper airway and ventilator circuit (135). Elevation of the head of the bed between 30 and 45 degrees, unless contraindicated, is recommended. For neonates, the bed should be elevated between 15 and 30 degrees. It is important to drain ventilator circuits prior to repositioning the patient to prevent pooled fluid in the circuit from flowing into the patient's lower respiratory tract. For children older than 12 years, the use of an endotracheal tube with a dorsal lumen above the endotracheal cuff facilitates drainage and suctioning. The adult ventilator bundle recommended by the Institute for Healthcare Improvement includes four components geared toward preventing complications common in intubated patients including VAP *(136)*. The components include elevation of the bed between 30 and 45 degrees, daily "sedation vacation" and assessment of readiness to extubate, peptic ulcer disease prophylaxis, and deep vein thrombosis prophylaxis. "Sedation vacations" are not appropriate in children because of the risk of unplanned extubation, although assessing the readiness to extubate should be performed daily. Addition of the last two components in children should be based on the age and condition of the child (135).

Proper cleaning and disinfection of ventilator equipment is always important. Contaminated equipment has been incriminated in numerous outbreaks of respiratory infections (47). Such reports have pointed out that many respiratory devices are capable of harboring and spreading pathogenic microorganisms, including in-line medication nebulizers, ventilator tubing (particularly when condensate is present), bedside resuscitation bags, and endotracheal tubes. Only sterile fluids should be nebulized or used in a humidifier, and disposable equipment should not be reused. Although endotracheal suctioning may dislodge bacterial aggregates often found in the lumina of endotracheal tubes, endotracheal suctioning should be performed, as needed, to remove secretions *(137)*. The role of the gastrointestinal tract as a source for endogenous upper airway colonization cannot be overlooked. Much of the attention has centered

on the stomach, and it is quite clear that this organ can serve as a reservoir for pathogenic microorganisms. The esophagus may serve as a conduit for the transmission of these microorganisms to the upper respiratory tract. The use of enteral feeding, antacids, and H_2-blockers in critically ill patients can elevate the gastric pH and facilitate gastric microbial colonization and growth *(138,139)*. These medications are used in intensive care patients for prophylaxis against upper gastrointestinal bleeding. If these medications are indicated, it is important to choose an agent that does not elevate the gastric pH *(140)*. In patients who have received prophylaxis with sucralfate, for example, a lower gastric pH and fewer healthcare-associated LRTIs have been demonstrated *(141)*.

Patients admitted to the hospital with pertussis should be placed on Droplet Precautions for the first 5 days of antimicrobial therapy. This therapy does not change the course of the disease but renders the patient noninfectious. Early pertussis is indistinguishable from viral upper respiratory tract infections, which often results in a delay in diagnosis, treatment, and appropriate isolation. This delay results in frequent exposures of healthcare workers. In 2005, a tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap), formulated for use in adults and adolescents, was licensed in the United States *(142)*. The Advisory Committee on Immunization Practices recommends that all healthcare workers who have direct patient contact should receive a single dose of Tdap if they have not previously received it *(142)*. The interval between the most recent tetanus, diphtheria vaccine and Tdap can be as short as 2 years *(142)*. For hospital personnel exposed to the patient before the diagnosis of pertussis, chemoprophylaxis with azithromycin, erythromycin, or clarithromycin is indicated. Patients may also receive prophylaxis with the latter macrolides. Trimethoprim-sulfamethoxazole (TMP-SMZ) may be used for healthcare workers or patients allergic to macrolides (Table 49-6). Therapies such as azithromycin have been well tolerated in treating hospital employees during hospital outbreaks *(119,143,144)*. Prompt erythromycin chemoprophylaxis effectively limits secondary cases and is recommended regardless of age or immunization status because pertussis immunity is not absolute. In addition to chemoprophylaxis, children younger than 7 years who are not immunized or who have had fewer than 4 doses of vaccine should undergo initiation or continuation of pertussis immunization according to schedule. If a child received the third dose of vaccine 6 months or more before exposure, the fourth dose should be given as soon as possible after the exposure *(144)*. Patients admitted

TABLE 49-6

Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis by Age Group

	Primary Agents			*Alternate Agent*[a]
Age group	*Azithromycin*	*Erythromycin*	*Clarithromycin*	*TMP-SMZ*
<1 mo	Recommended agent. 10 mg/kg/d in a single dose for 5 d (only limited safety data available)	Not preferred. Erythromycin is associated with infantile hypertrophic pyloric stenosis. Use if azithromycin is unavailable; 40–50 mg/kg/d in 4 divided doses for 14 d	Not recommended (safety data unavailable)	Contraindicated for infants aged <2 mo (risk for kernicterus)
1–5 mo	10 mg/kg/d in a single dose for 5 d	40–50 mg/kg/d in 4 divided doses for 14 d	15 mg/kg/d in 2 divided doses for 7 d	Contraindicated at age <2 mo. For infants aged ≥2 mo, TMP 8 mg/kg/d, SMZ 40 mg/kg/d in 2 divided doses for 14 d
Infants (aged ≥6 mo) and children	10 mg/kg in a single dose on d 1, then 5 mg/kg/d (maximum:500 mg) on d 2–5	40–50 mg/kg/d (maximum: 2 g/d) in 4 divided doses for 14 d	15 mg/kg/d in 2 divided doses (maximum: 1 g/day) for 7 d	TMP 8 mg/kg/d, SMZ 40 mg/kg/d in 2 divided doses for 14 d
Adults	500 mg in a single dose on d 1 then 250 mg/d on d 2–5	2 g/d in 4 divided doses for 14 d	1 g/day in 2 divided doses for 7 d	TMP 320 mg/d, SMZ 1,600 mg/d in 2 divided doses for 14 d

[a]Trimethoprim-sulfamethoxazole (TMP–SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.
(From Tiwari T, Murphy TV, Moran J; National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines. *MMWR Recomm Rep* 2005;54[RR14]:1–16.)

with *Legionella* infection do not need to be isolated (see also Chapters 22,36,90).

SKIN INFECTIONS

Cutaneous infections of infants and children have been reported to occur in 5% to 74% of healthcare-associated infections, with the highest rates occurring in neonatal intensive care units (*1,2*,3,*4,5*,6,*7–9*,145). Although most reported infections are associated with intravenous catheter sites, there is always a concern for the development of more invasive disease (i.e., bacteremia). Most of these infections are due to microorganisms already colonizing the patient or are transmitted to the patient via the hands of hospital personnel. In addition to poor hand hygiene practices by healthcare workers, improper cleaning of environmental surfaces can lead to an increase in infections. These infections commonly present as an intravenous catheter-site infection: impetigo, cellulitis, or less commonly, a life-threatening infection such as necrotizing fasciitis.

Catheter-Site Infections

Hospitalized infants and children usually require venous access while receiving medical therapy. Most venous access is obtained by cannulation of peripheral veins. Occasionally, more critically ill patients require cannulation of larger vessels. Semipermanent indwelling catheters (e.g., Infuse-a-port, Broviac, peripherally inserted central catheter [PICC] lines) are now widely used in children undergoing chemotherapy, long-term parenteral nutrition, or long-term antibiotic therapy. Phlebitis is the most common complication associated with peripheral vein cannulation *(146,147)*. Catheters in the antecubital fossa, the arm, or the leg and those used for hyperalimentation are among those most often complicated by phlebitis. Local infections such as exit-site infections or tunnel infections may develop. Microorganisms may gain access to the space between the catheter and the subcutaneous tissue during catheter insertion or migrate into the catheter tract after insertion. *S. aureus* or coagulase-negative staphylococci (i.e., *S. epidermidis*) cause the majority of these infections. The entrance site—the point at which the catheter enters the vein—or the intravascular portion of the catheter may also become infected. These latter infections are often associated with bacteremia.

Indwelling intravascular catheters become colonized when an overgrowth of microbes develops on either the external catheter surface below the skin or the endoluminal surface of the catheter. Semiquantitative cultures with a growth of at least 15 CFUs or quantitative cultures growing at least 100 CFUs of a microorganism are needed to confirm colonization. Colonization rates of between 4% and 13% occur after these catheters have been in place for 48 hours and increase to more than 30% if left in for longer than 6 days *(146–150)*. The coagulase-negative staphylococci are the most common microorganisms isolated, but colonization may occur with other microorganisms from the hospital flora. These colonized catheters then become a nidus for infection that may result in cutaneous infection or bacteremia. Local catheter-related infections usually present with signs of local inflammation such as erythema, warmth, tenderness, and/or purulent discharge from the catheter site. Cultures usually reveal the presence of colonization. There are two main types of local catheter-related infections: exit-site infections and tunnel infections. Exit-site infections are defined as erythema or tenderness within 2 cm of the exit site or purulent drainage from the exit site. In tunnel infections, the erythema and tenderness occur along the tract of the catheter at least 2 cm from the exit site. Inflammation or pus may or may not be present at the exit site *(151)*.

Materials used for venous catheters may affect colonization rates as well. Some microorganisms can actually metabolize components of the plastic catheters in the absence of other nutrients and use them to sustain growth on the surface of biomaterials *(152)*. Polyvinyl chloride and siliconized latex catheters have been demonstrated to have higher colonization rates than polyurethane, Vialon, or Teflon catheters *(153)*. Antibiotic and chlorhexidine–silver sulfadiazine coating of catheters may be anti-infective and prevent colonization for short periods (up to 1 week) *(154)*. Pediatric scalp vein needles, however, have been associated with a marked decrease in colonization and infections *(155)*. This may be true, because these needles cause less trauma to the vein, are shorter, and tend to stay in place for a shorter period.

Colonization of catheters is a key step to the development of catheter-site infections. Strict adherence to infection prevention strategies during both insertion and maintenance of the catheter is required to prevent catheter-site infections and more severe complications such as bloodstream infections. Intervention bundles have been developed to prevent the development of catheter-related infections with the primary focus on the prevention of bloodstream infections *(156)*. Adult intervention bundles have focused mainly on preventing infection at the time of catheter insertion. Successful implementation of these insertion bundles in adult hospitals has dramatically reduced infection rates (*157,158,*159). These bundles include hand hygiene; the use of maximum sterile barriers; cleaning the skin with chlorhexidine; attention to the site where the catheter is placed, such as avoiding femoral line placement; and the use of an all-inclusive catheter cart or kit *(160)*. Studies in pediatric settings have shown that focusing only on strategies to prevent contamination during catheter insertion is not enough; proper maintenance of the lines is also required *(161)*. Recently, a multicenter study that included 29 PICUs tested and implemented insertion and maintenance intervention bundles and showed considerable reduction in catheter-associated bloodstream infections (CA-BSIs) (162). The pediatric insertion bundle is similar to the adult bundle. The maintenance bundle includes daily assessment of catheter need; catheter-site care using a 30-second chlorhexidine gluconate scrub; only changing gauze dressings every 2 days or for clear dressings every 7 days unless they become soiled, dampened, or loosened; and specific instructions for catheter hub, cap, and tubing care (162). The focus of the adult and pediatric bundles has been to reduce CA-BSIs, but the various components work to prevent contamination and colonization. Therefore, these strategies should also prevent catheter-site infections. The catheter site and cannulated vein should be inspected daily for signs of inflammation and

the catheter removed promptly if they occur. If phlebitis or a local abscess should develop, the entire infusion system, including the bag of intravenous fluid, tubing, and needle or catheter should be removed. If purulent material is present, it should be sent for gram stain and culture (see also Chapters 17 and 18).

Impetigo

Impetigo contagiosa is a contagious superficial infection of the skin. The causative agent is usually *S. pyogenes* alone or in combination with *S. aureus*. Bullous impetigo is caused almost exclusively by *S. aureus*. Although this disorder is seen commonly in the community, impetiginous lesions often develop while patients are hospitalized, and the infection reflects the flora of the hospital. This infection occurs most often in the diaper region as a complication of diaper dermatitis. Usually, local care with soap and water or antimicrobial cream effectively eradicates the infection. Occasionally, parenteral therapy is indicated, and the agents chosen should be active against *Staphylococcus* species and *Streptococcus* species. Close attention to hand hygiene among hospital personnel and routine baths for the patients help alleviate this problem. Patients with impetigo should be placed on Contact Precautions until 24 hours of appropriate antibiotic therapy has been administered.

Staphylococcal scalded skin syndrome is an unusual skin infection caused by exfoliative toxin-producing strains of *S. aureus*. The syndrome starts as a bullous lesion and may spread to involve the entire body. The microorganism enters the skin through an area of trauma, such as a circumcision or other surgical procedure. It is generally spread on the hands of healthcare personnel or a family member. The microorganism is more likely to be recovered from the nares than the lesion itself. The preferred treatment is nafcillin or a first-generation cephalosporin, but MRSA isolates producing the exfoliative toxin have been identified; therefore, empiric therapy with vancomycin should be considered. Isolates should be saved for typing if an outbreak is suspected *(163)*.

Cellulitis

Cellulitis is an acute inflammation of the skin and subcutaneous tissues that may be associated with fever, warmth, erythema, edema, tenderness, lymphadenopathy, and an elevated peripheral leukocyte count *(164)*. This illness may represent a primary infection of the skin or may be secondary to bacteremia. *S. aureus* or *S. pyogenes* most commonly cause cellulitis of the extremities. In infants, in addition to *S. aureus*, GBS is a predominant microorganism. With facial involvement, *S. pneumoniae* is currently the most common cause, but *H. influenzae* type B should be considered as a potential pathogen in infants younger than 1 year who are not completely immunized. Healthcare-associated cellulitis most commonly involves microorganisms endemic to the hospital or endogenous to the patient. The diagnosis of cellulitis is based on physical examination. Aspiration of the leading edge or the area most intensely involved by the cellulitis may aid in identifying a microorganism. Most patients are not bacteremic unless they appear toxic.

Omphalitis is a severe form of cellulitis affecting the newborn infant. This usually results from colonization of the umbilical cord by *S. pyogenes*. In more recent years, gram-negative microorganisms have become more prominent causes of omphalitis because of the use of prophylactic agents on the umbilical cord *(165)*. Funisitis usually begins as a wet, malodorous umbilical stump with minimal inflammation. Inflammation may continue to develop and may spread to involve the wall of the abdomen. Patients with severe forms of omphalitis may develop necrotizing fasciitis. The infants become irritable, and a cellulitis surrounding the umbilical cord is noted on physical examination. Dissemination into the bloodstream is uncommon but may occur.

Adequate cord care is the key to preventing complications such as omphalitis. A single application of triple dye to the cord results in considerable reduction in all bacteria, including staphylococci, streptococcal species, and coliforms. However, triple dye has only limited effectiveness in preventing colonization with MRSA *(166)*. After the application of triple dye, the umbilical cord should be kept clean and dry. If the cord becomes wet or malodorous, it can be routinely cleaned with alcohol. Good hand hygiene technique should always be used, and immediate isolation of an infant who develops omphalitis due to *S. pyogenes* should be instituted. Infection control measures for identification and segregation of all colonized infants is necessary.

Methicillin-Resistant *Staphylococcus aureus*

MRSA has been an important cause of healthcare-associated infections for many years. Infections include cellulitis, soft tissue abscesses, wound infections, myositis, bone and joint infections, pneumonia, and bacteremia. Historically, these infections have resulted from healthcare-acquired strains, which often are resistant to multiple antibiotics. In recent years, community-acquired MRSA has become increasingly prevalent, resulting in infections in people who have not had recent healthcare or antibiotic exposures. Infections from community-acquired MRSA often result in skin and soft tissue abscesses. These strains are frequently susceptible to gentamicin, clindamycin, and trimethoprim/sulfamethoxazole, although local susceptibility patterns vary. Recently, the distinction between community-acquired and hospital-acquired MRSA has become blurred as patients have developed healthcare-associated infections with MRSA strains with resistance patterns that are more typical of community-acquired MRSA. To prevent transmission to other people, patients with MRSA infections should be placed on Contact Precautions. Because up to 80% of soft tissue abscesses in children are caused by MRSA, consider empirically placing patients with soft-tissue abscesses on Contact Precautions until another causative microorganism has been identified (167). Patients infected or colonized with MRSA should be placed in private rooms, if possible, or cohorted with other MRSA patients. In patients with MRSA infections, the environmental surfaces can become contaminated within a few hours (168,*169*). Thorough cleaning by environmental services is necessary.

Necrotizing Fasciitis

Necrotizing fasciitis is a rapidly progressive soft-tissue infection involving the skin, subcutaneous tissue, and superficial fascia. It is a rare but life-threatening complication following surgery or trauma in the infant or child. The infection may begin in an operative site or at the site of

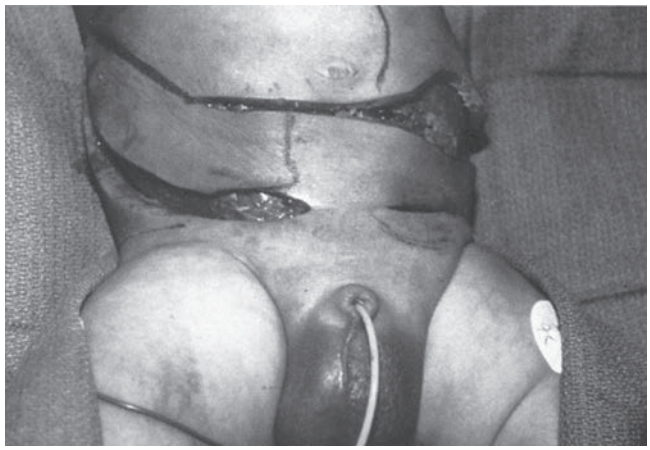

FIGURE 49-2 A patient has undergone the wide surgical debridement needed for treatment of necrotizing fasciitis.

an injury, or it may develop without apparent cause. The infection spreads rapidly along fascial planes, producing thrombosis of nutrient vessels, which results in the necrosis of overlying subcutaneous tissue and skin. Although *S. pyogenes* was initially described as the causative microorganism for this disorder, the infection in most individuals is polymicrobial *(170)*. This disorder has been described in postoperative cases after appendectomy, inguinal herniorrhaphy, and circumcision *(171)*.

The diagnosis of necrotizing fasciitis is based on clinical findings. Adults usually demonstrate a triad of cellulitis, crepitus, and the presence of gas in tissues on a radiograph. Children usually do not manifest these findings *(171)*. In infants and children, the diagnosis should be considered when a patient develops a new case of cellulitis with an area of induration that far exceeds the area of erythema. The patient appears toxic out of proportion to the area of cellulitis *(171)*. Gas or crepitus is uncommon in infants and children. The treatment for necrotizing fasciitis demands early wide surgical debridement and broad-spectrum antimicrobial agents (Fig. 49-2) *(172)*. To prevent necrotizing fasciitis, good hand hygiene and meticulous wound care are needed.

DISCLOSURE

The authors have no financial relationships relevant to this chapter.

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CHAPTER 50

Healthcare-Associated Gastrointestinal Tract Infections in Pediatric Patients

Douglas K. Mitchell

Gastrointestinal tract infections are a major cause of morbidity and mortality in children worldwide. Data from a group of private hospitals showed that gastroenteritis was the leading reason for the hospital admission of children in their population *(1)*. Children can develop diarrhea as the result of infections acquired prior to hospital admission or during hospitalization. Either mode of acquisition may result in considerable complications including dehydration, chronic diarrhea, prolonged hospitalization, and death. Each child infected with an enteropathogen may then become a potential source of further spread within the hospital population.

Healthcare-associated infection (HAI) refers to infections associated with healthcare in any setting. Nosocomial infection is a term that is now reserved specifically for infections acquired in a hospital (2). This approach in terminology now addresses the broader spectrum of infections related to multiple settings including hospitals, outpatient care settings, long-term care facilities, and home care.

The Centers for Disease Control and Prevention (CDC) defines healthcare-associated gastrointestinal system infections, as "gastroenteritis, hepatitis, necrotizing enterocolitis, gastrointestinal tract infections, and intra-abdominal infections not specified elsewhere." In this chapter, we address healthcare-associated gastroenteritis as defined by the CDC *(3)*:

Gastroenteritis must meet either of the following criteria:

1. Acute onset of diarrhea (liquid stools for more than 12 hours) with or without vomiting or fever (>38°C) AND no likely noninfectious cause (e.g., diagnostic tests, therapeutic regimen, acute exacerbation of a chronic condition, psychologic stress)
2. Two of the following with no other recognized cause: nausea, vomiting, abdominal pain, or headache AND any of the following:
   a. Enteric pathogen isolated from stool or rectal swab culture
   b. Enteric pathogen detected by routine or electron microscopy (EM) examination
   c. Enteric pathogen detected by antigen or antibody assay on feces or blood
   d. Evidence of enteric pathogen detected by cytopathic changes in tissue culture (toxin assay)
   e. Diagnostic single antibody titer (immunoglobulin M) or fourfold increase in paired serum samples (immunoglobulin G) for pathogens
   f. Enteric pathogen detected by molecular methods (polymerase chain reaction [PCR], reverse transcription PCR [RT-PCR], genotyping, etc.)

For an episode of diarrhea to be considered healthcare-associated, the onset of disease must occur during hospitalization or shortly after discharge, and the infection should not be present or incubating at the time of the patient's admission. This assessment of healthcare-associated versus community-acquired infection should also consider the expected incubation period for each possible enteropathogen. Most studies define healthcare-associated diarrhea as occurring more than either 48 or 72 hours after admission or within 48 hours after discharge. This definition is clearly fraught with difficulties because of the poor methods employed while screening for disease at the time of admission to the healthcare facility.

A review of 26 pediatric wards in 1949 revealed a cross-infection (nosocomial infection) rate of 7%, 21% of which was gastroenteritis *(4)*. Subsequent reports have described gastroenteritis as the first to the fifth most frequent type of HAI in children *(5,6)*. Gastroenteritis has been reported as the cause of 13% to 35% of HAIs in pediatric hospitals *(7–12)*. In addition, 5% to 14% of pediatric patients developed healthcare-associated gastroenteritis *(7,10)*. The incidence was from 0.68 to 6.1 cases per 100 inpatients with a rate of 0.11 to 1.1 episodes per 100 hospital days *(7,13–17)*.

A 9-year surveillance in a children's hospital identified diarrhea as the third most common HAI (15%) with 0.5 to 1.0 episodes per 1,000 patient days *(6)*. A pathogen was identified in 56% of episodes, including *Clostridium difficile* (32%), rotavirus (31%), adenovirus (30%), and other viral etiologies (7%). The median age of affected patients was 1.3 years, 0.8 years for viral diarrhea and 3.9 years with *C. difficile* diarrhea. Of the children with healthcare-associated diarrhea, 75% were diapered at the time of the episode. The ranges in incidence rates are attributable to studies with differing definitions, different age groups, and developing versus developed locations.

Reports by the CDC as part of the National Nosocomial Infections Surveillance (NNIS) system have included the incidence of nosocomial diarrhea in participating

hospitals. The NNIS system data from 1985 to 1991 demonstrated that nosocomial diarrhea occurred in newborn nurseries at a rate of 3 per 10,000 discharges. This rate is higher in high-risk nurseries, wherein the rate is 20 per 10,000 discharges. The NNIS system also reported that gastrointestinal tract infections cause 8% of all nosocomial infections in high-risk nurseries *(16)*. NNIS (1992–1997) reported gastrointestinal tract infections as 5% of nosocomial infections in pediatric intensive care units *(18)*. *C. difficile* was implicated in 52% of cases, and viruses were implicated in 44% of cases. Rotaviruses were the etiology in 74% of viral cases and enteroviruses were the etiology in 13%.

Data describing the ultimate economic or medical impact of pediatric healthcare-associated gastrointestinal tract infections in the United States are lacking. Two reports from developing countries indicated that healthcare-associated gastroenteritis increased the mean length of hospital stay by 7 and 20 days, respectively. Healthcare-associated rotavirus infection increased the length of hospital stay by 8 days in a French hospital *(19)*. An Austrian study estimated annual costs of 6.2 million EUR because of healthcare-associated rotavirus infections *(20,21)*. Many reports have described outbreaks of healthcare-associated gastrointestinal tract infections due to specific enteropathogens. These specific pathogens and their relative importance are discussed below *(8,9)*.

ETIOLOGY

Many viral, bacterial, and parasitic enteropathogens have been associated with HAIs (Table 50-1). The NNIS system reports for 1985 to 1991 indicate that an etiologic agent was identified in 97% of the adult and pediatric cases of nosocomial gastroenteritis and that bacteria accounted for 93% of the reported enteropathogens. *C. difficile* was the most frequent pathogen, but because this report included adults as well as children, it is not a true reflection of healthcare-associated gastroenteritis in children. In addition, most of the NNIS system participating hospitals lack diagnostic virology laboratories, so the relative importance of enteric viruses was underestimated. Rotavirus ranked second, accounting for 5% of all HAIs. Studies limited to the pediatric population have identified viral agents as the most frequent healthcare-associated enteropathogens, with rotavirus being the agent most frequently identified *(14)*. In one study in a pediatric hospital, the following nosocomial enteropathogens were detected: rotavirus, 43%; calicivirus, 16%; astrovirus, 14%; minireovirus, 12%; adenovirus, 8%; *Salmonella* spp., 4%; and parvovirus/picornavirus, 3% *(22)*.

TABLE 50-1

Enteropathogens and Other Microorganisms Associated with Healthcare-Associated Gastroenteritis

Bacteria
Campylobacter jejuni
Clostridium difficile
Escherichia coli
Enteroaggregative (EAEC)
Enterohemorrhagic (EHEC)
Enteroinvasive (EIEC)
Enteropathogenic (EPEC)
Enterotoxigenic (ETEC)
Leuconostoc species
Salmonella species
Shigella species
Vibrio cholerae
Yersinia enterocolitica

Viral
Enteric adenovirus
Astrovirus
Human calicivirus including Noroviruses and Sapoviruses
Rotavirus
Human Parechoviruses

Parasites
Cryptosporidium parvum
Cyclospora cayetanensis
Entamoeba histolytica
Giardia lamblia
Strongyloides stercoralis

Other
Candida species
Agents possibly associated with necrotizing enterocolitis

Potential healthcare-associated gastrointestinal tract pathogens
Aeromonas species
Klebsiella species
Pantoea agglomerans
Plesiomonas shigelloides
Pseudomonas aeruginosa

Known gastrointestinal tract pathogens (that are potential healthcare-associated pathogens)
Campylobacter upsaliensis
Vibrio parahaemolyticus
Isospora belli
Encephalitozoon intestinalis
Enterocytozoon bieneusi

Viral

Viruses are recognized as important healthcare-associated enteropathogens that spread via person-to-person transmission or point-source infection through food or water. Studies show that enteric viruses have caused 86% of healthcare-associated gastroenteritis in infants and children *(10,22–24)*.

Enteric Adenoviruses Enteric adenoviruses consist of two serotypes—40 and 41—which are members of group F adenoviruses *(25)*. These agents primarily infect children younger than 2 years and occur year-round *(26,27)*. Adenoviruses cause a spectrum of conditions ranging from asymptomatic infection in 40% of infected children to diarrhea and vomiting lasting for 7 to 10 days. The incubation period is 3 to 10 days. Illness is frequently associated with fever and respiratory tract symptoms *(28)*. Transmission occurs via the fecal–oral route and readily transfers from person to person *(26)*. Treatment is nonspecific, and fluid

replacement is dictated by the patient's condition. The frequency of dehydration and fever due to enteric adenovirus gastroenteritis appears to be similar to that of other enteric viruses *(29)*. In several reports, enteric adenovirus was the third most frequent cause of viral gastroenteritis in hospitalized infants and young children *(28–32)*. In one study, 54% of 127 enteric adenovirus infections were healthcare associated *(31)*. Adenovirus type F41 caused an outbreak in a pediatric bone marrow transplant unit and was shed in the stool for up to 64 days in these immunocompromised patients (33). These viruses have been shown to be a major cause of morbidity in hospitalized infants who have undergone ileostomy or colostomy procedures for necrotizing enterocolitis (NEC) *(34)*. The HAI rate in these patients was higher than other nursery patients, and infection resulted in a prolonged hospital stay. Diagnosis of enteric adenovirus-associated gastroenteritis can be made by an evaluation of stool specimens using either EM or a commercially available enzyme immunosorbent assay (EIA). Research methods use PCR and gene sequencing for detection, genotyping, and outbreak analysis (33).

Astrovirus Eight antigenic types of human astrovirus have been identified. Gastroenteritis due to astrovirus occurs worldwide and has been associated with outbreaks of mild diarrhea in schools *(35,36)*, childcare centers *(37,38)*, nursing homes *(39,40)*, and pediatric hospital wards *(41–43)*. Astroviruses are responsible for approximately 3% to 5% of hospital admissions for gastroenteritis. Illness occurs mainly in children younger than 2 years and frequently causes asymptomatic infection *(44)*. The illness lasts for 1 to 4 days following an incubation period of 24 to 36 hours. Gastrointestinal tract symptoms are nonspecific, consisting of vomiting, diarrhea, fever, and abdominal pain. The mode of transmission is person to person among children. Astrovirus has been reported to be responsible for 5% to 7% of nosocomial gastroenteritis in children's hospitals *(41,43,45–48)*. An attack rate of between 7% and 62% was reported during an outbreak of nosocomial infection in a children's ward *(43)*. Astrovirus caused a prolonged outbreak of diarrhea among immunocompromised patients in a pediatric bone marrow transplant unit *(49)*. Astrovirus-associated gastroenteritis is diagnosed by an examination of a stool specimen by EM, EIA, or RT-PCR *(37,49,50)*. Commercial EIAs for the detection of human astroviruses are not available in the United States but may be used in other countries.

Caliciviruses Four genera of the family *Caliciviridae* have been described including Noroviruses (formerly known as Norwalk-like viruses) and Sapoviruses (formerly known as Sapporo-like viruses) *(51)*. Human calicivirus infections occur year-round, although some studies suggest a seasonal predominance. The incubation period is 12 hours to 4 days, and the clinical symptoms include vomiting and diarrhea, which last for 1 to 4 days. The severity of symptoms caused by caliciviruses is indistinguishable from that of symptoms caused by other enteric viruses *(52,53)*. Persistent excretion may occur in immunocompromised hosts. Caliciviruses have been identified in stools for up to 2 weeks after the onset of symptoms *(54)*. Calicivirus is transmitted by the fecal–oral route through food-borne and waterborne transmission *(55)*. Calicivirus can be detected in stool specimens of 0.2% to 6% of children hospitalized for gastroenteritis. When calicivirus was detected in hospitalized children, it was healthcare-associated in approximately 40% of cases *(46,53,56)*. Caliciviruses have tremendous antigenic and genetic diversity that make detection assays insensitive. Multiple strains have been detected in pediatric hospitals *(57)*. It is apparent that most studies have certainly underreported the significance of calicivirus infections because of these insensitive assays. Caliciviruses can be detected in stool specimens by EM, immune EM, RT-PCR, or EIA, but these tests are available only in research laboratories *(25)*.

Two of these genera—the Noroviruses and Sapoviruses—infect humans. Many of the Noroviruses are known only from a single outbreak and have been named after the sites at which the outbreaks occurred. They include Norwalk; Hawaii; Snow Mountain, MX (Mexico); and Lordsdale *(51,58,59)* Norwalk virus is the best-studied member of the genus. Norwalk virus illness follows an incubation period of 18 to 48 hours and is characterized by vomiting, diarrhea, abdominal pain, and low-grade fever lasting 1 to 2 days *(60)*. Epidemics of Noroviruses have been reported in nursing homes, schools, recreational areas, cruise ships, and hospitals *(61–67)*. Waterborne *(55)*, food-borne *(68,69)*, and person-to-person transmission have all been implicated in epidemics *(58,70,71)*, and the results of volunteer studies suggest the possibility of fecal–oral transmission. There is evidence of the survival of noroviruses in environmental reservoirs (72). Aerosolization of vomitus has also been implicated as a mode of transmission. In one hospital outbreak, 55% of elderly patients and 61% of the healthcare workers on one floor became ill *(73)*. The healthcare workers most likely spread the infection from patient to patient. Another reported outbreak affected 57 patients and 69 staff members over a 26-day period. The index case was a patient hospitalized with acute abdominal pain and diarrhea 2 days prior to the outbreak. The epidemic curve indicated person-to-person transmission *(74)*. In another report of an outbreak in a children's ward, 15 children had the Norwalk virus in stool specimens, and the ward had to be closed to control the outbreak *(61)*.

Norovirus infections in enclosed settings were studied for the effectiveness of control measures. One review identified norovirus outbreaks as the most common cause to result in the closure of a medical department (75). The median outbreak duration was 16 days. Other studies have not shown interventions that successfully shortened the outbreaks *(76)*.

The Sapoviruses have also been associated with sporadic outbreaks and have been named after the location of the outbreak. They include Sapporo, Houston, London, Manchester, and Parkville *(77–79)*. Illness due to Sapoviruses is similar to that associated with the Noroviruses.

Rotavirus Rotavirus is the most thoroughly investigated and described etiology of healthcare-associated viral gastroenteritis and is one of the most important enteric pathogens worldwide. There are six distinct rotavirus groups, three of which infect humans. Group A rotavirus is the most common cause of diarrhea in infants and children throughout the world, including the United States. Groups B and C cause human disease in the Far East *(25,27,80)*.

Rotavirus has an incubation period of 1 to 3 days. Excretion of rotavirus in stool can precede the onset of illness by several days and can persist for 8 to 10 days after symptoms of illness have abated *(81)*. The illness usually has an abrupt onset characterized by explosive, watery diarrhea and is often associated with vomiting either before or after the onset of diarrhea. Dehydration occurs in 40% to 80% of patients and is usually mild, but severe dehydration and death have been reported in children and adults *(82)*. Rotaviruses are transmitted principally by the fecal–oral route. They are found in nearly 50% of stool specimens from children admitted to the hospital with gastroenteritis. The majority of patients with rotavirus infection are between 6 and 24 months old *(83)*. In North America, the annual rotavirus season begins in late fall in Mexico and moves across the continental United States from the southwest to the northeast, resulting in a peak of rotavirus activity in March and April in eastern Canada and the northeastern United States *(84)*.

A 5-year retrospective study of 577 children with confirmed rotavirus gastroenteritis revealed that 121 (20%) were healthcare associated. The incidence was 4.2 cases per 10,000 patient days. The median age was 11 months. All healthcare-associated rotaviruses were type G1 with four different PCR subtypes described. The long-term and intensive care units had a considerably higher proportion of nosocomial infection than the more acute care medical beds where the majority of community-acquired rotavirus infections were treated (85).

Healthcare-associated transmission of rotavirus has been well documented on pediatric hospital wards; 2% to 24% of children admitted to the hospital with other diagnoses acquire rotavirus in the hospital *(21,30,86–93)*. In several reports, up to 70% of infants in a nursery have healthcare-associated rotavirus *(94–97)*. Hospital surveillance for rotavirus using molecular methods has detected newly emerging strains and the nosocomial transmission of those new strains *(96–100)*. Immunocompromised children acquire rotavirus in the hospital with an infection rate of 12% to 25%. Immunocompromised children have an extended period of virus excretion and may be a source of virus for transmission to others *(101,102)*. Community-acquired symptomatic rotaviral infection in children admitted to the hospital and asymptomatic rotavirus shedding by neonates and other hospitalized infants appear to be the primary reservoirs for nosocomial rotavirus infection in susceptible children *(103–105)*. Fomites may play a role in rotavirus transmission. Rotavirus contamination was detected by PCR in 19% of inanimate objects in a childcare center during an outbreak *(106,107)*. Nosocomial rotavirus infection may cause both outbreaks and endemic diarrheal disease in newborn nurseries; however, infection is usually asymptomatic *(94,105,108–115)*. Asymptomatic rotavirus infection also occurs in older children, with evidence of asymptomatic rotavirus infection occurring in 24% to 50% of the infections in infants younger than 2 years during the rotavirus season *(116–118)*. Asymptomatic excretion of rotavirus by healthcare personnel has been proven (119). The incidence of confirmed nosocomial rotavirus diarrhea in a large pediatric hospital was found to be 0.5 to 0.9 per 1,000 admissions *(120,121)*.

HAIs in developing countries occurred in 12% to 22% of all rotavirus cases with an incidence of 0.024 to 1.6 cases per 1,000 child-days. No HAIs occurred in children older than 4 years (*122,123,*124).

Prospective surveillance for rotavirus gastroenteritis in three Spanish hospitals in the winter of 2006 to 2007 identified nosocomial rotavirus infection in 2.8 cases per 100 inpatients and 0.48 cases per 100 patient days. Rotavirus was the etiology of 59% of healthcare-associated gastroenteritis. G9P[8] and G1P[8] were the predominant serotypes *(15)*.

A review of healthcare-associated rotavirus gastroenteritis in European hospitals made several conclusions. Healthcare-associated rotavirus infections have an incidence from 1.6 to 6.3 cases per 1,000 children younger than 5 years; these infections represent 1.6 to 15.8 cases per 1,000 hospital days and account for 3,000 to 20,000 rotavirus infection cases in children younger than 5 years. Rotavirus gastroenteritis lengthens hospital stay by 1.8 to 5.0 days. Hand washing, and specifically the use of alcohol-based hand sanitizers, is very effective in reducing the number of HAIs (125,126). Unique serotypes that occur in a community will be seen as a cause of HAIs during that season *(127)*.

Breast feeding was protective against both infection and symptoms, whereas 32% of formula-fed and 11% of breast-fed infants acquired rotavirus in the hospital ($p < .005$). No breast-fed infant had symptomatic infection *(128)*.

Rotavirus is detected in stool specimens by EIA, latex agglutination, EM, polyacrylamide gel electrophoresis, and PCR *(129–132)*. Several EIA and latex agglutination assays are commercially available. Detection rates depend on which assay is employed because of their varying sensitivities.

Universal mass vaccination against rotavirus in Austria resulted in a considerable decrease in hospitalization for rotavirus gastroenteritis and a considerable decrease in the number and percentage of healthcare-associated rotavirus infections *(133–135)*. Rotavirus vaccination in the United States has lowered the frequency of severe diarrhea and, therefore, hospitalizations. The impact on HAIs remains to be seen.

Human Parechoviruses Human parechoviruses belong to the family *Picornaviridae*. A retrospective evaluation identified human parechoviruses type 4 to 6 in association with gastrointestinal tract symptoms in addition to respiratory tract symptoms. Twenty of 277 children with the virus detected in fecal samples had gastrointestinal symptoms. The authors describe at least one child who acquired the virus nosocomially, because it was a 3-month-old infant who had never left the hospital. The virus was detected by RT-PCR in nasopharyngeal aspirates, feces, and plasma. It could be detected in fecal samples for up to 40 days after initial detection (136).

Bacteria

Healthcare-associated bacterial gastroenteritis is less common than viral gastroenteritis. In the United States, the majority of information about healthcare-associated bacterial gastroenteritis consists of reports of outbreaks, many of which are food-borne or waterborne. Several prospective studies of healthcare-associated diarrhea in children failed to demonstrate any bacterial etiologies *(14,22)*, although *C. difficile* is common in adults. Bacterial infections are much more common in less-developed countries. A patient with poor nutritional status or an immunocompromised

patient is at particularly high risk for healthcare-associated bacterial gastroenteritis.

Campylobacter Species Twenty-one species have been identified in the family *Campylobacteraceae*, but only 12 cause disease in humans. *Campylobacter jejuni*, *Campylobacter coli*, *Campylobacter upsaliensis*, and *C. jejuni* subspecies *doylei* are the most common species isolated from children. *Campylobacter fetus* is a rare cause of bloodstream and systemic infections occurring mostly in immunocompromised and debilitated hosts, as well as a cause of perinatal infection and abortion. Since *C. jejuni* is the species that usually causes intestinal illness, many laboratories place stool specimens on selective media with incubation temperatures to isolate this species. With this method, several other *Campylobacter* species will be missed as a cause of diarrhea. Therefore, the extent of HAIs involving many of the *Campylobacter* species is not known. Isolation of *Campylobacter* spp. from blood and other sterile body sites does not present the same isolation problem as isolation from feces *(137)*.

Predominant symptoms are diarrhea, abdominal pain, malaise, and fever. Stools may contain blood. *C. jejuni* has been reported as a cause of severe infection in neonates following vertical transmission. Vertical transmission of a microorganism is considered a nosocomial infection in the nursery for purposes of surveillance reporting. Postnatal person-to-person transmission has also been documented with reports of nursery epidemics of *Campylobacter* spp. diarrhea and meningitis *(138)*. The incubation period is 1 to 7 days.

Healthcare-associated transmission of *Campylobacter* spp. is not common. The gastrointestinal tract of domestic and wild birds and animals is the reservoir of infection. A Finnish hospital reported a waterborne nosocomial outbreak of *C. jejuni* gastroenteritis in both patients and hospital staff *(139)*. Several community-acquired outbreaks caused by *C. jejuni* have been reported, usually due to ingestion of contaminated raw milk, water, or food. In addition, infection can occur through person-to-person transmission or contact with infected animals *(140)*. For example, an outbreak involving two very closely related strains of *C. upsaliensis* in four childcare centers implicated person-to-person transmission *(141)*.

Clostridium Difficile Healthcare-associated gastrointestinal tract infection caused by *C. difficile* in adults and children is discussed in Chapter 37. The role of *C. difficile* in antibiotic-associated diarrhea has been more difficult to establish in infants and young children than in adults, since *C. difficile* is commonly recovered from the stools of asymptomatic infants and young children.

The reported incidence of neonatal colonization varies, with isolation rates as high as 90% in neonatal intensive care units (NICUs) and between 2% and 30% in healthy newborn infants. The *C. difficile* toxin has been detected in up to 36% of sick neonates without gastrointestinal tract symptoms. The incidence of *C. difficile* toxin detection in stool specimens declines with age and approaches 1% to 3% in healthy adults *(142)*. Pseudomembranous colitis has been reported in infants and children, but the incidence is difficult to assess. *C. difficile* was described as the etiology of 13% to 16% of healthcare-associated gastrointestinal tract infections *(9,143)*. Outbreaks of diarrhea associated with *C. difficile* have been reported in childcare centers *(144)*. The incubation period is unknown. The virulence and mortality of *C. difficile*-associated disease are increasing (145). This may be associated with hypertoxigenic strains.

C. difficile may be isolated from stool using a selective cycloserine cefoxitin fructose agar in an anaerobic environment. *C. difficile* produces two toxins. The *C. difficile* cytotoxin B may be detected by cell culture cytotoxicity assay or EIA. Some commercially available EIAs will detect both toxins A and B *(146)*. There have been reports of toxin A negative, toxin B positive *C. difficile* antibiotic-associated diarrhea in adults *(147)*. Arbitrarily primed PCR has been used for genotypic differentiation of strains in hospital outbreaks *(148)*.

Escherichia Coli *Escherichia coli* strains that cause acute diarrheal disease may be classified into five groups: enterotoxigenic (ETEC), enteroaggregative (EAEC), enteroinvasive (EIEC), enteropathogenic (EPEC), and enterohemorrhagic (EHEC) *(149)*. ETEC usually infects infants and children in developing countries or adults following travel to developing countries. EAEC produces acute or chronic diarrhea in all age groups, but predominantly infants, by attachment to and effacement of the intestinal mucosa. EIEC infects all ages and causes diarrhea containing blood and mucus as a result of tissue invasion. These infections may occasionally be food-borne or occur as the result of travel to developing countries. EPEC produces acute and chronic diarrhea, generally in infants under 2 years old in developing countries *(150)*. EHEC causes abdominal pain and bloody diarrhea in children and adults, mostly in developed countries. The illness may be complicated by hemolytic uremic syndrome (HUS) in children or thrombotic thrombocytopenic purpura in adults. It is most frequently spread by undercooked contaminated meat, but many other vehicles of transmission have been described.

The reported incidence of healthcare-associated gastroenteritis caused by these five groups of *E. coli* is low. This may be a reflection of the unavailability of detection methods in most clinical microbiology laboratories. The incubation periods range from 10 hours to 6 days.

Reports of healthcare-associated ETEC-associated diarrheal outbreaks in special care nurseries due to heat-stable enterotoxin–producing strains include one report from Spain with six ETEC-associated neonatal diarrheal outbreaks *(151)*. In another report, ETEC was cultured from infants, nurses, family members, infant formula, and surfaces in the nursery *(152)*. This report implicated person-to-person transmission and food-borne transmission by formula. In another report of a hospital outbreak, a rare phage type further differentiated the infected strain *(153)*. *E. coli* has also been reported as a contaminant of expressed human milk, which caused both asymptomatic infections and gastroenteritis in a nursery *(154)*.

A single report described person-to-person transmission of EIEC in students and staff of a school for mentally retarded adults and children: 48% of the students and 28% of the staff were ill. Control of the outbreak was achieved by cohorting and an emphasis on hand washing *(155)*.

Community-acquired food-borne outbreaks of EHEC serotype O157:H7 are well documented. *E. coli* O157:H

phage type 8 caused a hospital outbreak with food brought to a party from the outside *(156)*. Many outbreaks have occurred in nursing homes, and a report of an outbreak in an institution for mentally retarded children and adults demonstrated the devastating effects of this microorganism in an outbreak. Eight of 20 infected residents developed HUS, and four died of complications *(157)*. Twenty-nine children with *E. coli* O157:H7 in nine childcare centers were reported. There was evidence of person-to-person transmission in all nine facilities *(158)*. Spread of *E. coli* O157:H7 from a patient to a nurse in the hospital setting has been reported *(159)*.

EPEC is the strain most commonly associated with HAIs. It was the etiology of 1.3% of gastrointestinal tract infections in a children's hospital in the United States *(10)* and of 6 of 10 nosocomial bacterial gastrointestinal tract infections in a South African hospital *(9)*. Many studies of outbreaks of diarrhea in NICUs have demonstrated person-to-person transmission by the hands of hospital personnel. Premature infants are the most susceptible to severe morbidity and to mortality resulting from these infections *(160–165)*. Detection of EPEC requires a high level of suspicion. Colonies of *E. coli* from a routine bacterial culture must be screened by type-specific antisera. Research methods for identifying related serotypes include adherence of microorganisms in HEp-2 cells, DNA probes, and PCR to detect EPEC strains with the enteroadherence plasmid.

Leuconostoc Species *Leuconostoc* species are members of the family *Streptococcaceae* and commonly found in dairy products, vegetable matter, and in the soil. They are not considered part of the normal gastrointestinal flora. These microorganisms have been described as the etiology of bacteremia and central catheter-associated infections in children with underlying gastrointestinal disease. The most common reports include children with short bowel syndrome receiving enteral feeds and/or total parenteral nutrition. Several of the children had concomitant gastrointestinal symptoms, thereby implicating the gastrointestinal tract as the source of infection (166).

Salmonella Species The genus *Salmonella* is now considered to comprise a single species named *Salmonella enterica* based on DNA structure and biochemical properties. Within this species are seven subspecies with almost all serotypes pathogenic for humans classified into subgroup I (*S. enterica* subspecies *enterica)*. The subspecies can be divided into serotypes based upon their O (somatic) and H (flagellar) antigens. Two main clinical syndromes are associated with *Salmonella*. The first is the protracted bacteremia of typhoid (*Salmonella typhi*) and paratyphoid (*S. paratyphi*) fevers. The second is the predominantly gastrointestinal tract illness caused by animal adapted *Salmonella* strains. *S. typhimurium* is the serotype most commonly reported as the cause of *Salmonella* infections in humans in the United States. Many outbreaks of *Salmonella* gastroenteritis in hospitalized patients due to a variety of serotypes have occurred through various methods of transmission. Person-to-person transmission may occur among patients or from healthcare personnel. Common-source outbreaks have also been traced to diagnostic agents and medications *(167–169). Salmonella* infections have been acquired from reptiles, highlighting the importance of avoiding exposure to pet reptiles in a hospital setting *(170)*. The incubation period for gastroenteritis is from 6 to 12 hours. For enteric fever, the incubation period is from 3 to 60 days but is usually 7 to 14 days.

Food-borne *Salmonella* outbreaks simultaneously may affect patients in multiple hospitals. In 1962 and 1963, a large outbreak of healthcare-associated gastroenteritis caused by *S. derby* occurred among patients, medical staff, and employees of 53 hospitals in 13 states *(171)*. Contaminated eggs that were eaten raw or undercooked were responsible for this and many other outbreaks *(172–175)*. Person-to-person transmission to hospital staff and to other patients has been documented *(174,176,177)*. Food-borne outbreaks have also occurred following the ingestion of improperly cooked and stored poultry *(178,179)*. Food-borne outbreaks may originate in hospital personnel or in patients *(180–183)*. An epidemic caused by *S. kottbus* was traced to contaminated pooled human milk *(184)*. *S. poona* mastitis was the source of infection for a 5-week-old infant. This case was not healthcare associated but indicated the need to consider pumped breast milk as a potential source of infection (185).

Common-source *Salmonella* outbreaks have also been traced to contaminated diagnostic reagents and medications. These types of outbreaks generally do not present as typical common-source outbreaks and, therefore, may be difficult to recognize. An interstate outbreak of *S. cubana* occurred in 1966 due to contaminated carmine dye used as a marker of gastrointestinal tract transit *(167–169)*. Healthcare-associated outbreaks of salmonellosis have also been traced to bile salts, gelatin, pancreatin, pepsin, vitamins, and extracts of various endocrine glands *(186,187)*. Eight cases of *S. enteritidis* occurred in hospitalized patients receiving enteral nutrition containing lyophilized egg albumin (188). These outbreaks appeared to be sporadic and, therefore, required a high index of suspicion to document their association with a common vehicle.

Outbreaks of *Salmonella* gastroenteritis have also been associated with a variety of medical instruments or procedures, including upper gastrointestinal tract endoscopy *(189)*, fiberoptic colonoscopy *(190)*, rubber tubing attached to a suction apparatus *(191,192)*, rectal thermometers *(193)*, and contaminated mattresses *(194)*. Healthcare-associated *S. hadar* infection occurred in laundry personnel at a nursing home following a food-borne outbreak in the nursing home residents. This report implicated the handling of soiled laundry in the absence of person-to-person contact *(195)*.

Outbreaks of *Salmonella* infection have been reported in nurseries. The microorganism is generally introduced to the nursery by an infant recently born to a mother with clinical or asymptomatic salmonellosis *(196)* or a child with community-acquired *Salmonella* infection. In another report, a 12-day-old infant acquired *S. brandenburg* from his visiting mother (197). *Salmonella* is transmitted among the staff and patients through person-to-person contact. The acquisition of multiple resistant microorganisms by premature infants in special care nurseries results in increased rates of morbidity and mortality *(198,199)*. A case–control study of an outbreak of *Salmonella infantis* in a neonatal care unit in Brazil demonstrated protection

by increased birth weight, and peripheral IV catheter use was a risk factor. Overcrowding and understaffing were associated with the outbreak *(200)*.

Extended-spectrum beta-lactamase–producing *S. isanga* of a single pulsed-field gel electrophoresis (PFGE) type was the etiology of a healthcare-associated outbreak in a South African hospital with immunocompromised children *(201)*.

Salmonella can be cultured from stool, rectal swabs, blood, urine, bone marrow aspirates, and other foci of infection. Serotyping with specific antisera provides further identification for epidemiologic investigation. Determining serotypes remains a useful epidemiologic tool for investigations of outbreaks in both the hospital and the community setting. Plasmid profile analysis (PPA) and PFGE are useful methods for determining the relatedness of infecting strains during an outbreak *(179,202,203)*.

Shigella Species Shigellosis occurs worldwide, although its prevalence differs by location. It is largely a disease associated with poverty, crowding, poor levels of personal hygiene, inadequate water supplies, and malnutrition *(204)*. There are four species of *Shigella* (*S. dysenteriae*, *S. flexneri*, *S. boydii*, and *S. sonnei*), which are differentiated by group-specific polysaccharide antigens of lipopolysaccharides, designated A, B, C, and D, respectively, biochemical properties, and phage or colicin susceptibility. *S. sonnei* is the most common cause of bacillary dysentery in the United States, with *S. flexneri* being responsible for most of the remaining cases. *S. dysenteriae* type 1 and *S. flexneri* are the most common species causing disease in developing countries. Direct fecal–oral transmission can contribute to endemic shigellosis in institutional environments such as mental hospitals, childcare centers, nursing homes, prisons, and outdoor gatherings *(205,206)*. The incubation period is 1 to 7 days. Healthcare-associated outbreaks have seldom been reported despite the low inoculum necessary to cause infection *(207)*. *Shigella* was the etiology of 3% of nosocomial gastrointestinal tract infections among patients in a hospital in a developing country and also caused HAIs among the staff of the clinical microbiology laboratory of a large university-affiliated hospital *(208,209)*.

In one large healthcare-associated outbreak, hospital workers had dysentery caused by *S. dysenteriae* type 2 after eating at the salad bar in the hospital cafeteria. Ninety-five workers were ill, but only three hospital inpatients became ill following person-to-person transmission *(210)*.

Both *S. flexneri* and *S. sonnei* have been reported in newborn infants who acquired the microorganism from an infected mother during labor and delivery. Bacteremia in neonates has been reported but is uncommon *(211,212)*. In one report, 3 of 32 healthcare providers caring for an infected neonate acquired shigellosis *(213)*. *Shigella* is detected by routine microbiologic culture of stool specimens; ribotyping and PPA have been used to differentiate strains.

Vibrio Species *Vibrio cholerae* O1, the etiologic agent of cholera, and *V. cholerae* non-O1 strains, including *V. cholerae* O139, are recognized as important causes of acute, often severe, diarrheal disease in developing countries. A number of other *Vibrio* species have been identified and associated with gastroenteritis including *(214,215)*: *V. parahaemolyticus*, *V. mimicus*, *V. fluvialis (216)*, *V. furnissii (217)*, and *V. hollisae (218)*. *V. parahaemolyticus* is a common marine isolate that has been found in water, shellfish, fish, and plankton. *V. parahaemolyticus* has caused food-borne outbreaks in the United States, but there have been no reports of healthcare-associated gastroenteritis *(214,215)*. Food-borne healthcare-associated *V. parahaemolyticus* has been reported in Asia *(219)*. In countries with endemic cholera, all ages are affected, although children over 1 year old are disproportionately involved. *V. cholerae* O1 is primarily a problem in Asia, Africa, and South America, although there is a focus in the Gulf Coast of the United States, where the microorganism has been associated with undercooked shellfish consumption *(220)*. *V. cholerae* O139 has been reported in several countries in southeast Asia since 1992 in epidemic proportions *(221)*. The incubation period of cholera is usually 1 to 3 days.

Healthcare-associated transmission of cholera has been described in developing countries but not in the United States. Close person-to-person contact and sharing of food was implicated in these outbreaks *(222–225)*. In one hospital in Thailand, the microorganism was isolated from water used for bathing in a pediatric ward *(226)*.

Vibrio spp. may be isolated from stool specimens on thiosulfate-citrate bile salts sucrose agar. Serotyping is performed to distinguish O1 and non-O1 strains. Enterotoxins may be detected by animal or tissue culture assays, EIA, and DNA probes *(214)*.

Yersinia Enterocolitica

Yersinia enterocolitica is associated with a wide spectrum of clinical and immunologic manifestations. The clinical illness caused by this pathogen ranges from self-limited enterocolitis to potentially fatal systemic infection; postinfection manifestations include erythema nodosum and reactive arthritis. *Y. enterocolitica* enterocolitis is characterized by diarrhea with blood-streaked stools, fever, vomiting, and abdominal pain *(227,228)*. Serogroups O:3, O:8, and O:9 are most commonly implicated as a cause of enterocolitis in the United States. *Y. enterocolitica* has been isolated from a variety of animate reservoirs, including birds, frogs, fish, flies, fleas, snails, crabs, oysters, and a wide array of mammals with swine being the major reservoir for human pathogens *(229)*. Animal products including raw milk, whipped cream, ice cream, beef, lamb, and poultry may also harbor the microorganism. Inanimate reservoirs include lakes, streams, well water, soil, and vegetables *(230)*. The most frequent outbreaks in the United States have been associated with the preparation of chitterlings for holiday meals in the south *(231,232)*.

Several mechanisms of healthcare-associated transmission have been described. Transfusion-related yersiniosis has been reported in several countries including the United States and in Europe. In 1987 through 1991, 7 deaths occurred among the 10 reported patients with transfusion-associated *Y. enterocolitica (233)*. Blood donors apparently had low-grade *Y. enterocolitica* bacteremia at the time of donation, and the microorganism replicated at the storage conditions provided for units of red blood cells *(234,235)*. Children and adults with hematologic conditions resulting in iron overload are at greater risk of yersiniosis than healthy individuals *(229)*.

There is a report of an 11-day-old infant with *Y. enterocolitica* enterocolitis acquired either during delivery from an infected mother or postnatally during routine care *(236)*. The incubation period in single-source outbreaks is 1 to 14 days, so either method of transmission was possible in this case. Acquisition and excretion of *Yersinia* spp. has been associated with consumption of pasteurized milk in a pediatric ward *(237)*. The same serotype of *Y. enterocolitica* was isolated from the patients and the pasteurized milk.

Person-to-person spread to both patients and staff within adult and pediatric inpatient populations has also been reported *(238,239)*. In one study, 28% of *Y. enterocolitica*–infected patients acquired the microorganism in the hospital *(240)*.

The detection of *Y. enterocolitica* requires isolation on selective media. Cold enrichment techniques may increase the rate of recovery from stool cultures. Serotyping is performed to identify the most common serotypes in human disease and may be used for outbreak evaluation. Chromosomal DNA restriction fragment length polymorphism *(231)*, PPA, and phage typing have been used to evaluate the relatedness of serotypes during outbreaks.

Parasites

Cryptosporidium Cryptosporidia are small coccidian parasites that infect the microvillus region of epithelial cells lining the digestive and respiratory organs. Since 1982, these microorganisms have been recognized as an important cause of widespread diarrheal illness in humans and some domesticated animals. In immunocompetent persons, *Cryptosporidium parvum* may cause a short-term (3–20 days) diarrheal illness that resolves spontaneously. However, in the immunocompromised patient, cryptosporidiosis usually presents as a life-threatening, prolonged, cholera-like illness *(241,242)*. Nitazoxanide was recently approved for the treatment of cryptosporidiosis in children *(243)*. Highly active antiretroviral therapy has reduced the frequency and severity of cryptosporidiosis in patients with acquired immunodeficiency syndrome (AIDS). Person-to-person transmission is common; and outbreaks of cryptosporidiosis among children in childcare centers have been reported, hospital-acquired infections have been investigated, waterborne outbreaks have been documented, and *Cryptosporidium* is recognized as a cause of traveler's diarrhea. The incubation period is estimated to be 2 to 14 days.

Healthcare-associated *Cryptosporidium* infections have occurred by person-to-person transmission, particularly among immunocompromised patients. Outbreaks have been reported among patients with AIDS, patients on a bone marrow transplant unit, and severely malnourished children in a developing country *(244–247)*. Transmission among patients with AIDS has also occurred following the contamination of an ice machine on a nursing unit by a patient infected with *Cryptosporidium (248)*. There has also been a report of transmission to hospital workers after caring for a patient with chronic cryptosporidiosis *(249)*.

The detection of *Cryptosporidium* is accomplished by microscopic examination of fresh or concentrated stool specimens followed by staining with a modified Kinyoun acid-fast stain *(250)*. The microorganism can also be seen on intestinal biopsies. A monoclonal antibody-based fluorescein-conjugated stain for detecting oocysts in stool and an EIA for detecting antigens in stool are commercially available *(251)*. PCR may be a useful tool for the diagnosis and study of the molecular epidemiology of *Cryptosporidium* infections *(252)*. Outbreak control has been achieved by intensified enteric precautions and cleaning *(244)*.

Cyclospora *Cyclospora cayetanensis* have been associated with diarrhea. It has been reported as an etiology of food-borne diarrhea outbreaks with fresh berries most commonly implicated. Watery diarrhea, abdominal cramping, decreased appetite, and low-grade fever characterize the illness. Symptoms can occur in cycles of remission and exacerbation lasting up to several weeks. A hospital-associated outbreak among staff was associated with stagnant water in a storage tank *(253)*.

Cyclospora are detected by identifying the 8- to 10-μm spherical bodies that auto-fluoresce or by acid-fast staining *(254,255)*. Direct person-to-person transmission is unlikely because *Cyclospora* oocysts require time and favorable conditions to become infectious.

Entamoeba Histolytica Amebiasis is a major health problem in Asia, Latin America, and Africa. Childhood intestinal amebiasis generally presents with diarrhea containing blood and mucus and no fever. Diarrhea without blood, fever, fulminating colitis, appendicitis, and ameboma occur infrequently in children. The cyst form is resistant to environmental stresses and is in the infective stage. Transmission is by the fecal–oral route. The incubation period is variable, ranging from a few days to months or years; commonly, it is 2 to 4 weeks. HAI is rare but has been reported in hospitalized adults in a developing country *(256)*. A colonic irrigation machine was implicated in an outbreak of amebiasis in adults after therapy at a chiropractic clinic *(257)*.

Entamoeba histolytica is detected by the direct examination of fresh stool specimens. *E. histolytica* actually comprise two genetically distinct but morphologically indistinguishable species. *E. histolytica* is pathogenic and causes invasive amebiasis; and *E. dispar* is probably nonpathogenic and is often reported as *E. histolytica* due to the microscopic resemblance of the two species. *E. histolytica* and *E. dispar* have been differentiated using restriction fragment analysis of DNA amplified by PCR, PCR, isoenzyme analysis, and antigen detection *(258,259)*.

Giardia Lamblia *Giardia lamblia* is transmitted directly from person to person by fecal–oral transmission of cysts or, indirectly, by transmission in water and, occasionally, food *(260)*. Travelers often become infected when they ingest contaminated ground water or surface water. The cyst is highly infectious for humans, and infections can occur following ingestion of as few as 10 to 100 cysts *(261)*. Infection by *G. lamblia* may produce flatulence, foul-smelling stools, abdominal cramps, abdominal distention, anorexia, nausea, and weight loss *(262)*. Outbreaks of infection and endemic infections occur in childcare centers and other institutional settings and among the family members of infected children *(263,264)*. The incubation period is usually 1 to 4 weeks. Healthcare-associated hospital outbreaks are uncommon, but outbreaks among children in childcare

centers are well documented *(265,266)*. An outbreak of giardiasis with person-to-person and food-borne transmission in nursing home residents, employees, and children in a combined childcare center with an adopted grandparent program has been reported *(267)*.

G. lamblia may be detected by the microscopic examination of fresh or formalin-preserved concentrated stool or by use of a commercially available EIA. Specific DNA probes for *Giardia* may assist in the diagnosis in the future.

Strongyloides Stercoralis *Strongyloides stercoralis* is a nematode that infects humans and, sometimes, other animals. It has a complicated life cycle that may have both parasitic and free-living phases. Strongyloidiasis has a worldwide distribution. The prevalence of infection varies inversely with socioeconomic level and is highest in warm, moist regions where sanitary practices are poor. The parasite is endemic in certain southern areas of the United States including eastern Kentucky, Tennessee, and elsewhere in southern Appalachia. Most human infections are acquired outdoors when polluted soil containing filariform larvae comes in contact with the skin. The filariform larvae then penetrate the intact skin of the new host, travel through the blood vessels to the lungs, penetrate the alveoli, are coughed up and swallowed, and then establish infection in the mucosa of the small intestine *(268,269)*. There have been no reports of HAIs within a hospital, but human-to-human transmission of *S. stercoralis* has been reported in residents of homes for the mentally retarded *(270–272)*. The incubation period is not known.

Disseminated strongyloidiasis has been reported in two recipients of kidney allografts from a single cadaver donor *(273)*. Neither recipient had previous evidence of parasitic infection or risk factors for strongyloidiasis. Disseminated strongyloidiasis has also been reported as a complication of immunosuppression. Patients with a history of exposure to *S. stercoralis* many years previously have experienced hyperinfection with the parasite during immunosuppression following renal transplantation *(274,275)*.

S. stercoralis is detected by a microscopic examination of fresh stool to identify the rhabditiform larvae. The method of placing stool in an agar plate and observing worms and worm tracks on the agar is an efficient method of detecting the parasite *(276)*. Several immunoassays for the detection of serum antibodies against filarial larvae or larval antigens are available *(277)*.

Isospora Belli *Isospora belli* is an obligate, intracellular protozoan. Humans are the only known host for *I. belli*, and transmission is believed to occur by the ingestion of oocysts contaminating food, water, or environmental surfaces. *I. belli* infection usually has an acute onset with fever, diarrhea, and colicky abdominal pain. The illness may be self-limiting with spontaneous resolution in the healthy host. Prolonged watery diarrhea accompanied by malabsorption, weight loss, and asthenia may occur in immunocompromised patients. The incubation period is 8 to 14 days. Isosporiasis has been encountered in 15% of patients with AIDS in Haiti but is much less frequent in the United States *(278,279)*. There have been no reports of healthcare-associated isosporiasis; in fact, 170 healthy siblings, friends, and spouses of patients with AIDS did not have *I. belli* in their stool specimens *(279)*.

Diagnosis is made by the demonstration of oocysts in feces or duodenal aspirates or by finding developmental stages of the parasite in biopsy specimens of the small intestine. Oocysts can be detected by a modified Kinyoun acid-fast stain and by auramine–rhodamine stains.

Microsporidia *Microsporidia* are ubiquitous, spore-forming, intracellular protozoal parasites that cause disease in a wide range of vertebrate and invertebrate animals. Manifestations of disease in humans range from asymptomatic infections to fulminant cerebritis and/or nephritis; ocular infections are recognized infrequently. Since 1985, enteric microsporidial infections have been reported with increasing frequency in patients with AIDS and chronic diarrhea. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the species associated with diarrhea *(280)*. Common epidemiologic characteristics have not been identified, and the mode of transmission in humans is not known for certain. Fecal–oral transmission is the likely route of infection in humans with intestinal microsporidiosis, but the source of ocular infections is not clear. To date, there have been no reports of HAIs with this microorganism.

Routine histopathologic studies can provide presumptive identification, but diagnostic confirmation requires EM visualization of the microorganism's characteristic ultrastructure *(281)*. *Microsporidia* have been detected from formalin-fixed stool specimens following staining by a chromotrope-based technique and light microscopy *(282)*. PCR has also been used for detection from stools or from a small-intestine biopsy *(283)*.

Other

Candida Species *Candida* spp. have been associated with gastroenteritis in two settings: noninvasive enteritis in healthy persons *(284,285)* and invasive enteritis in patients with underlying diseases *(286,287)*. *Candida* is a saprophyte in healthy humans and is present in approximately 60% of stool specimens *(288)*. Since *Candida* spp. can frequently be isolated from the gastrointestinal tract of healthy individuals, its presence does not necessarily signify disease. Gastroenteritis associated with *Candida* spp. is characterized by intermittent, watery, explosive diarrhea that is not bloody and is rarely accompanied by fever, nausea, anorexia, or vomiting. These symptoms can be chronic and have been reported for up to 3 months *(289)*.

A prospective study of healthcare-associated diarrhea in newborns and infants isolated *Candida* spp. from 5% of stool specimens. *Candida* was the third most common etiology *(290)* and appeared most frequently in premature infants. The causative role of *Candida* in diarrhea was not clear in this study. Healthy patients who develop *Candida* gastroenteritis generally do not develop candidemia and usually respond to either nystatin or clotrimazole within 72 hours *(289)*. Healthcare-associated diarrhea associated with *Candida albicans* is particularly prevalent in immunocompromised or malnourished patients *(291,292)* and in patients receiving antibiotic or antineoplastic drugs *(256,293)*. *Candida* is detected by a routine microscopy of stool specimens or by growth on agar plates.

Necrotizing Enterocolitis NNIS system data showed that NEC occurred in 6 out of 10,000 discharges; that is, 8.7 out of 100,000 patients overall and 60 out of 10,000 infants in high-risk nurseries. Microorganisms associated were *C. difficile* (28%), *E. coli* (19%), *Klebsiella pneumoniae* (15%), coagulase-negative staphylococci (5%), *Enterobacter cloacae* (7%), and enterococci (6%). Gerber and others did not identify a cause in an outbreak of NEC, but nurses caring for infants involved in the outbreak also became ill *(114,294,295)*. A review of several outbreaks included the etiologies above and added viral enteropathogens including coronavirus, adenovirus, rotaviruses, and Echovirus type 22 as isolates during outbreaks *(296,297)*. Further discussion of NEC can be found in Chapter 52.

Potential Healthcare-Associated Gastrointestinal Tract Pathogens

Aeromonas Species Species of *Aeromonas*, including *Aeromonas caviae, Aeromonas hydrophila,* and *Aeromonas sobria* have been associated with acute gastroenteritis *(298–303)*, but other studies do not support this finding *(304)*. *Aeromonas* spp. have been implicated in healthcare-associated diarrhea, but this association is debated. *A. hydrophila* has been described as the etiology of an acute diarrheal outbreak in a geriatric long-term care facility *(305)*. In a study in childcare centers, *Aeromonas* was identified in the stool specimens of 25% of children during an outbreak of diarrheal illness *(306)*. These outbreaks of diarrhea were unusual in that several different *Aeromonas* spp. were involved in each outbreak. In another study, *Aeromonas* spp. were recovered from the stool specimens of 15 hospitalized children, but all were community acquired *(307)*. Surveillance in a French hospital revealed a seasonal variation in nosocomial *A. hydrophila* infection that was correlated with the number of *Aeromonas* microorganisms in the hospital water supply *(308,309)*.

Aeromonas spp. are recovered by culture and identified by biotyping. DNA hybridization has been used to investigate the relatedness of strains in hospital outbreaks *(306,310,311)*. PFGE was useful in the investigation of outbreaks in childcare centers *(306)*.

Klebsiella Species *Klebsiella* spp. are members of the Enterobacteriaceae family. They can cause a wide variety of clinical infections including urinary tract infections, pneumonia, and bacteremia. *Klebsiella* spp. have not been proven to cause enteritis. *Klebsiella* is mentioned here because of a report of an outbreak of *Klebsiella* spp. bacteremia following nasoduodenal feeding of premature infants with human milk contaminated with *Klebsiella (312)*. None of the bacteremic infants had diarrhea. Diarrhea was reported in preterm infants who had *Klebsiella* isolated from stool specimens, but a causal association was not established *(162,313)*.

Pantoea Agglomerans NICU infections caused by *Pantoea agglomerans* were definitely associated with parenteral nutrition. The microorganism colonized a large number of children in the NICU. Investigators hypothesized that gastrointestinal tract colonization may precede septicemia (314,*315*).

EPIDEMIOLOGY

Descriptive Epidemiology

The behavior of infants and children places them at increased risk of healthcare-associated acquisition of enteropathogens compared with adults. The close, frequent contact among children facilitates person-to-person transmission. Infants and children do not wash their hands and frequently place their fingers, toys, and other items in their mouths. Children cared for in childcare centers have a threefold greater risk of acquiring diarrhea than children cared for at home *(316,317)*. Hospitalized children display these same behavior patterns, which place them at a similarly high risk of fecal–oral transmission of enteropathogens. This is particularly true of infants and toddlers who are not toilet trained.

Reservoirs and Sources of Infection

The pattern and timing of an outbreak of diarrhea in a hospital may provide clues about the reservoir or source and mode of transmission. The possible reservoirs and sources of these microorganisms will be considered first (Table 50-2). Patients may act as a reservoir for enteropathogens. As described above, many potential enteropathogens are frequently excreted asymptomatically. If an asymptomatic patient is not isolated because the infection is not suspected, microorganisms may be introduced into the healthcare environment. The second scenario of the patient as the reservoir is a child admitted for management of an acute gastrointestinal tract infection. Enteropathogens may be transmitted to other patients, to hospital personnel, or to hospital visitors. Immunosuppressed patients may become infected with enteric microorganisms that are part of their own normal flora.

Healthcare personnel may act as a reservoir of infection. The same conditions occur as with patients. An employee may be an unknown chronic carrier of an enteropathogen or may be present in the hospital with an acute illness. The enteropathogen may then be transmitted to patients or coworkers by direct person-to-person contact or indirectly through fomites.

Food products may serve as a point source for HAIs if patients, hospital personnel, visitors, or all three groups eat the implicated food items. The food reservoir may originate outside or within the hospital. Several *Salmonella* spp.

TABLE 50-2

Factors Important in the Introduction of Healthcare-Associated Infectious Gastroenteritis

Short-term, asymptomatic carriers of enteropathogens
Colonized, asymptomatic prolonged carriers of enteropathogens
Patient-to-patient transmission via hands of hospital personnel, generally after contact with a child with diarrhea
Contaminated medications, food, or medical instruments
Hospital crowding
Lack of adherence to infection control procedures

outbreaks have been traced to intact and properly stored eggs *(172)*. Improperly stored foods have been implicated in several food-borne diarrheal outbreaks among both patients and employees *(178,318)*. Norwalk virus has been described as a cause of food-borne outbreaks in the hospital setting *(68)*. In addition to prepared foods, enteral feedings and infant formulas have become contaminated during storage *(182)*.

The CDC's definition for surveillance purposes of waterborne disease outbreaks is restricted to illness that occurs after the consumption or use of water intended for drinking. Outbreaks have been associated with private wells, small water systems, and community water systems *(319)*. Reservoirs for waterborne outbreaks may also include drinking water contaminated at the faucet, as occurs with *Aeromonas*, or in ice *(308,309)*. The contamination may occur away from the hospital, as has been reported in outbreaks due to *G. lamblia*, *Cryptosporidium, Cyclospora, microsporidia,* and viruses *(319)*. Various reservoirs exist within the hospital where water-holding units such as whirlpools, storage tanks, or common bathing tanks may be contaminated *(226). C. difficile* spores remain on surfaces in patient rooms after cleaning *(320)*.

All healthcare devices should be considered potential reservoirs. The reservoir may exist as the result of inadequate cleaning and sterilization, as occurred with endoscope-transmitted infections *(189,190)*; lack of proper cleaning, as in the use of common suction traps and tubing *(191,192)*; or inadequate sterilization, as occurred when a breast pump used by several mothers in an NICU became contaminated *(192)*. Some enteropathogens such as *C. difficile*, rotavirus, and norovirus may survive on contaminated fomites (72,321).

Blood products are a well-known risk factor for HAIs such as hepatitis B and C, human immunodeficiency virus (HIV), and cytomegalovirus. The contamination of whole blood units with *Y. enterocolitica* resulted in bacteremia in recipients. It is thought that the blood donors had a mild bacteremia at the time of their donation and that the refrigerated storage supported the growth of *Y. enterocolitica (233–235)*.

Other reservoirs may include animals outside the hospital or pets used in pet therapy programs within the healthcare system (see Chapter 94) *(322)*. There have been no reports of gastrointestinal tract disease resulting from pet therapy, but immunosuppressed patients may be particularly at risk. The association of salmonellosis with reptiles warrants the restriction of reptiles from the healthcare setting.

Modes of Transmission of Infection

The mode of transmission describes how the enteropathogen gets from the reservoir to the host. The pattern and timing of an outbreak may provide clues about transmission. Several cases occurring in a short period may be easy to recognize and trace to a point source such as food or a specific patient or employee. Other point sources such as an endoscope may be more difficult to recognize, because the number of infections may be few and may appear sporadically. Routine surveillance is an important tool in the recognition of these sources.

Person-to-person transmission may occur as the result of many practices. Poor hand washing by personnel results in direct spread to patients or self-inoculation. The patients may secondarily infect *(4)* other family members either as hospital visitors or after returning home. Fomites play a role in patient-to-patient transmission. Many items within a room or within common areas may become contaminated by enteropathogens. Subsequent contact with these items results in transmission. This is particularly important for microorganisms for which the transmission of infection is associated with a low inoculum, such as rotavirus, *Shigella*, *Giardia*, enteric adenovirus, astrovirus, calicivirus, *E. coli* O157:H7, and *Cryptosporidium*. Person-to-person spread also occurs through the vertical transmission of a microorganism from a mother to her newborn at the time of delivery. Several enteropathogens, such as *S. sonnei (211)*, *S. flexneri (212)*, *C. fetus,* and *C. jejuni* have been transmitted to neonates in this manner.

Food-borne transmission results from ingesting contaminated foods, poorly cleaned fresh foods, or nasoduodenal infusion of contaminated nutritional supplements or infant formulas. Nasoduodenal feedings may be a greater risk than nasogastric feedings, since the feeding tube bypasses the normal protective acidic environment of the stomach. Infections have resulted from *Salmonella* spp. *(184)*, *Campylobacter* spp. (*140*,*323*), *Klebsiella* spp. (*312*), and ETEC contamination of milk *(152)*, as well as *Campylobacter* spp. *(140)* contamination of poorly cleaned vegetables. *Salmonella (171–173,176,182)*, *Staphylococcus aureus, E. coli (159)*, and Norwalk virus *(68)* have all been described in food-borne HAIs in the hospital setting.

A gastroduodenal endoscope transmitted *Helicobacter pylori* in adults *(324,325). Salmonella newport* was transmitted by fiberoptic colonoscopy in 8 of 28 patients who underwent the procedure after the colonoscope had been used in a patient with acute disease due to *S. newport (324)*. Transmission resulted from inadequate cleaning and sterilization of the biopsy forceps. Chapter 62 describes HAIs associated with endoscopic procedures.

Transmission of enteric pathogens by hospital instruments occurs most frequently in NICUs. Nursery isolettes have been implicated in the transmission of ETEC and *C. difficile*. Common-use suction tubing and an overflow reservoir were reported to transmit *Salmonella worthington* in an NICU *(192). Klebsiella* was cultured from the tubing of a breast-milk pump following an outbreak of bacteremia in preterm infants receiving donor human milk by nasoduodenal feedings *(312)*. Rectal thermometers have been reported to spread *Salmonella eimsbuttel* among newborn infants *(193)*.

Risk Factors for Infection

The most severely ill patients are at greatest risk for healthcare-associated gastrointestinal tract infections for several reasons. The patients may be immunocompromised by the severity of illness, by poor nutritional status, and/or by therapeutic modalities. The use of antacids and H2 blockers in intensive care units may decrease the protective effect of gastric acidity. Children in intensive care units require frequent manipulation by multiple hospital personnel, which increases the risk of person-to-person transmission.

Neonates, particularly premature infants, are unique in that they are immunocompromised. The incidence of healthcare-associated gastrointestinal tract infection is twice as high in the high-risk nursery as it is in the general pediatric population *(10)*. The types of HAIs of

the gastrointestinal tract that occur in the nursery include NEC, rotavirus, *Klebsiella* spp., *C. difficile*, EPEC, and *Salmonella*. See Chapter 52 for a review of HAIs in hospital nurseries.

Immunocompromised patients constitute a special high-risk group. Patients infected with HIV have an increased risk of infection with microorganisms previously not shown to be enteropathogens. *C. parvum* and Microsporidia have been described as enteropathogens in this population. There have been no reports of healthcare-associated transmission, but such occurrences may occur. Patients with severe combined immunodeficiency disease acquire healthcare-associated enteropathogens and suffer prolonged disease with significant morbidity and often a fatal outcome *(101,326)*. Malnourished persons are at high risk for severe gastrointestinal tract disease. This is particularly evident in the reports of healthcare-associated gastroenteritis from developing countries.

Patients receiving chemotherapy for malignancies or persons who are immunosuppressed after organ transplantation are at a increased risk for infection by microorganisms that are part of their normal flora. *C. difficile* and *Candida*, in particular, have been reported to cause gastroenteritis under these conditions *(327)*. Forty percent of bone marrow transplant patients developed healthcare-associated gastroenteritis in one study, and another unit had a prolonged healthcare-associated astrovirus outbreak *(49,328)*.

Prolonged hospital stay is another risk factor for healthcare-associated gastroenteritis. These children are at risk both because of their underlying medical condition and their continued exposure to a variety of enteropathogens. Children in long-term care facilities have an increased risk of food-borne, waterborne, and person-to-person transmission of enteropathogens *(16, 329–331)* compared with children who receive care at home. In one study, 10% of children with an infected roommate developed healthcare-associated diarrhea. The risk was directly proportional to the number of roommates. Younger hospitalized children were at a greater risk than older ones: 10% of diapered children developed healthcare-associated diarrhea, compared to only 2% of nondiapered children *(22)*. The viral healthcare-associated diarrhea rate decreases with age. The rate at 0 to 11 months was 9%; at 12 to 35 months, 4%; and at 36 months or more, 0.6%. The rate does not significantly increase with the length of hospital stay *(10,22–24,332)*.

PATHOGENESIS

Viral enteropathogens are transmitted by the fecal–oral route. Enteric viruses tend to infect the small intestine, with replication occurring in epithelial cells at the tips of the villi; infection is confined primarily to these cells. The changes include the shortening and blunting of the villi and increased infiltration of the lamina propria with mononuclear cells. Mucosal damage is repaired rapidly, as early as 3 weeks after onset. Many children with acute viral gastroenteritis have lactose malabsorption and intolerance. Loss of fluids and electrolytes in viral gastroenteritis can lead to severe dehydration and even death and requires fluid- and electrolyte-replacement therapy. The severity of intestinal mucosal injury varies among the enteric viruses.

The major virulence properties of bacterial enteropathogens include adherence, enterotoxin production, cytotoxin production, epithelial cell invasion, and translocation. Certain enteropathogens may produce diarrhea by other mechanisms, and enteric pathogens may possess one or several of these virulence properties. Enterotoxins are bacterial products that act on the mucosal epithelium of the small intestine, causing fluid secretion and profuse watery diarrhea without damage to the intestinal mucosa. Functionally similar enterotoxins are produced by *V. cholerae*, ETEC, *Aeromonas*, *C. difficile*, *C. jejuni*, *Salmonella*, and *Y. enterocolitica*. Presumptive evidence indicates that rotavirus nonstructural glycoprotein (NSP4) functions as an enterotoxin *(333,334)*. Cytotoxins kill mammalian cells, usually by the inhibition of protein synthesis. *In vivo,* they cause damage to the intestinal epithelial cells and destruction of the normal absorptive mechanisms, which results in diarrhea containing blood. Fluid loss is probably related to impaired absorption due to intestinal damage; unlike enterotoxins, cytotoxins do not cause active fluid secretion by the gut. Microorganisms such as *Shigella,* EIEC, *C. jejuni*, *Salmonella*, and *Y. enterocolitica* can invade the mucosa of the colon or small intestine and result in an inflammatory host response. This invasion is characterized clinically by fever, abdominal pain, tenesmus, and stools containing blood, mucus, and fecal leukocytes. Adherence, the ability of microorganisms to attach to and colonize gut epithelium, is the least specific virulence property in terms of related clinical findings. The ability of ETEC to adhere to and colonize the upper small intestine, where it causes disease by production of enterotoxin, has been well described.

Parasitic enteropathogens possess a variety of pathogenetic mechanisms. The spore-forming protozoa (cryptosporidia, microsporidia, isospora, and cyclospora) produce abnormalities in the absorption, secretion, and motility of the small bowel and are associated with inflammatory infiltrates. This may be associated with villus blunting and crypt hyperplasia but not mucosal invasion. Gastrointestinal tract function and morphology relate to the number of microorganisms present. *Giardia* produce disease and malabsorption by producing varying degrees of mucosal injury and by influencing conditions in the intestinal lumen, which could impair digestion and absorption. *Strongyloides* is acquired by the penetration of intact skin by the filariform larvae. All other parasitic enteropathogens are acquired by fecal–oral transmission through ingestion of cysts or oocysts that are resistant to physical destruction.

CLINICAL MANIFESTATIONS

Localized

The approach to hospitalized patients with acute infectious diarrhea begins with a carefully obtained medical history including epidemiologic considerations and a physical examination. Acute diarrhea can be caused by one of the many microorganisms discussed previously. Clinical

manifestations occurring in patients with diarrhea reflect either localized involvement of the gastrointestinal tract or systemic involvement, manifested by generalized symptoms or signs. The presence of a specific clinical manifestation is not pathognomonic of any causative agent; however, some clinical features occur more frequently as a result of infection by certain microorganisms. The most common localized manifestations may occur with varying degrees of severity. These include diarrhea, nausea, anorexia, vomiting, and abdominal discomfort or cramping. The character of the diarrhea may provide a clue as to the associated enteropathogen. Bacterial microorganisms that invade intestinal mucosa often cause abdominal cramps, tenesmus, fecal urgency, and passage of stools containing blood and mucus and fecal leukocytes. Patients with secretory diarrhea have abdominal cramps and pass a low to moderate number of large-volume watery stools that, when passed, may be associated with temporary relief. Patients infected with *E. coli* O157:H7 and *E. histolytica* may have bloody diarrhea without fecal leukocytes and severe cramps. Patients with giardiasis or cryptosporidiosis often have watery, foul-smelling stools associated with nausea and flatulence or chronic diarrhea with malabsorption and abdominal distention. Diarrhea due to viral enteropathogens generally occurs in infants who present with low-grade fever, vomiting, and watery diarrhea.

Generalized

Many enteropathogens present with systemic manifestations of illness. Fever is a common, but not universal, manifestation of these infections. The parasitic enteropathogens that involve the small intestine rarely cause febrile illness, whereas acute infection with many of the enteric viruses and bacteria may result in fever. Dehydration is the most common reason for hospitalization of children with gastroenteritis in the United States. Dehydration occurs as the result of increased fluid losses from vomiting, diarrhea, and increased insensible losses associated with fever. Dehydration may result in shock if not recognized or corrected early. Shock may lead to multiple organ system involvement. Mild to moderate dehydration is most appropriately treated with an oral rehydration solution *(335)*. This has been demonstrated to be effective in developing countries and is the mainstay of therapy in cholera.

Enteric pathogens have extraintestinal manifestations. These include cutaneous involvement by *S. typhi* and strongyloidiasis; bacteremia and other organ system involvement by bacterial and parasitic enteropathogens; the complications of HUS with *E. coli* O157:H7, other EHEC, and *S. dysenteriae* type 1; and pulmonary compromise in immunosuppressed patients with strongyloidiasis. A wasting syndrome of malnutrition occurs in HIV-infected patients with microsporidiosis or cryptosporidiosis. In addition, several immune-mediated conditions can occur following enteric infections including reactive arthritis, Reiter's syndrome, Guillain-Barré syndrome, glomerulonephritis, erythema nodosum, and hemolytic anemia. These manifestations have been associated with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Giardia*, or *Cryptosporidium*.

DIAGNOSIS AND EVALUATION OF OUTBREAKS

The evaluation of either endemic infections or outbreaks of healthcare-associated gastroenteritis has two purposes. The first is to identify the enteropathogen and determine the method of transmission. The second is to evaluate isolated strains of the enteropathogens for relatedness. For epidemiologic purposes, the more closely related the strains of microorganisms are, the stronger is the proof that an outbreak is due to a common epidemic strain. Merely proving that several patients are infected with the same species does not substantiate the occurrence of an outbreak. Many techniques are available to evaluate genetic relatedness (see Chapter 95). The identification of microorganisms may be approached in a stepwise fashion. First, nonspecific tests are used to support infection and identify the type of enteropathogens (viral, bacterial, or parasitic). Next, phenotypic techniques are used to identify the microorganism based on characteristics expressed by the microorganism. Finally, genotypic techniques that involve direct DNA-based analyses of chromosomal or extrachromosomal genetic elements are utilized for molecular fingerprinting. In general, these three approaches to diagnosis move from evaluation at the bedside, to routine laboratory evaluation, to testing in research or referral laboratories *(336–338)*. See Table 50-3 for a list of methods and Chapter 8 for further information about outbreak investigations. The techniques generally available will be briefly described, but more detailed descriptions may be found in the listed references.

The timing of the onset of diarrhea in relationship to the admission to the hospital should be used to guide the evaluation. Diarrhea occurring more than 3 days after admission is unlikely to be caused by either bacterial or parasitic etiologies. Viral or *C. difficile*–associated diarrhea is more likely. Therefore, routine bacterial cultures and studies for ova and parasites are not cost-effective for the initial testing of diarrhea occurring more than 3 days after admission *(339–342)*.

The utility of the age-old technique of microscopy permits the evaluation of fresh stool specimens for the presence of fecal leukocytes. This single procedure differentiates inflammatory diarrhea from noninflammatory diarrhea, thereby narrowing the differential diagnosis considerably. Microscopic examination of either fresh or concentrated stool specimens is the mainstay in the diagnosis of parasitic diseases. Trophozoites, cysts, oocysts, or worms can be identified in stool specimens *(279,282)*. Gram stain of a stool specimen may not be useful to identify a specific enteric gram-negative bacterium, but yeast cells can be identified in this manner, as can the spiral-shaped *Campylobacter* microorganisms. Testing a stool sample for occult blood is a simple, inexpensive, and rapid method for evaluating the presence of gastrointestinal tract inflammation or mucosal damage.

The interpretation of a complete blood count and differential cell count also provides nonspecific evidence to determine the etiology. Anemia or hemolysis may occur, particularly with HUS. Leukocytosis is more frequently seen with a bacterial gastrointestinal tract infection. Eosinophilia would support further investigation for a parasitic infection.

TABLE 50-3

Laboratory Tests Used to Evaluate Healthcare-Associated Outbreaks of Infectious Gastroenteritis

Nonspecific tests
Stool fecal leukocytes
Microscopy
Stool occult blood
Complete blood cell count
Stool culture
Electron microscopy
Immunoelectron microscopy
Phenotypic techniques
Biotyping
Antibiograms (antimicrobial susceptibility patterns)
Serotyping
Bacteriophage typing
Immunoblotting
Enzyme immunoassay (EIA)
Multilocus enzyme electrophoresis (MEE)
Genotypic techniques
Electropherotyping
Plasmid profile analysis (PPA)
Restriction endonuclease analysis (REA)
Southern hybridization analysis (SHA) using specific DNA probes
Ribotyping
DNA profiling using pulsed-field gel electrophoresis (PFGE)
Polymerase chain reaction (PCR)
Nucleotide sequence analysis

Several phenotypic methods are used to characterize microorganisms and include biotyping, antimicrobial susceptibility testing, serotyping, bacteriophage typing, immunoblotting, EIA, and multilocus enzyme electrophoresis. The mainstay of the diagnosis of bacterial diarrheal illness is the stool culture. Many of the microorganisms discussed in this chapter are not detected with routine stool culture methods. Selective media and special conditions for growth may be necessary for isolation of many microorganisms. Communication with the clinical microbiology laboratory is essential for identification of these enteropathogens. The microbiologist should be notified about the suspected microorganisms so that appropriate media and techniques may be used for identification. *C. jejuni* and other *Campylobacter* species, *Y. enterocolitica*, *V. cholerae* and other *Vibrio* species, pathogenic *E. coli*, and *C. difficile* all require special procedures for isolation.

EIA is a relatively rapid technique to identify many of the microorganisms and toxins described above. Commercially produced EIAs are available for detection of *Cryptosporidium*, *G. lamblia*, rotavirus, enteric adenovirus, astrovirus, calicivirus, cholera toxin, and *C. difficile* toxins. Other EIAs for detection of other enteropathogens are available in reference or research laboratories.

Evaluation of the molecular structure of enteropathogens is useful for analysis of different strains of the same microorganism. These methods add nothing to the identification of a specific microorganism but are used for comparison of strains based on genetic similarities or dissimilarities. Application of one or more of these methods to various collections of healthcare-associated pathogens has shown that DNA-based typing methods are useful in studying the relationship between colonizing and infecting isolates in an individual patient, distinguishing contaminating from infecting strains, documenting cross-infection among hospitalized patients, and evaluating reinfection versus relapse in patients being treated for an infectious process. Examples of genotypic methods include electropherotyping, PPA, restriction endonuclease analysis, Southern hybridization analysis, ribotyping, PFGE, PCR, random amplified polymorphism of DNA, and nucleotide sequence analysis *(343–350)*.

Biopsy may be the only possible method to identify some of the microorganisms mentioned in this chapter. *Microsporidia* are identified on EM of intestinal biopsy specimens. Microscopic examination of biopsy material may accurately identify *Giardia, Strongyloides, E. histolytica*, EPEC, and EAEC.

PREVENTION AND CONTROL

Healthcare-associated gastrointestinal tract infections are best prevented by surveillance and identification of methods to improve hospital procedures. It is important that infection control methods be based on scientific data, not just speculation. It is difficult to know how many healthcare-associated enteric infections can be prevented. The CDC's Study of the Efficacy of Nosocomial Infection Control project noted that surveillance by infection control practitioners decreased HAIs by 32%, but in this study, gastrointestinal tract infections and pediatric hospital infections were not addressed specifically *(351)*. One study of pediatric healthcare-associated gastrointestinal tract infections indicated that educational intervention programs decreased the incidence of healthcare-associated rotavirus infection (125,*352*). It is accepted universally that effective hand washing is the mainstay of prevention of HAIs including gastroenteritis *(353)*. Observational studies have noted that physicians wash their hands before only 30% to 85% of patient contacts, indicating the need for continuing education for healthcare providers about appropriate infection control procedures including hand washing *(121,354,355)*. Alcohol-based products reduce rotavirus on the hands by approximately 99% in reported studies *(356)*. No antiseptic agents are sporicidal against microorganisms such as *C. difficile*; therefore, the use of gloves is recommended *(356)*. For more information, see Chapter 37.

Cohorting or grouping neonates and their nursing staff was not effective for the prevention of HAIs in an NICU *(357)*. In another study, Klein and coworkers demonstrated that protective isolation of patients in a pediatric intensive care unit using gowns and gloves decreased the HAI rate in that environment *(358)*. Unfortunately, this study did not address gastrointestinal tract infection rates.

Appropriate isolation of patients that are excreting enteropathogens is a necessary part of prevention. Table 50-4 shows diseases transmitted by the fecal–oral route. All patients are to be managed using Standard

TABLE 50-4

Diseases Transmitted by the Fecal–Oral Route

Amebic dysentery
Cholera
Coxsackie virus disease
Diarrhea, acute illness with suspected infectious etiology
Echovirus disease
Encephalitis (unless known not to be caused by enteroviruses)
Enterocolitis caused by *Clostridium difficile*
Enteroviral infection
Gastroenteritis caused by:
- *Campylobacter* species
- *Cryptosporidium*
- *Dientamoeba fragilis*
- *Escherichia coli* (EAEC, ETEC, EPEC, EIEC, or EHEC)
- *Giardia lamblia*
- *Isospora belli*
- *Salmonella* species
- *Shigella* species
- *Vibrio cholerae*
- *Vibrio parahaemolyticus*
- Viruses, including rotavirus, astrovirus, calicivirus (including Noroviruses), and enteric adenovirus
- *Yersinia enterocolitica*
- Unknown etiology but presumed to be an infectious agent

Hand, foot, and mouth disease
Hepatitis, viral, type A
Herpangina
Meningitis, viral (unless known not to be caused by enteroviruses)
Necrotizing enterocolitis
Pleurodynia
Poliomyelitis
Typhoid fever *(Salmonella typhi)*
Viral pericarditis, myocarditis, or meningitis (unless known not to be caused by enteroviruses)

Precautions. Those patients with acute diarrhea with a likely infectious cause or diarrhea in an adult with a history of recent antibiotic use should be managed using additional Contact Precautions (Table 50-5) (see Chapter 90 for more details). Patients in the same room as an index patient should be managed with the same precautions. Exposed patients may be incubating the enteropathogen, and they should not be transferred into a room with unexposed children. Exposed patients may be isolated as a cohort. In addition, gloves should be considered for diaper changing of all hospitalized children. A uniform hospital policy would be advantageous rather than unit-specific guidelines. *C. difficile*–associated diarrhea incidence was decreased among adult bone marrow transplant patients by cleaning the rooms with sodium hypochlorite rather than quaternary ammonium products *(359)*.

Surveillance is integral for the identification of HAIs, their source(s), and modes of transmission. If the source and mode of transmission are not identified, control of an outbreak will be difficult, if not impossible.

TABLE 50-5

Contact Precautions

Use Standard Precautions for all patients
Masks are not indicated
Gowns are indicated
Gloves are indicated
Hands must be washed after touching the patient or potentially contaminated articles and before taking care of another patient
Single room is indicated, if possible

Employee health plays an important role in the prevention of healthcare-associated gastroenteritis. Any staff member with symptoms that suggest infection should be excluded from contact with potentially susceptible persons for at least 2 days after resolution of illness *(83)* (see Chapter 93).

Appropriate antimicrobial agents may be given to patients known to be infected with an enteropathogen. This therapy may shorten the time that a patient excretes the microorganism, although there is concern that treatment of salmonellosis may increase the period of excretion. Table 50-6 lists enteropathogens for which antimicrobial therapy may be useful. Conversely, limiting antibiotic use for other infections may decrease *C. difficile*–associated diarrhea *(360)*.

Immunizations may play a role in prevention and control of HAIs by some enteropathogens, but commercially available enteric vaccines are limited. Typhoid, cholera,

TABLE 50-6

Potential Benefit for Antimicrobial Therapy for Enteropathogens

Potential Benefit	*Enteropathogen or Disease*
No therapy available	Enteric viruses
Established benefit	Necrotizing enterocolitis
	Antimicrobial-associated colitis (*Clostridium difficile*)
	Cholera
	Cryptosporidium parvum
	Cyclospora cayetanensis
	Entamoeba histolytica
	Enterotoxigenic *E. Coli*
	Giardia lamblia
	Isospora belli
	Shigella spp.
	Strongyloidiasis
Absolute	Any bacterium that produces bacteremia (e.g., typhoid fever)
Questionable or unknown	*Aeromonas* spp.
	Campylobacter jejuni
	Candida spp.
	Enterohemorrhagic *E. coli*
	Intestinal salmonellosis
	Microsporidia
	Yersinia enterocolitica

and rotavirus vaccines are available and may be useful for prevention of disease in developing countries.

Human milk decreases the frequency and severity of diarrhea in infants. Therefore, all providers should encourage the initiation and continuation of breast-feeding during the first year of life.

There is increasing support for the use of probiotics for the prevention and treatment of gastrointestinal track infections. These live culture "good" bacteria may be beneficial in both prevention and treatment of diarrhea. Lactobacillus GG was effective in preventing symptomatic infections due to rotavirus in hospitalized infants in a randomized, double-blinded study *(361)*.

Gastrointestinal tract decontamination by giving enteral antibiotics to modify the gut flora and delay gastrointestinal tract colonization has had mixed success. Studies in adults in intensive care units have shown both decreased infection rates and no difference in infection rates *(362,363)*. The studies reported to date have evaluated invasive infections and did not comment on prevention of diarrheal illness.

The CDC lists the following items as necessary steps for the control of an outbreak of viral gastroenteritis. Common sources should be identified and eliminated. Employee transmission of illness should be prevented by use of appropriate gowns and gloves when handling infectious materials. Soiled linens and clothing should be handled as little as possible. Since environmental surfaces in some settings have been implicated in the transmission of enteric viruses, bathrooms and rooms occupied by ill persons should be kept visibly clean on a routine basis.

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CHAPTER 51

Healthcare-Associated Measles, Mumps, Rubella, and Human Parvovirus B19

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Healthcare-associated measles and rubella are well recognized and have been the cause of substantial morbidity among both patients and hospital workers. Immunocompromised patients and healthcare personnel (HCP) are particularly vulnerable to severe infections and even death with some of these diseases. Because of highly successful vaccination programs that resulted in an interruption of endemic disease transmission and the elimination of measles and rubella in the United States, measles and rubella are no longer primarily childhood diseases *(1,2)*. However, children may still acquire measles or rubella, particularly if they travel abroad and are unvaccinated or live in communities with lower rates of vaccine coverage and/or pockets of unvaccinated persons *(3,4)*. Because of the severity of measles, patients frequently access medical care and may expose HCP to the disease in emergency rooms or in hospitals. In 2008, the United States experienced the largest healthcare-associated measles outbreak in more than two decades with seven cases acquired in hospital settings, including one case in an unvaccinated HCP following the hospital admission of an adult foreign visitor with measles (5). Healthcare-associated outbreaks of rubella have not been reported in the United States since its elimination was declared; however, HCP in the United States remain at risk for exposure to cases of imported rubella. Mumps outbreaks are not commonly described in hospital settings, probably because of the lower complication rate of mumps compared with measles; nevertheless, during community outbreaks, HCP in hospitals may be exposed to mumps (6). The transmission and impact of parvovirus B19 in hospital settings are less well understood, though outbreaks in hospital settings involving adult patients as well as HCP have been described. Patients with erythema infectiosum are likely to be infectious before, and not after, the onset of clinical manifestations, and persons who are immunocompromised with a chronic B19 infection can be infectious for prolonged periods. Vertical transmission of B19 infection from mother to fetus has also been documented (*178*). Understanding the transmission, infectiousness, and at-risk populations of parvovirus B19 is critical to prevention and control.

HCP are at risk for exposure to each of these viral diseases, and if susceptible, may transmit these infections in healthcare settings. This draws attention to the critical need for comprehensive prevention and control programs. One important component of such programs is providing basic education to HCP on the modes of transmission of these nosocomial pathogens and methods of prevention and control.

Integral to any prevention and control efforts are systematic screening and vaccination programs for HCP, prompt diagnosis and management of potentially transmissible illnesses or exposures among hospital workers, and the implementation of patient management techniques that lower the risks of transmission (Table 51-1).

All medical institutions (inpatient and outpatient, private and public) should ensure that all HCP who work within their facilities (i.e., medical or nonmedical, paid staff, student or volunteer, full time or part time, with or without patient care responsibility) have evidence of immunity to measles, mumps, and rubella (Table 51-2). A comprehensive program of HCP immunization should include screening for evidence of immunity (Table 51-2) of existing staff as well as routine evaluation of incoming staff (see also Chapter 80). Some hospitals require evidence of immunity to some or all of these vaccine-preventable diseases, particularly measles, as a condition of employment.

All hospitals should have standard guidelines and procedures for identifying HCP with or exposed to infectious diseases and for managing situations in which personnel have been exposed or may be infectious. For situations involving measles, rubella, and mumps, these procedures are greatly simplified if the HCP already possess documented evidence of immunity, preferably through rapidly retrievable electronic records. Since the elimination of measles and rubella in the United States, the number of reported cases of these two diseases has declined substantially. Nevertheless, importations continue to occur, and the occurrence of even a single case in a hospital setting requires immediate reporting to the local or state health department and rapid response and control efforts in collaboration with local public health agencies.

Promptly instituting and complying with proper isolation precautions for patients with known or suspected communicable infections protects personnel and patients. In addition, hospital-acquired infections have been demonstrated to spread from patients and hospital personnel to their community contacts, as well as from the community to hospital settings. Transmission of infectious diseases is theoretically possible anywhere in hospitals where individuals, including HCP, patients, volunteers, trainees, and

TABLE 51-1

Measles, Mumps, Rubella and Parvovirus B19 (Erythema Infectiosum): Incubation, Infectious and Isolation Periods

	Measles	*Mumps*	*Rubella*	*Parvovirus B19 Erythema Infectiosum*
Incubation period	10–12 d (range: 7–18 d),	16–18 d (range: 12–25 d)	14–16 d (range: 12–23 d)	7–21 d (range: 4–28 d)
Infectious period	4 d before until 4 d after rash onset	2 d before to 5 d after onset of parotitis	7 d before to 7 d after rash onset	7 d before to onset of rash
Isolation precautions	Standard and Airborne Precautions for 4 d after rash onset. Airborne infection isolation room is required. Respiratory etiquette to be followed.	Standard and Droplet Precautions for 5 d after onset of parotitis. Respiratory etiquette to be followed.	Rubella: Standard and Droplet Precautions for 7 d after the onset of rash. Room doors can remain open and special ventilation is not required. Respiratory etiquette to be followed. CRS: First year of life: Standard and Contact Precautions to be followed. After first year: Standard Precautions if nasopharyngeal and urine cultures are repeatedly negative after 3 mo of age	Standard and Contact Precautions

CRS, congenital Rubella syndrome.

visitors, may come into contact with those diseases. This includes waiting areas, cafeterias, playrooms, and other locations. Because visitors, friends, and relatives of hospital staff (including small children) may be infected or incubating infections, the important relationship between hospitals and their communities must be considered in developing prevention and control programs. Visitors, particularly children, may need to be screened for present or incubating infectious diseases before they are allowed to enter all or some patient care areas.

MEASLES

Epidemiology

Prior to the licensure and availability of a live measles vaccine in 1963, approximately 95% of persons living in urban areas of the United States were infected with measles by the age of 15 years, and 3 to 4 million cases occurred annually *(7,8)*. From 1950 to 1959, an average of 549,000 measles cases and 495 measles deaths were reported annually *(9)*. After vaccine licensure, the incidence of measles declined rapidly with >99% reduction in the reported incidence in the United States by 1988 *(10)*. This was associated with declines in measles-related hospitalizations and deaths.

In 1989, in response to outbreaks occurring in vaccinated school-aged children, two doses of measles, mumps, and rubella (MMR) vaccine were recommended for children (*11,*12). A major resurgence of measles occurred in the United States from 1989 to 1991 with 55,662 cases, 11,000 hospitalizations, and 124 deaths reported; the highest incidence was among preschoolers (<5 years) followed by adolescents (10–19 years)(13,*33*). Implementation of the two-dose MMR vaccine requirement and increased focus on improving vaccine coverage among preschool-aged children resulted in further declines in incidence with <140 measles cases reported annually between 1997 and 2001, an incidence of <1 measles case per million population *(14)*. With this reduced incidence and lack of sustained endemic transmission, measles was declared "eliminated" from the United States in 2000 *(1)*. During the postelimination era (2001–2008), 557 measles cases were reported in the United States (median: 56 cases, range: 37–140 cases per year) of which 232 (42%) cases were imported from 44 different countries, and the majority of the remaining cases were associated with these importations (15). As measles remains endemic in many other parts of the world, importations into the United States will continue to occur (*3*,15,*16*).

Once a disease primarily of childhood, measles may now affect persons of any age in the United States. Although the incidence of measles remains highest in the most susceptible age groups (infants <12 months and children aged 12–15 months, because they have not yet been vaccinated), the highest proportion of cases in the postelimination era has been among adults (40%), followed by preschool children (32%) (15). Measles epidemiology

TABLE 51-2

Measles, Mumps and Rubella: Presumptive Evidence of Immunity and Vaccination Requirements for Healthcare Personnel

	Measles	*Mumps*	*Rubella*
Presumptive evidence of immunity	1. Documentation of administration of two doses of appropriately spaced live measles virus vaccine on or after the first birthday, or 2. laboratory evidence of immunity, or 3. laboratory confirmation of disease, or 4. birth before 1957[a]	1. Documentation of administration of two doses of appropriately spaced live mumps-containing vaccine on or after the first birthday, or 2. laboratory evidence of immunity, or 3. laboratory confirmation of disease, or 4. birth before 1957[a]	1. Documented administration of one dose of live rubella virus vaccine on or after the first birthday, or 2. laboratory evidence of immunity, or 3. laboratory confirmation of disease, or 4. birth before 1957[a] (except women of childbearing age who could become pregnant)
Vaccination requirement			
Routine	Two doses of live, attenuated measles virus or MMR vaccine.	Two doses of live, attenuated mumps virus or MMR vaccine.	One dose of live, attenuated rubella virus or MMR vaccine.
Outbreak	Two doses of MMR vaccine are recommended for HCP who lack evidence of immunity, even if they were born before 1957.	Two doses of MMR vaccine are recommended for HCP who lack evidence of immunity, even if they were born before 1957.	One dose of MMR vaccine is recommended for HCP who lack evidence of immunity, even if they were born before 1957.

[a]For unvaccinated personnel born before 1957 who lack laboratory evidence of measles, mumps, or rubella immunity or laboratory confirmation of disease, health-care facilities should consider vaccinating personnel with two doses of MMR vaccine at the appropriate interval.

is now mainly determined by the characteristics of the imported case and the people they come into contact with.

In addition, in recent years, there has been an increase in the number of measles outbreaks among populations who choose not to vaccinate because of personal beliefs. In the United States in 2008, 140 measles cases were reported—the highest number of cases annually since measles was declared eliminated (15). Of the nine outbreaks that year, six were related to personal-belief exemptors, and almost all these cases were children (15), including two children who were infected while visiting their mother in the hospital (5). In 2009, six of the eight outbreaks were associated with personal-belief exemptors (*CDC, unpublished data*). To maintain measles elimination in the United States, it will be necessary to sustain high MMR vaccine coverage among children and other groups at high risk of exposure and transmission, including HCP.

Measles in Medical Settings Prior to measles elimination in the United States, measles was commonly transmitted to and among patients in outpatient departments, in-patient wards, and emergency departments, and instances of measles transmission and outbreaks in medical settings in the United States and other countries have been well described *(17–20)*. Visiting a hospital emergency room was identified as a risk factor for measles infection during community measles outbreaks in Houston and Los Angeles in 1989 *(21)*. The predominant setting of transmission for 24 (20%) of the 120 measles outbreaks reported during 1993 to 2001 was healthcare facilities *(22)*. Measles outbreaks have resulted in lost productivity and high containment costs for healthcare facilities *(23–25)*. In addition, medical facilities can contribute to the propagation and amplification of community measles outbreaks *(21,26,27)*.

Because of the severity of measles, patients usually seek medical care, and as a result, HCP have a higher risk of being exposed to and acquiring measles. In a study of a measles outbreak in Clark County, Oregon, in 1996, HCP were 19 times more likely to be infected with measles than the general adult population of the county *(23)*. Measles has been reported in persons of virtually all occupations providing patient or ancillary services including nurses, physicians, laboratory and radiology technicians, clerks, nursing assistants, and medical and nursing students *(28)*. Transmission has been reported between patients, between HCP, from patient to HCP, and from HCP to patient. In many instances, the patient contact that led to measles in the HCP did not qualify as direct patient care, which illustrates the extreme transmissibility of measles virus. Visitors were rarely identified as the source for measles transmitted in these settings.

Almost 30% of HCP who acquired measles in medical settings from 1985 to 1991 were born before 1957 (i.e., they were older than the age for routine vaccination) *(28)*. Studies among HCP indicated that up to 5% of HCP born before 1957 lacked measles antibodies *(29,30)*. A recent study on measles seroprevalence among 469 newly

hired hospital HCP born before 1957 revealed that only 1.3% were measles seronegative *(31)*.

In 2008, a measles outbreak occurred in Arizona with 14 confirmed cases, including 7 healthcare-associated-acquired infections—the largest reported healthcare-associated measles outbreak in the United States since 1989 (5). Healthcare-associated transmission included patient-to-HCP, patient-to-patient, patient-to-visitor, and HCP-to-patient. During the screening of 7,195 HCP in two hospitals during this outbreak, 1,776 (25%) were found to lack evidence of measles immunity in their employee health record. Among the 1,583 of these HCP who underwent serologic testing for measles IgG antibodies, 18 of the 506 HCP (4%) born before 1957 and 121 of the 1,077 (11%) HCP born during or after 1957 were found to be seronegative. The two hospitals spent US$799,136 responding to and containing 7 cases in these facilities.

Between 2001 and 2008, 27 reported measles cases were transmitted in healthcare facilities, accounting for 5% of all reported US measles cases; 8 cases occurred among HCP, 6 (75%) of whom were unvaccinated or had unknown vaccine status (15).

Clinical Description

Measles is an acute viral infection that is characterized by a generalized maculopapular rash and high fever. Following an incubation period of 10 to 12 days (range: 7–18 days), the patient typically develops a prodrome consisting of fever and malaise, followed by cough, coryza, and conjunctivitis. The characteristic maculopapular rash usually appears 2 to 4 days after onset of the prodromal symptoms and first appears on the face, and then spreads to the trunk and extremities. The rash lasts 5 to 7 days and fades in order of appearance. An enanthem, characterized by small bluish-white spots on a red background (Koplik's spots), may be seen on the buccal mucosa from 2 days before to 2 days after onset of rash. A person with measles is considered to be infectious from 4 days before until 4 days after rash onset.

Measles may be associated with serious complications. The most common complications of measles are otitis media, diarrhea, and pneumonia. Pneumonia is the most common cause of death and may be caused by the measles virus or by a secondary bacterial or viral infection. Measles encephalitis is reported once in every 1,000 cases and can result in permanent neurologic sequelae or death. The age-specific complication rates are highest among infants, children between 1 and 4 years old, and adults over 20 years, and lowest in children 5 to 19 years old *(32)*. Measles can be severe in immunocompromised patients, particularly in those with abnormalities of cellular immunity. From 2001 to 2008, 23% of reported measles cases in the United States required hospitalization (15). In the United States between 1987 and 2002, the case fatality rate for measles was 2 to 3 per 1,000 cases *(33)*; two deaths due to measles occurred among the 557 reported cases between 2001 and 2008 (15). Another serious complication is subacute sclerosing panencephalitis (SSPE), which is a rare progressive neurologic disorder caused by a persistent infection of the brain with aberrant measles virus. The onset of behavioral and intellectual deterioration usually occurs 6 to 8 years after wild-type measles infection. SSPE is almost universally fatal *(34)*.

Pathogenesis

The measles virus is a single-stranded RNA virus of the *Paramyxovirus* family. The measles virus can survive for at least 2 hours in fine droplets, and airborne spread in medical and other settings has been documented *(35)*. Secondary attack rates of over 90% have been documented among susceptible populations *(36,37)*. Neither a long-term infectious carrier state nor an animal reservoir is known to exist. Infection with measles virus is thought to confer lifelong immunity from clinical measles.

The primary site of measles infection is the respiratory epithelium of the nasopharynx. Generally, primary viremia with infection of the reticuloendothelial system occurs 2 to 3 days after invasion and replication in the respiratory epithelium. A second viremia occurs 5 to 7 days after initial infection, following further viral replication in regional and distal reticuloendothelial sites. During this viremia, there may be infection of the respiratory tract, skin, conjunctiva, and other organs. The characteristic pathologic feature of measles infection is the presence of multinucleated giant cells, which are found in the reticuloendothelial (Warthin–Finkeldey cells) or in the respiratory epithelium. In an immunocompetent person, measles virus is shed from the nasopharynx beginning with the prodrome until 4 days after rash onset. Immunocompromised persons with measles may shed the virus for a longer time.

Diagnosis

Since measles has become a rare disease in the United States, few younger clinicians have ever seen a patient with measles. The key to diagnosing measles is having a high index of suspicion in any patient with a generalized rash, fever and cough, coryza, or conjunctivitis and performing the appropriate laboratory tests. Recent international travel or exposure to persons with recent international travel should increase the diagnostic suspicion of measles. A history of vaccination, even with multiple doses of measles vaccine, does not preclude the diagnosis.

Laboratory testing is critical in confirming the diagnosis of measles. Measles may be confirmed by the presence of measles immunoglobulin M (IgM) antibodies in a single serum specimen, immunoglobulin G (IgG) seroconversion, a fourfold rise in IgG antibodies, isolation or detection of the measles virus by reverse transcriptase polymerase chain reaction (RT–PCR) *(38)*. For IgM testing, enzyme immunoassay (EIA) is the most common assay currently in use and is commercially available. IgM antibodies appear with or soon after rash onset, peak 1 to 2 weeks later, and fall to nondetectable levels 1 to 2 months after the appearance of the rash. Serum specimens for IgM testing should be collected at the first clinical contact with a person with suspected measles. In previously vaccinated persons, the IgM response may be absent or short-lived, and additional testing, particularly viral testing, may be warranted *(39)*.

The measles virus can be cultured from throat swabs, urine, nasal swabs, or whole blood. A throat or nasopharyngeal swab collected from first day of rash through 3 days following onset of rash is the preferred specimen for viral testing, although swabs collected up to 7 days after rash onset may still yield virus. Isolation of measles virus in culture or detection of measles virus by RT–PCR confirms

the diagnosis of measles *(38)*. As most measles cases in the United States are currently associated with importations, the genotyping of viral specimens is of importance since this allows for a better understanding of the measles viruses being imported into or detected in the United States and the global epidemiology of the disease.

Prevention and Control

Because of the ease of transmission of measles, the fact that cases may present in medical facilities before onset of rash and recognition of measles as the diagnosis and because measles cases are frequently misdiagnosed, particularly during the prodrome, prevention of healthcare-associated measles transmission is challenging. However, a number of strategies will lower the risk. These include strategies to (a) maintain a high awareness among staff that a measles case could enter the facility, (b) assess the presumptive evidence of immunity of HCP, (c) maintain high vaccine coverage in the health facility staff, (d) promptly identify and isolate HCP and patients with febrile rash illness clinically compatible with measles, (e) identify and vaccinate potentially exposed patients, (f) exclude potentially infectious HCP from duty in the healthcare facility, (g) observe appropriate procedures for standard and airborne isolation in separate waiting areas, (h) inform health authorities promptly of suspected and confirmed measles cases, and (i) administer immune globulin as needed to selected immunocompromised patients and HCP where live viral vaccines, such as measles vaccine, are contraindicated (12,*38,40,41*,42).

Routine Vaccination Recommendations Live, attenuated measles vaccine is now available in the United States only as combined MMR vaccine. The Advisory Committee for Immunization Practices (ACIP) and Hospital Infection Control Practices Advisory Committee (HICPAC) recommend that all HCP should have documented immunity to measles. Vaccination with two doses of live, attenuated MMR vaccine is recommended for all HCP who lack evidence of immunity (see below) unless otherwise contraindicated (Table 51-2).

Presumptive Evidence of Immunity to Measles All HCP should have documented evidence of immunity to measles (Table 51-2). Adequate presumptive evidence of immunity to measles is defined as (a) documentation of administration of two doses of appropriately spaced live measles virus vaccine on or after the first birthday, (b) laboratory evidence of immunity, (c) laboratory confirmation of disease, or (d) birth before 1957 (43). Although most persons born in the United States before 1957 are likely to have been infected with measles naturally, ACIP and HICPAC suggest that healthcare facilities should consider vaccinating personnel without laboratory evidence of immunity or disease born before 1957 because of the potential for measles exposure in healthcare facilities and disruption that may result if an outbreak does occur. For HCP who have two documented doses of MMR vaccine or other acceptable evidence of immunity to measles, postvaccination serologic testing for immunity is not recommended. In the event that an HCP who has two documented doses of MMR vaccine is serologically tested and found to have negative or equivocal measles titer results, it is not recommended that the individual receive an additional dose of MMR vaccine. Documented age-appropriate vaccination is acceptable evidence of immunity irrespective of the results of subsequent serologic testing.

Management of Patients and Healthcare Personnel with Measles Patients with suspected or confirmed measles should be placed on Airborne Precautions for 4 days after the onset of rash (42). If airborne infection isolation rooms are not available, the patient should be placed in a room with the door closed and asked to wear a surgical mask (44). Only HCP with adequate presumptive evidence of immunity should provide care to a person with suspect or confirmed measles. Immunocompromised persons with measles (e.g., persons with acquired immunodeficiency syndrome) may shed virus for extended periods and should be kept on Airborne Precautions for the duration of their hospitalization for the acute illness.

If an HCP is suspected of having measles, they should be excluded from work until a diagnosis of measles can be ruled out. An HCP with confirmed measles should be excluded from duty for 4 days from the day of onset of rash.

Management of Measles Exposures and Outbreaks in Healthcare Settings If measles exposures occur in a healthcare facility, all contacts (those exposed during the infectious period) should be immediately evaluated for evidence of measles immunity.

Exposed HCP who cannot document evidence of measles immunity should be offered the first dose of MMR vaccine immediately and be excluded from work from the 5th through the 21st day following exposure (12). The second dose should be administered 28 days after the first. Those with documentation of one vaccine dose may remain at work and should receive the second dose. During an outbreak, HCP born before 1957 without laboratory confirmation of immunity or disease should receive two doses of the MMR vaccine; the first dose should be immediately followed by the second dose at least 28 days later. Serologic testing of HCP before vaccination is not recommended during an outbreak because arresting measles transmission requires rapid vaccination of HCP who lack evidence of measles immunity. The need to screen, wait for results, and then contact and vaccinate seronegative persons can impede the rapid vaccination needed to curb the outbreak. Serologic testing performed prior to vaccination may be used to guide the need for a second dose. HCP without evidence of measles immunity, for whom MMR vaccine is contraindicated, should receive immune globulin and should be excluded from work, and observations should continue for signs and symptoms of measles for 28 days after exposure, because immune globulin might prolong the incubation period.

Exposed patients without evidence of immunity should be offered the first dose of MMR vaccine or measles immune globulin (if vaccine is contraindicated) and should be discharged from hospital, if feasible. If they remain in the hospital, they should be quarantined from the 5th through the 21st day following exposure and should receive their second MMR vaccine 28 days after the first dose. If they have received immune globulin, they should be excluded for 28 days.

Other contacts (e.g., visitors, persons exposed in emergency rooms) should be identified, and information about them should be provided to local and state health departments so that these contacts can be followed up for evidence of measles immunity, need for vaccination or immune globulin, and for development of signs and symptoms of measles.

Any hospital contact who develops measles-compatible symptoms should be evaluated, isolated/excluded from work (as appropriate), and appropriate infection-control measures should be implemented to prevent further spread.

MUMPS

Epidemiology

Prior to the availability of mumps vaccine, epidemics of mumps occurred in the United States approximately every 3 years with peak incidence during the winter and spring *(45)*. The infection largely occurred among children aged 5 to 9 years; by age 14, approximately 90% of children living in urban areas had already been infected with mumps *(46)*. The epidemiology of the disease significantly changed following the licensure of a mumps vaccine in 1967. After that, reported cases of mumps in the United States began to decline steadily from 152,209 cases reported in 1968 to 2,982 cases reported in 1985 (*47,*48). Between 1986 and 1991, the United States experienced a resurgence of mumps, particularly among 10- to 14-year-olds and 15- to 19-year-olds, caused initially by a failure to vaccinate older cohorts of children and later characterized by one-dose vaccine failures *(49,50)*. The recommendation for a routine two-dose schedule for MMR to improve measles control in 1989 likely contributed to further declines in the incidence of mumps throughout the 1990s, and in 2003, a record low of 231 cases was reported nationally (48); this number represented a >99% decline from the 152,209 cases reported in 1968—the year after the live mumps vaccine was licensed.

During 2006, the United States experienced a large mumps outbreak with 6,584 cases—the largest number of cases reported since 1987 (51). The outbreak primarily affected college students from the Midwest, many of whom had already received two doses of the MMR vaccine. Mumps incidence again declined after this outbreak with 800 cases of mumps reported in 2007 and 454 cases reported in 2008 *(52,53)*. Again in 2009 to 2010, a large outbreak of mumps occurred in orthodox Jewish communities, primarily in the northeastern United States. The majority of cases (61%) occurred among persons aged 7 to 18 years; 75% of cases, where vaccine status was known, had previously received two doses of MMR vaccine *(54)*. In 2006 and 2009–2010 outbreaks, crowded social, religious, educational, or living environments appeared to be fueling the transmission of mumps. Although the effectiveness of the mumps component of the MMR vaccine is lower than that of the measles and rubella components, it appears sufficient to maintain mumps control and prevent outbreaks in most community settings. Estimates of the effectiveness of the mumps vaccine using the Jeryl Lynn or derived strains have varied in previous studies, ranging from 62% to 91% after one dose and from 79% to 95% after two doses (*55–57,*58).

Although most cases of mumps in HCP may be community acquired, sporadic transmission of mumps within hospitals to patients and staff is well documented (6). Cases of mumps in HCP and patients have been reported following healthcare-associated exposure, particularly in long-term care facilities housing adolescents and young adults. Outbreaks of mumps within hospitals, however, have only rarely been reported *(59,*60*)*. Presumably, the rare occurrence of healthcare-associated mumps outbreaks is because mumps virus is less communicable than measles and many other viruses, and mumps results in hospitalization less commonly. The level of mumps transmission in the surrounding community may also affect the risk for introduction into hospitals (6). During the 2006 mumps outbreak, a single healthcare institution experienced ongoing transmission of mumps for 1 month, affecting seven employees and two inpatients (60).

Clinical Description

Mumps is an acute viral illness, classically characterized by the presence of unilateral or bilateral parotitis. Onset of the disease usually occurs with nonspecific prodromal symptoms such as anorexia, myalgia, malaise, headache, and low-grade fever lasting up to several days. Parotitis, the predominant clinical feature, usually develops an average of 16 to 18 days (range: 12–25 days) after exposure. However, mumps infection may present only with nonspecific, primarily respiratory, symptoms or may be a subclinical infection *(56)*. Parotitis may be accompanied by earache and pain on chewing and may involve other salivary glands, including the submaxillary and sublingual glands. Parotitis is usually accompanied by moderate fever, but temperature may range from normal up to 40°C (104°F). Symptoms tend to decrease after 1 week and are usually gone by 2 weeks.

Complications of mumps include orchitis, affecting up to 37% of postpubertal males *(61)*, and mastitis, affecting up to 31% of females older than 15 years *(62)*. Oophoritis occurs in 5% of postpubertal females. Sterility or long-term infertility is thought to be a rare sequelae associated with orchitis and oophoritis. Meningeal signs may appear in up to 15% of cases, and pancreatitis, usually mild, may be present in up to 4% of cases *(63)*. An association between maternal mumps infection during the first trimester of pregnancy and an increase in the rate of spontaneous abortion or intrauterine fetal death has been reported in some studies but not in others *(64,65)*.

Serious complications of mumps are rare. Encephalitis occurs in <0.3% of apparent mumps infections *(66,67)*. Permanent sequelae are rare, but the reported encephalitis case fatality rate has averaged 1.4% (*67a*). Transient high-frequency deafness may occur in up to 4% of mumps cases *(63)*. Permanent deafness may occur at a rate of 1 case per 15,000 to 20,000 cases of mumps.

Pathogenesis

The mumps virus is single-stranded RNA virus in the *Paramyxovirus* family. The mumps virus is transmitted in saliva and respiratory secretions *(63,68)*. Mumps is acquired through the nose or mouth by direct contact with infected

droplets, saliva, or contaminated fomites but appears to be less efficiently transmitted than some other infectious diseases such as measles and chickenpox; the secondary clinical attack rate in susceptible household contacts <15 years was estimated to be 31%, 61%, and 76% for mumps, chickenpox, and measles respectively *(69)*. Primary viral replication occurs in the epithelium of the respiratory tract and possibly in regional lymph nodes. This is followed by viremia, which persists for 3 to 5 days, disseminates mumps virus throughout the body with localization in glandular tissue, and terminates with the development of humoral antibody *(70)*. Mumps virus has been isolated in saliva from 7 days before parotitis to 8 days after onset of disease; cessation of viral shedding coincides with the appearance of virus-specific secretory immunoglobulin A *(63,68,*71*,72,73*). However, viral shedding and therefore transmission risk are highest 1 to 2 days prior to and following parotitis onset, and most transmission likely occurs before and within 5 days of parotitis onset. During viremia, virus may be disseminated to the salivary glands, meninges, kidneys, testes, and other organs. Viruria is frequent and may last 10 days or more. Virus can be isolated from breast milk of infected women *(74)*. Parotitis accounts for most of the observed elevation of serum and urine amylase. Development of measurable neutralizing antibodies appears to correlate best with immunity to mumps.

Diagnosis

When parotitis is present, the clinical diagnosis of mumps is generally apparent. Although parotitis may be caused by other agents such as parainfluenza and coxsackievirus, bacterial infections, systemic diseases such as lupus and sarcoid, and certain drugs, mumps virus is the only known cause of epidemic parotitis. Because mumps is now a rare disease in the United States, diagnostic testing for persons with parotitis with no other apparent cause is recommended *(75)*. Laboratory diagnosis of mumps requires either detection of mumps IgM antibodies, a significant rise in serum IgG antibody titers between acute and convalescent phase sera, IgG seroconversion from negative to positive, isolation of mumps virus, or detection of virus by RT–PCR *(76)*.

Laboratory diagnosis of mumps in highly vaccinated populations may be challenging, and the timing of specimen collection and the utility of testing depend on the vaccination history of the person suspected of having mumps. In general, sera for IgM testing or as the acute specimen for examining seroconversion should be collected as soon as possible after onset of parotitis. In unvaccinated persons, IgM antibody is detectable within 5 days of onset of symptoms, peaks in about 1 week, and remains elevated for up to several months; for persons who have been previously vaccinated, the IgM response may be absent, and a negative result should not be used to rule out the diagnosis of infection. The IgM-capture EIA is the most sensitive method for detecting antibodies but has limited commercial availability. Other IgM test methods are more variable in their sensitivity and specificity.

The convalescent specimen for IgG detection should be collected approximately 2 to 3 weeks after the acute specimen. In unvaccinated individuals, mumps IgG antibody rises early after the onset of symptoms and is long-lasting. Previously vaccinated individuals may already have high levels of IgG present at the time that the acute specimen is collected. Oral or buccal swab samples should be collected as soon as mumps disease is suspected. Samples collected when the patient first presents with symptoms, usually within 3 days of parotitis, have the best chance of having a positive result by RT-PCR.

Prevention and Control

Because viral shedding occurs before clinical symptoms begin and because mumps may occur as a nonspecific respiratory illness or as an asymptomatic infection, effective methods to reduce mumps transmission can be challenging. Preventing mumps through an effective vaccination program is the best approach to controlling this disease. Strategies for mumps prevention and control should be applied in all healthcare settings and include (a) assessing the presumptive evidence of immunity of HCP, (b) vaccination of those without evidence of immunity, (c) exclusion of HCP with mumps as well as those lacking presumptive evidence of immunity who are exposed to persons with mumps, (d) isolation of patients in whom mumps is suspected, and (e) implementation of Standard and Droplet Precautions.

Routine Vaccination Recommendations Live, attenuated mumps vaccine is now available in the United States only as combined MMR vaccine. The ACIP and HICPAC recommend that all HCP should have documented immunity to mumps. Since 2006 (77), vaccination with two doses of MMR vaccine has been recommended for all HCP who lack evidence of immunity (see below) unless otherwise contraindicated (Table 51-2).

Presumptive Evidence of Immunity to Mumps All HCP should have documented evidence of immunity to mumps (Table 51-2). Acceptable presumptive evidence of immunity to mumps is defined as (a) documentation of administration of two appropriately spaced doses of live mumps-containing vaccine on or after the first birthday, (b) laboratory evidence of immunity, (c) laboratory confirmation of disease, or (d) birth before 1957 (43). Most persons born before 1957 are likely to have been infected naturally and generally may be considered to be immune even if they may not have had clinically recognizable mumps. However, a recent serosurvey conducted in 488 HCP born before 1957 showed that 3.7% of persons tested did not have serologic evidence of mumps antibody *(31)*. ACIP and HICPAC suggest that healthcare facilities should consider vaccinating personnel without laboratory evidence of immunity or disease born before 1957 because of the potential for mumps exposure in healthcare facilities and disruption that may result if an outbreak does occur.

Management of Patients and Healthcare Personnel with Mumps To prevent transmission, Standard and Droplet Precautions are recommended for patients with mumps, including a private room and use of masks for those providing care to the patient (42). These precautions should be maintained for 5 days after onset of parotitis. HCP with mumps should be excluded from work for 5 days after onset of parotitis (71).

Management of Mumps Exposures and Outbreaks in Healthcare Settings If mumps exposure occurs in a healthcare facility, all contacts (those exposed during the infectious period) should be evaluated for evidence of mumps immunity.

Exposed HCP without evidence of mumps immunity who are exposed to a person with mumps should be offered the first dose of MMR vaccine and should be excluded from duty from the 12th day after the first unprotected exposure through the 25th day after the last exposure. They should receive the second dose 28 days after the first dose. HCP with documentation of one vaccine dose may remain at work and should receive the second dose. During an outbreak of mumps, unvaccinated personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory evidence of disease should be vaccinated with two doses of MMR vaccine, 28 days apart. Serologic testing of HCP before vaccination is not recommended during an outbreak. The need to screen, wait for results, and then contact and vaccinate seronegative persons can impede the rapid vaccination needed to curb the outbreak. Serologic testing performed prior to vaccination may be used to guide the need for a second dose.

Exposed patients without evidence of immunity should be offered the first dose of MMR vaccine and should be discharged from the hospital, if feasible. If they remain in the hospital, they should be quarantined from the 12th day after the first unprotected exposure through the 25th day after the last exposure.

Other contacts (e.g., visitors, persons exposed in the emergency rooms) should be identified, and information about them should be provided to local and state health departments so that these contacts can be followed up for evidence of mumps immunity, the need for vaccination, and development of signs and symptoms of mumps.

Any hospital contact that develops mumps-compatible symptoms should be evaluated, isolated/excluded from work (as appropriate), and appropriate infection-control measures should be implemented to prevent further transmission.

RUBELLA

Epidemiology

During the global rubella pandemic that occurred between 1962 and 1965, an estimated 12.5 million cases of rubella occurred in the United States, resulting in considerable morbidity and mortality, including 11,250 therapeutic or spontaneous abortions, 2,100 neonatal deaths, and 20,000 infants born with congenital rubella syndrome (CRS) *(78,79)*. The licensure of rubella vaccine in the United States in 1969 *(80)*, and its use, primarily in children, led to dramatic declines in the number of reported rubella cases in the United States from 57,686 cases in 1969 to 12,491 cases in 1976 *(81)*. CRS cases also decreased dramatically from 68 in 1970 to 23 in 1976 *(82)*. A resurgence of rubella from 1977 to 1978, primarily among older adolescents and young adults (12,*83*), led to a modification of the rubella vaccination strategy to target additional groups for vaccination including susceptible postpubertal girls and women, military recruits, college students, and persons in certain work settings (e.g., healthcare) *(83–86)*. These recommendations resulted in a decrease in rubella cases in these age groups in the 1980s. During the mid 1990s to 2000, the majority of cases in rubella outbreaks were among foreign-born Hispanic adults from countries without a history of routine rubella vaccination programs *(87–89)*. Between 2000 and 2004, the median number of rubella cases reported annually was 18 (range: 7–176 cases) *(90)*. In 2004, rubella was declared eliminated from the United States on the basis of data showing that the virus was no longer circulating endemically within the country's borders *(2)*.

During the post-elimination era (2005–2009), 54 cases of rubella were reported for an average of 11 rubella cases reported annually (range: 3–16 cases); the majority of the cases occurred among individuals aged 20 years and above. Of the reported cases, 23 (43%) were imported or associated with importations; only two outbreaks of rubella were reported during this time and both were small ($n = 3$) (*CDC, unpublished data*). Since 2005, reported cases of CRS have remained low, and most infections were acquired overseas, with two cases reported in 2009 (*CDC, unpublished data*).

Although the virus has been eliminated in the United States since 2004 *(2)*, a national survey where specimens were collected between 1999 and 2004 indicated that approximately 12% of adults aged 30 to 39 years remain susceptible to rubella *(91)*. In 2011, these adults are now approximately a decade older. Although not as infectious as measles, rubella can be transmitted effectively whenever a large number of susceptible persons congregate in one place, and outbreaks continue to be a possibility in these settings, which include hospitals. Because rubella remains endemic throughout most of the world, the likelihood of future importations of rubella into the United States is high.

Rubella in Medical Settings

Although healthcare-associated outbreaks of rubella have not been reported in the United States since elimination was declared, U.S. HCP remain at risk for exposure to cases of imported rubella. In the decades prior to rubella elimination, healthcare-associated transmission of rubella was well documented (*92–95,*96). Transmission of rubella has occurred from HCP to susceptible coworkers and patients, from patients to HCP, and from patient to patient. Medical and dental students have been sources of infection and have facilitated transmission in rubella outbreaks *(95,97)*. Outbreaks have resulted in serious consequences including therapeutic abortions, disruption of hospital routine, time loss from work, costly control or containment measures, adverse publicity, and the potential for legal action.

Clinical Description

Rubella is generally a mild viral illness characterized by a generalized erythematous maculopapular rash, lymphadenopathy, and fever. Approximately 50% of infections may be subclinical or inapparent *(98)*. The incubation period ranges from 12 to 23 days *(99,100)*, with most persons developing a rash 14 to 16 days after exposure. In adults, a prodrome frequently occurs. It precedes the rash, lasts 1 to 5 days, and consists of malaise; low-grade fever; postauricular, occipital, and posterior cervical adenopathy;

and upper respiratory infection. The maculopapular erythematous rash begins on the face and spreads rapidly to the chest, abdomen, and extremities. Lymphadenopathy is a major clinical manifestation of rubella, and in addition to the characteristic suboccipital and postauricular nodes, there can be generalized involvement as well. Transient polyarthralgia and polyarthritis sometimes accompany or follow rubella, particularly among adult women (up to 70%). Rubella virus has been recovered from the synovial fluid of patients with acute disease *(101)* and, in some instances, from individuals with chronic arthritis in the absence of clinical rubella *(102,103)*, although the overall risk of persistent arthritis appears to be low. Central nervous system complications (encephalopathy or encephalomyelitis) and thrombocytopenia have been reported at rates of 1 per 6,000 cases and 1 per 3,000 cases, respectively. Hemorrhagic manifestations occur with an approximate incidence of 1 per 3,000 cases, occurring more often in children than in adults.

By far the most important consequences of rubella are the abortions, miscarriages, stillbirths, and multiple anomalies in infants that result from maternal infection in early pregnancy, particularly in the first trimester. The most commonly described anomalies associated with CRS are auditory (sensorineural hearing impairment), ophthalmic (cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (patent ductus arteriosus, pulmonary artery stenosis, atrial or ventricular septal defects), and neurologic (microcephaly, meningoencephalitis, developmental delay). Preventing fetal infection and the consequent CRS is the primary objective of rubella vaccination programs.

Pathogenesis

Transmission of rubella virus, an RNA virus in the *Togavirus* family, is from person to person via droplets shed from the respiratory secretions of infected persons. The disease is most contagious when the rash is erupting, but the virus may be shed from 7 days before to 7 days after the rash onset (infectious period). The mucosa of the upper respiratory tract and the nasopharyngeal lymphoid tissue are the primary portals for virus entry and the initial sites of viral replication. Virus spreads via the lymphatic system, or viremia may seed regional lymph nodes. The appearance of the rubella rash coincides with the detection of rubella-specific antibodies. Immunity is generally long lasting, but reinfection may occur following either naturally acquired rubella or vaccine-induced immunity *(104,105)*. Although some individuals have antibody levels that are not detectable by Hemagglutination Inhibition antibody testing following previous vaccination or infection, the clinical significance of such low-level antibody has not been well documented. Limited data suggest that reinfection with the rubella virus may occur in persons with low antibody levels. During reinfection, there is limited viral replication in the nasopharynx, and viremia and systemic manifestations are uncommon.

In fetal infection, transmission occurs during maternal viremia when the placenta is seeded with the virus followed by development of inflammatory foci in the chorionic villi, granulomatous changes, and necrosis *(106,107)*. CRS following maternal reinfection has been documented, although such instances have been rare *(108,109)*.

Diagnosis

Clinical diagnosis of rubella is difficult in the post-elimination era because of absence of disease and nonspecificity of clinical features. Laboratory confirmation is required for diagnosis. Although suboccipital and postauricular lymphadenopathy are characteristic, enlargement of these nodes can occur in adults with other conditions such as infectious mononucleosis, acquired toxoplasmosis, and *Mycoplasma pneumoniae* infection. Serologic diagnosis can be made by demonstrating IgM antibody in an acute specimen, by IgG seroconversion, or by demonstrating a fourfold rise in antibody titer between acute and convalescent serum samples. Because of its sensitivity, availability, and ease to perform, EIA is the most commonly used diagnostic testing for the detection of rubella IgM and IgG antibodies.

Rubella virus grows slowly in tissue culture. The preferred clinical specimens for culture of rubella virus and detection of rubella virus RNA are throat swabs or nasal aspirate secretions. Viral specimens should be collected as soon after symptom onset as possible and no later than 10 days postonset. Virus can also be recovered from the blood and urine.

Prevention and Control

An effective vaccination program is the best approach to preventing and controlling rubella. Strategies for rubella prevention and control should be applied in all healthcare settings, including outpatient facilities and long-term care facilities and should include (a) assessing the presumptive evidence of immunity of HCP, (b) vaccination of those without evidence of immunity, (c) exclusion of HCP with rubella as well as those lacking presumptive evidence of immunity who are exposed to persons with rubella, (d) isolation of patients in whom rubella is suspected or confirmed, and (e) implementation of Standard and Droplet Precautions.

Routine Vaccination Recommendations Live rubella vaccine is now available in the United States only as a combined MMR vaccine. The ACIP and HICPAC recommend that all HCP should have documented immunity to rubella. Vaccination with one dose of MMR vaccine is recommended for all HCP who lack evidence of immunity (see below) unless otherwise contraindicated (Table 51-2).

Women of childbearing age should receive rubella-containing vaccines only if they state that they are not pregnant and only if they are counseled not to become pregnant for 3 months after vaccination (12,*110*). Women without evidence of rubella immunity from whom vaccine is withheld because they state they are or may be pregnant should be counseled about the potential risk for CRS and the importance of being vaccinated as soon as they are no longer pregnant (111).

Presumptive Evidence of Immunity to Rubella All HCP should have documented evidence of immunity to rubella (Table 51-2). Adequate presumptive evidence of immunity to rubella is defined as (a) documented administration of one dose of live rubella virus vaccine on or after the first birthday, (b) laboratory evidence of immunity, (c) laboratory confirmation of disease, or (d) birth before 1957 (except women of childbearing age who could become pregnant) (43). For unvaccinated personnel born before

1957 who lack laboratory evidence of rubella immunity or laboratory confirmation of disease, healthcare facilities should consider vaccinating personnel with one dose of MMR vaccine.

Persons born before 1957 are generally considered to be immune to rubella. However, in a recent study among 477 newly hired HCP at a hospital in North Carolina, who were born before 1957 serologic testing, revealed that 14 (3.1%) lacked IgG antibodies to rubella *(31)*. Because rubella could occur in persons born before 1957 and because congenital rubella and CRS can occur in the offspring of women infected with rubella virus during pregnancy, although pregnancy is now expected to be a rare occurrence in this age group, birth before 1957 is not considered acceptable evidence of rubella immunity for women who could become pregnant.

Management of Patients and Healthcare Personnel with Rubella Patients diagnosed with rubella should be isolated for 7 days after rash onset and Droplet Precautions and respiratory etiquette should be followed (42). Isolation with Contact and Standard Precautions are also recommended for infants diagnosed with CRS, including placement in a private room and use of gowns and gloves when soiling is likely or for touching infective material. These Precautions should be maintained during any admission for the first year after birth unless nasopharyngeal and urine cultures, obtained at least 1 month apart, after the age of 3 months are negative for rubella virus.

HCP diagnosed with rubella should be excluded from work for 7 days after the onset of rash (43,112).

Management of Rubella Exposures and Outbreaks in Healthcare Settings The primary strategy for responding to rubella exposures and for controlling rubella outbreaks should be to ensure that persons without evidence of rubella immunity are vaccinated rapidly (or excluded from work if a contraindication exists).

Exposed HCP without evidence of rubella immunity should receive one dose of MMR vaccine and be relieved of direct patient contact from the 7th day after the first exposure through the 23rd day after the last exposure (43). All unvaccinated HCP born before 1957, who lack laboratory evidence of rubella immunity or laboratory confirmation of disease, should receive one dose of MMR vaccine during an outbreak of rubella. Serologic screening before vaccination is not recommended because rapid vaccination is necessary to halt disease transmission (12). Mandatory exclusion and vaccination of HCP who cannot document rubella immunity is recommended in medical settings, because pregnant women may be exposed.

Exposed patients without evidence of immunity should receive a dose of MMR vaccine and should be discharged from the hospital, if feasible. If they remain in the hospital, they should be quarantined from the 7th day through the 23rd day following the exposure.

Other contacts (e.g., visitors, persons exposed in the emergence rooms) should be identified, and information about them should be provided to local and state health departments so that these contacts can be followed up for rubella immunity, the need for vaccination, and development of signs and symptoms of rubella.

Any hospital contact that develops rubella-compatible symptoms should be evaluated, isolated/excluded from work (as appropriate), and appropriate infection-control measures should be implemented to prevent further transmission.

HUMAN PARVOVIRUS B19

Overview

Parvoviridae are small nonenveloped, single-stranded DNA viruses that infect invertebrates (subfamily: *Densovirinae*) and vertebrates (subfamily: *Parvovirinae*) *(113,114)*. Within the subfamily *Parvovirinae*, there are five genera, and viruses within these genera are known to infect many vertebrates, including cats (feline panleukopenia virus), dogs (canine parvovirus), pigs (porcine parvovirus), nonhuman primates (e.g., simian parvovirus), and humans. Currently, at least four different parvoviruses have been detected in humans (adeno-associated viruses, PARV4, human bocavirus, and human parvovirus B19). B19, the best characterized, is classified within the genus *Erythrovirus* and was discovered in the mid-1970s while evaluating a hepatitis B assay among human blood donors (plate B, position 19) *(115)*. It was not until 1981 that B19 was linked to a disease—transient aplastic crisis among children with sickle cell anemia *(116)*. Since then, B19 has been definitively linked to a number of diseases including erythema infectiosum (fifth disease), B19 arthropathy, transient aplastic crisis, chronic anemia, and hydrops fetalis and has been implicated in several others (e.g., autoimmune disorders, hepatitis, myocarditis, thyroiditis, and vasculitis).

Epidemiology

Prevalence B19 infections are common worldwide, demonstrating seasonal and year-to-year variations, occurring as sporadic cases or as community-wide outbreaks *(113,117)*. In temperate climates, most cases of erythema infectiosum occur during winter and early spring, with epidemics following a cyclical pattern every 3 or more years *(118–121)*. School outbreaks of erythema infectiosum may be protracted, often beginning in winter or spring and frequently lasting until the school year ends months later *(122)*. Prevalence of B19-specific antibodies rise steeply during childhood from 2% to 15% among children 1 to 5 years old to 35% to 60% at 11 to 19 years old *(118,123,124)*. This rise in prevalence is consistent with the fact that B19 infection is most commonly diagnosed in school-age children. The seroprevalence of IgG antibodies continues to increase during adulthood, reaching 75% to 90% among persons over 50 years old. In the absence of community outbreaks, the annual incidence of B19 infection in HCP is approximately 1% *(125)*.

Transmission Transmission for B19 parvovirus is primarily through contact (i.e., direct, droplet) with respiratory secretions, but it may also be transmitted transplacentally (*in utero*) or via fomites, blood components, and transplantation (e.g., stem cell, solid organ). Respiratory secretions are known to contain parvovirus B19 DNA, suggesting that they are likely to be important in viral transmission *(126–128)*. Fomite transmission is facilitated by the

stability of parvoviruses on environmental surfaces (129). Parvoviruses can also be transmitted via the administration of contaminated blood and plasma-derived products *(130–133)*; since they are small and very stable, they are resistant to common inactivation or removal methods (e.g., heat, solvents, detergents, filtration).

Transmission is very efficient in household settings in which half of susceptible exposed household members can become infected *(127,128,134)*. Although 25% to 50% of students in a school outbreak can have clinical or serologic evidence of infection, adult staff in schools and childcare settings generally have less-pronounced seroconversion rates of 5% annually *(125)*; however, in one outbreak, 20% of staff had serologic evidence of acute infection *(122)*.

Healthcare-associated transmission of parvovirus B19 among hospitalized patients and hospital staff has been described *(135–139)*, but in such cases, an index viremic patient is often not identified *(135,140–142)*. Based on the presence of B19 DNA in blood and respiratory secretions, the capacity to transmit B19 virus varies by the clinical syndrome of the index patient: patients with erythema infectiosum are likely to be infectious before, and not after, the onset of the typical clinical manifestations associated with erythema infectiosum (e.g., rash, arthralgias) *(126–128)*; however, patients with transient aplastic crisis can be infectious a week after onset of illness *(136,143)*, and immunocompromised patients with chronic B19 infection can be infectious for prolonged periods *(144–147)*. Some outbreaks of B19 infection that were initially presumed to be of nosocomial origin were, on careful evaluation, more likely to have been manifestations of community outbreaks (129,*138,146*). Therefore, the possibility of a community-based outbreak should be evaluated before attributing hospital-associated cases of B19 to healthcare-associated transmission.

B19 viral transmission has also been documented in other settings. As determined by serologic testing, vertical transmission of B19 infection occurs in 25% to 50% of infants born to mothers with B19 infection during pregnancy *(148–150)*, and fetal B19 infection is the cause of an estimated 5% to 20% of nonimmune hydrops fetalis *(151–153)*. Laboratory workers have also become infected following exposure to specimens from viremic patients *(154,155)*.

Disease transmission by transfusion of blood components is uncommon. B19 antigen has been found in 1 of 20,000 units of blood for transfusion, and B19 DNA has been found in 1 of 100 to 1 of 3,000 units, depending on the detection assay used *(130–132)*. However, units positive by DNA assays are frequently also positive for B19 antibodies, presumably reducing the likelihood of transmitting infection. B19 can also contaminate a variety of plasma-derived products *(133)*. Transmission of B19 infection to recipients of heat or solvent-treated blood products has been described *(156–159)*; and the seroprevalence of B19 is also higher among persons receiving plasma-derived products for treatment of chronic medical conditions *(130,152–156,160)*.

B19 viral transmission or suspected transmission by transplantation (e.g., stem cell, solid organ) has been documented in the literature, although it is considered an uncommon event *(161–167)*. Transplant recipients may present with mild symptoms that are consistent with erythema infectiosum or with more significant complications, including refractory or severe anemia and allograft dysfunction.

Clinical Description

In outbreaks of erythema infectiosum, the incubation period before the onset of rash is most commonly 1 to 2 weeks but can be as long as 3 weeks. Outbreak investigations have shown nearly half of infected persons do not report a rash, and one-quarter report no symptoms *(125,127,168)*. When illness does occur, it is often biphasic. An initial phase of nonspecific systemic symptoms (fever, malaise, and myalgias) develops at 1 to 2 weeks and correlates with the onset of viremia at 5 to 7 days *(126)*. The level of B19 DNA in blood during the acute phase of viremia may be $>10^9$ to 10^{12} genome copies per mL *(169)*. The second phase of illness begins 2 to 5 days after viremia is cleared and is associated with the appearance of antibodies and the onset of rash and arthralgias—the classic symptoms of B19 infection (170,*171–173*).

The most commonly recognized clinical condition associated with B19 infection, the rash illness—erythema infectiosum—was well characterized (as fifth disease) centuries before the discovery of the etiologic agent *(143)*. This illness is defined by a bilateral, intensely erythematous, maculopapular facial rash affecting the cheeks but sparing the bridge of the nose and circumoral region. Patients with this rash are often described as having a "slapped-cheek" appearance. In addition, a lace-like rash can concurrently affect the trunk and extremities but usually spares the palms and soles. Vesicles, papules, purpura, and desquamation have also been reported in some cases. The rash normally fades over a period of 2 weeks, but for several weeks afterward, the rash may reappear transiently following nonspecific stimuli, such as changes in ambient temperature, exposure to sunlight, exercise, or stress. Fever, if noted, is usually low grade; other symptoms may include sore throat, headache, and pruritus. Because there is variability between individuals in the intensity and distribution of the rash, sporadic cases of erythema infectiosum cannot be distinguished on the basis of clinical criteria alone from other exanthemas caused by rubella, enteroviruses, and other viruses or from some drug rashes. Adults may also develop erythema infectiosum, but the facial rash is usually less prominent; consequently, the diagnosis of B19 in adults is difficult to make if there is no laboratory confirmation or epidemiologic link to a child with typical erythema infectiosum.

A self-limited symmetric peripheral polyarthropathy particularly affecting the hands, wrists, and knees has been reported with B19 infection of children and adults, but it is most often found in adult women. The arthropathy can occur with or without a rash. Joint manifestations frequently include arthralgias or stiffness and less commonly include swelling or other signs of inflammation. These signs and symptoms usually improve within a few days or weeks but occasionally last for months and, rarely, for years and can mimic rheumatoid arthritis. B19-associated joint disease cannot be distinguished clinically from other arthropathies without B19-specific laboratory testing.

Persons with underlying hematologic disorders characterized by decreased red cell production (e.g., thalassemia) or increased red cell destruction (e.g., sickle cell disease

and hereditary spherocytosis) can acutely develop severe symptomatic anemia (e.g., fatigue, pallor, tachycardia, and congestive heart failure) because of the red blood cell aplasia. This transient aplastic crisis can be complicated by bone marrow necrosis or stroke and can lead to death. Hematologic recovery generally occurs within 7 to 10 days of presentation. Medical management of the patient may necessitate hospitalization and supportive care including red cell transfusions. Prior to hematologic recovery, the patient is viremic and should be considered infectious. Erythema infectiosum and arthropathy are usually not observed in persons with transient aplastic crisis. In some cases, by precipitating transient aplastic crisis, B19 infection may serve to unmask a previously undiagnosed, preexisting condition such as autoimmune hemolytic anemia.

Immunocompromised patients may develop chronic B19 infection and chronic anemia. This complication of B19 infection has been identified most often in children undergoing treatment for leukemia, in persons infected with human immunodeficiency virus (HIV), and in some cases, following transplantation (e.g., solid organ and stem cell) *(144,172–177)*. The clinical course varies. In leukemic patients, completion, modification, or interruption of chemotherapy may lead to spontaneous viral clearance. In persons with HIV infection, viral clearance can be achieved by administering intravenous immunoglobulins (IVIGs), but relapse can occur. Chronic B19 infection has rarely been documented in patients without recognized immunodeficiency.

Maternal B19 infection during pregnancy is associated with a risk for fetal anemia, nonimmune hydrops fetalis, spontaneous abortion, and fetal death (*117,171–181,*182). These conditions are dependent on several factors including maternal susceptibility to B19 infection, the prevalence of B19 infection (e.g., epidemic years, seasonality), and the timing of maternal infection relative to gestation age. The fetus is particularly susceptible to severe anemia with B19 infection owing to its expanding red cell volume, increased erythrocyte turnover, and immature immune system that often cannot control infection. Vertical transmission of B19 infection from mother to fetus can lead to chronic fetal anemia with high-output congestive heart failure with fetal death *(150,178,183,184)*. However, the natural history of fetal B19 infection is varied: approximately 30% to ~50% of maternal infections may lead to fetal infection *(145,150)*, with most neonates being born normal *(145,148,149,178,185,186)*. Fetal death appears to be highest in association with infection between the 10th and 20th weeks of gestation (*178–181,*182). This may be due to increased transplacental transfer of maternal antibody during the second trimester. Chronic red cell aplasia in infancy has been reported as a complication of intrauterine B19 infection in a few cases *(187)*. Infants born to women with B19 infection during pregnancy do not have a significantly increased incidence of congenital anomalies *(117,148,150,185,186)*. Rare case reports have presented findings of congenital anomalies following intrauterine B19 infection, but no associations have been proven *(148,188–191)*.

In addition to the well-established disease associations described above, acute and chronic B19 infections have been reported in sporadic cases of hemophagocytic syndrome, peripheral and central neurologic disorders, autoimmune conditions, hepatitis, thyroiditis, myocarditis, systemic vasculitis, and a variety of other conditions that are reviewed elsewhere (*113,117,*170,*171–173,192–195*). Etiologic links between B19 and many of these conditions have not been confirmed in controlled studies or by histopathologic criteria, and for some of these conditions, B19 infection may be coincidental or represent an opportunistic pathogen in an abnormal host. Associations with these less common conditions is often prompted by the identification of B19 DNA via PCR in patients' blood or tissues. B19 DNA has been found in asymptomatic healthy patients months after infection—the significance of this is currently not well understood *(196)*.

Pathogenesis

There is one serotype of B19 and three currently recognized genotypes *(113–115,197–200)*. B19 binds to the blood group P-antigen (globoside) *(201)* and infects and replicates in human erythroid progenitor cells *(202)*. Bone marrow is the primary tissue for viral replication, but as a result of extensive extramedullary hematopoiesis, fetal liver is also an important site of infection *in utero (203)*.

The natural history of B19 infection has been evaluated through human volunteer studies *(204,205)*. Viremia is usually detectable at day 6 after intranasal inoculation, peaks between 6 to 12 days, and resolves by 11 to 16 days. Viremia is associated with cessation of new red cell production and reticulocytopenia along with nonspecific signs and symptoms including fever, headache, myalgia, and chills. During the peak of the viremia, B19 DNA can also be detected in respiratory secretions (170,*204*). In immunocompromised patients with chronic B19 infection, such as pure red-cell aplasia, viremia persists in the absence of or low antibody production. In immunocompetent persons, the humoral immune response is best characterized with the production of specific immunoglobulin antibodies (IgM, IgG) (*143,144,*170,*204*). IgM antibody response is first detectable at 10 to 14 days after infection. The timing of the IgM response correlates with clearing of the viremia and onset of immune-mediated rash and arthralgias. IgM can be typically detected 2 to 3 months or longer after initial infection. High levels of IgM antibodies usually denote acute infection. An IgG response is detectable several days after the appearance of the IgM response and persists long term in immunocompetent persons and presumably confers lifelong protection against disease and reinfection. The importance of IgG in protection is emphasized by the efficacy of IVIG in controlling and sometimes curing B19 infection in immunocompromised patients *(144)*.

Lytic infection of red cell progenitors and arrest of hematopoiesis lead to the anemia commonly associated with B19 infection. Anemia is not clinically significant in persons without underlying illness primarily because of the brief interruption of hematopoiesis and the long lifespan of the red blood cell. However, among persons with underlying medical problems resulting in increased demand or turnover of red blood cells, including sickle cell disease, hereditary spherocytosis, thalassemia, and acquired hemolytic anemias, B19 infection can lead to a transient aplastic crisis, with hemoglobin levels falling 30% or more. In such cases, a hypoplastic or aplastic erythroid and normal myeloid series are seen in the patient's

bone marrow. A brisk reticulocytosis is seen with the onset of host immune response and termination of viremia. Some patients with an impaired immune response cannot control infection and develop chronic hypoplasia or aplasia of the erythroid series in the bone marrow.

Laboratory Diagnosis

Virus Isolation Although erythroid cell lines have been developed that support B19 cultivation *(206,207)*, these are not efficient virus isolation tools and therefore have not been used for clinical diagnosis.

Antibody Detection Antibody assays are currently the cornerstone of laboratory diagnosis for most B19 infections. Acute B19 infection in the immunologically normal patient can be diagnosed by detection of B19 IgM antibodies that develop within 10 to 12 days after infection and can remain present for months. B19 IgG antibodies usually become detectable several days after the appearance of IgM; IgG can persist for years and perhaps for life. Over 90% of patients with erythema infectiosum or arthropathy will have both B19 IgM and IgG antibodies at the time of presentation with acute onset of rash. IgM antibody is present in 80% of patients with transient aplastic crisis *(123,208)*; however, serologic studies can be misleading for persons presenting in the early stages of anemia prior to the rise of B19-specific antibody. Serologic studies of mother and infant can also be of use in diagnosing acute B19 fetal infections.

Unless removed, high levels of B19-specific IgG can compete with and block detection of IgM antibodies, and since rheumatoid factors or nonspecific binding of IgM antibodies can yield false-positive reactions, indirect IgM assays tend to have lower sensitivity and specificity than IgM-capture assays *(209)*. Acute infection can also be evaluated using non–IgM-based assays designed to detect either a high frequency of low-avidity antibodies *(210)* or antibodies recognizing antigens indicative of acute or early convalescent infection *(211–213)*. Antibody assays are not useful for diagnosing B19 infection in immunodeficient patients who may not have a normal antibody response to the infection. In such situations, immunohistology and nucleic acid detection are more appropriate diagnostic tools.

Antigen Detection Current antigen detection assays (enzyme-linked and radioimmune assay) are not sensitive enough to reliably diagnose acute infection *(123,208)*. Immunohistologic techniques have been useful for detection of B19 antigens in fetal tissues and bone marrow samples *(123,213)*.

Nucleic Acid Detection Polymerase chain reaction (PCR) assays are highly sensitive and specific tests that are commonly used to detect both acute and chronic B19 infections, as well as to perform the screening of blood products for the presence of B19 parvovirus. Sensitivity and specificity of these assays can vary greatly between laboratories *(214)*. Qualitative and quantitative PCR assays have both been used in clinical diagnoses *(215–217)*. Quantitative PCR assays can detect as few as 10^2 genome copies per mL and are used to measure viral load in blood components. Results from B19 PCR assays must be carefully interpreted because of the potential for false–positive results from amplicon contamination and because low viral loads may not be indicative of acute B19 infection or associated with disease.

Prevention and Control

Currently, no vaccine is approved for B19 infection. Although the majority of B19 infections are mild and self-limiting, a vaccine would be beneficial, particularly in specific populations such as pregnant women, immunocompromised persons, and those with underlying hemolytic disorders or increased erythropoiesis where B19 infection can cause significant morbidity. Preliminary results from a randomized, double-blinded, phase 1 trial were promising—adult volunteers receiving a recombinant parvovirus B19 vaccine developed neutralizing antibody titers *(218)*. The public health intervention of a vaccine for a high-risk population has prompted the investigation into the relationship of B19 infection and severe anemia among children in areas endemic for malaria *(219–222)*.

Because B19 infection is primarily transmitted through respiratory secretions and close contact (e.g., droplet and fomite), attention to handwashing and not sharing food or drinks should be effective for preventing spread of the virus. However, since the classic signs and symptoms of B19 infection (e.g., rash and arthralgias) are not apparent until after the patient has been viremic, good hygienic practices, particularly during outbreaks, need to be universally applied to be effective at prevention.

Parvoviruses, in general, are highly resistant to disinfection procedures and can remain infectious in the environment for prolonged periods of time; the virus is stable in lipid solvents such as ether and chloroform. There are no specific data about the viability of B19 in the environment, but on the basis of properties exhibited by other members of the *Parvoviridae* family, surfaces contaminated with bodily fluids containing B19 should be considered infectious. In one case, vaginal delivery of a B19-infected fetus resulted in widespread contamination of environmental surfaces in the patient's room with B19 DNA (129).

Patients and staff with the classic signs of erythema infectiosum or B19-associated arthropathy are past the infectious period and therefore do not require special precautions (42,44,*223*). Patients with transient aplastic crisis and patients with chronic B19 infection may be viremic for up to a week after presentation and do pose a risk of healthcare-associated transmission. Little is known about the risk for transmission from immunodeficient patients. The HICPAC recommends maintaining Droplet Precautions for the duration of hospitalization when chronic disease occurs in an immunocompromised patient; for patients with transient aplastic crisis or red-cell crisis, Droplet Precautions should be maintained for 7 days (42). Most patients with transient aplastic crisis will mount an effective immune response that cures the infection; isolation precautions can be removed after hematologic recovery, which usually occurs 7 to 10 days after presentation. For chronically infected patients treated with immunoglobulins, isolation precautions can be removed if hematologic recovery occurs and if available virologic surveillance (e.g., PCR testing) demonstrates that the B19 viremia has been cleared. In pregnant women with suspected or proven intrauterine B19 infection, amniotic

fluid and fetal tissues should be considered infectious, and Contact Precautions should be used in addition to Standard Precautions if exposure is likely (129).

B19 community outbreaks, particularly those associated with schools and day-care centers, are often associated with heightened concern about infection of persons at risk for complications, particularly pregnant women. Depending on the community and on the assay used, 40% to 60% of women of childbearing age test positive for B19 IgG antibodies and therefore are not thought to be susceptible to infection. The risk of fetal death in pregnancy can be estimated to be 0.4% to 3% after exposure to B19 in the household and 0.16% to 1.2% after exposures associated with working in a school or childcare setting with a B19 disease outbreak. The American College of Obstetrics and Gynecology (ACOG) recommends that pregnant women exposed to B19 parvovirus should have serologic testing for B19 performed to determine susceptibility and possible evidence of acute B19 infection (182). Pregnant women with evidence of acute B19 infection should be closely monitored (e.g., serial ultrasound examinations) by their healthcare provider. The CDC recommends that persons be informed of potential exposures to B19 and that efforts to lower the risk of exposures (e.g., avoiding the workplace or school environment) be made on an individual basis after consultation with family members, healthcare providers, public health officials, and employers or school officials *(223)*.

Many HCP already have B19 IgG antibodies from prior infection and are believed to be at low risk of becoming reinfected or of transmitting B19 to patients or other staff (44). Serologic screening of asymptomatic HCP to identify susceptible staff is not currently recommended by the CDC. HCP should be advised that they are at risk of B19 infection after exposure in the hospital or in the community and that there may be a risk for further transmission to patients. Routine infection control practices, particularly hand washing, should minimize the risk for transmission. Pregnant personnel should be advised about potential risks of B19 infection to the fetus and advised to consult with their healthcare providers; the CDC and ACOG do not recommend that pregnant personnel routinely be excluded from caring for patients with B19 infection (182,*223*).

In July 2009, the U.S. Food and Drug Administration issued guidance for nucleic acid testing (NAT) to reduce the possible risk of human parvovirus B19 transmission by plasma-derived products *(224)*. The goal was to identify and prevent the use of plasma-derived products containing high levels of parvovirus B19. Parvovirus B19 viral loads in manufacturing pools should not exceed 10^4 IU/mL. B19 NAT should also be performed on minipool samples to screen plasma units intended for manufacturing into plasma-derived products.

Treatment

No specific antiviral drugs are currently available for treatment. Most cases of erythema infectiosum or B19-associated arthropathy are mild and self-limited and require no treatment other than supportive care. Transient aplastic crisis can be a life-threatening event, but if diagnosed early, it can be managed with red cell transfusions to relieve signs and symptoms associated with anemia. Chronic B19 infections in immunosuppressed patients have been successfully controlled and sometimes cured with IVIG *(225,226)*. Relapses of anemia have been successfully treated with additional IVIG doses. Use of immunoglobulins to prevent or treat other types of B19 disease has not been studied. HIV-infected persons with chronic B19 infection can benefit from optimizing antiretroviral therapy to improve immune status. There are no definitive or established guidelines for clinical management of pregnancies complicated by intrauterine B19 infection and fetal hydrops *(117)*; however, ACOG has published guidelines to aid practitioners with decisions concerning diagnosis and clinical management, including serologic testing and serial ultrasound examinations (182). Intrauterine blood transfusions can be considered for treatment of B19-associated hydrops. However, since fetuses can survive free of sequelae without treatment and since transfusions can be associated with fetal death, it is not possible to determine when the benefits of this procedure outweigh the risks.

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CHAPTER 52

Healthcare-Associated Infections in Newborn Nurseries and Neonatal Intensive Care Units

Kristina Bryant

The neonate is a vulnerable host. While advances in newborn intensive care have permitted the survival of low-birth-weight and sick infants, life-saving, invasive therapies and prolonged hospitalizations place these infants at risk for infection. The immunologic immaturity of the newborn infant, particularly the infant born prematurely, increases this risk. Healthcare-associated infections (HAIs) contribute substantially to morbidity and mortality in hospitalized neonates *(1–3)*.

EPIDEMIOLOGY

In general, infections not present or incubating at the time of admission are considered healthcare-associated. A practical adaptation of this definition for newborns has been to define HAIs as those that present after 48 hours of age. This convention may result in misclassification of some infections, as some that result from perinatal exposure to maternal genital flora may not manifest until ≥48 hours. Likewise, failure to use aseptic technique for invasive procedures such as umbilical catheter placement may result in HAIs that manifest in <48 hours. Because of the difficulty in correctly classifying infections, the Centers for Disease Control and Prevention (CDC) has defined all neonatal infections, whether acquired during delivery or during hospitalization, as healthcare-associated unless evidence indicates transplacental acquisition *(4)*.

Rates of HAIs in well newborn nurseries are low, ranging from 0.3 to 1.7 per 100 newborns *(5–7)*. Short hospital stays and exposure to few invasive devices or procedures account for the low rates of infection. The difficulty of performing postdischarge surveillance for infection may lead to underrecognition of HAIs such as conjunctivitis and pustulosis. Outbreaks in newborn nurseries have been linked to vertical transmission from a mother to her infant with subsequent transmission to other infants, or occasionally sick healthcare workers *(8)*.

Reported rates of HAIs in neonatal intensive care units (NICUs) have ranged from 6% to 25% *(9–12)*, while a multicenter study in Europe reported rates of 7% *(13)*. Lack of consistent definitions, heterogeneous patient populations, and variable exposure to invasive devices make comparison of these studies difficult. A national point-prevalence survey conducted in the United States by the Pediatric Prevention Network identified HAIs that met CDC definitions in 11.4% of NICU patients (14). National prevalence studies from Spain *(15)* and Norway *(16)* yielded similar results, with reported rates of 16.7% and 14%, respectively.

Rates of healthcare-associated neonatal infections are 3 to 20 times higher in resource-limited countries *(17)*. A 10-year prospective surveillance study of six NICUs in Brazil identified HAIs in 69% of admitted infants *(18)*.

Prematurity and low birth weight are consistently identified as a significant risk factors for infection. According to data reported by the National Institute of Child Health and Human Development (NICHD) National Research Network over a 2-year period, 21% of very low birth weight (VLBW) infants developed late-onset sepsis. Rates of infection were inversely related to birth weight and gestational age *(19)*.

An overall infection rate is of limited use, because it is influenced by hospital or nursery type, patient mix, referral patterns, whether or not newborn surgery is performed, the infections targeted for surveillance, and the definitions used for these infections *(20–22)*. Also, total infections must be distinguished from the numbers of infected patients, because many patients have more than one infection. Infection rates expressed per admission or per patient-day may be useful for following infection rates in a specific NICU over time or for interhospital comparison, provided that the rates are adjusted for severity of illness or are expressed by risk group.

Birth weight is commonly used as a marker for severity of underlying illness in the NICU. Goldmann et al. *(23)* found a strong correlation between infection and low birth weight, with a mean birth weight of 1,581 g for infants with major HAIs versus 2,607 g for those without infections. Use of invasive devices may be an even more relevant marker for average severity of illness and for the type of NICU. NICU infection rates vary with intensity of device use. In a study involving 35 hospitals, assessment of device use (central or umbilical lines and ventilators) by total device-days and calculation of device-associated infection rates by device-days controlled for this variation. Stratification

by birth weight did not eliminate the need to control for device use.

The National Nosocomial Infection Surveillance (NNIS) system was established by the CDC in 1970 as a voluntary, national surveillance system for HAIs. NNIS utilized standardized definitions and developed risk-adjusted infection rates for different kinds of intensive care units, including NICUs. Participating NICUs could report data on all HAIs at all body sites. In 2006, NNIS and two other national surveillance systems administered by the CDC were replaced by the National Healthcare Safety Network (NHSN), a secure, Internet-based surveillance system. Between 2006 and 2008, more than 1,500 hospitals, including 150 NICUs, contributed data about device-associated and procedure-associated infections (24). Definitions of HAI in the newborn are based on those for older children and adults with modifications for children <12 months of age *(4)*, and device-associated infections in NICU patients are stratified by birth weight.

RISK FACTORS FOR INFECTION

Immunologic Immaturity

Immaturity of the newborn immune system and defects in structural defenses make the neonate, especially the neonate born prematurely, uniquely susceptible to infection. The skin, for example, normally provides a mechanical barrier between the host and the environment. In infants born before 32 weeks of gestation, the stratum corneum is poorly developed, and the skin is fragile, very permeable, and easily traumatized by routine procedures such as cleansing or removal of adhesive tape. Injured skin provides a portal of entry for infectious agents. Similar defects are seen in the alimentary tract, where low levels of mucosal immunoglobulin A, high gastric pH, and short gastric emptying times increase the susceptibility of the newborn to gastrointestinal infections.

Immune function in the newborn has been extensively reviewed elsewhere *(25)*. Term and preterm newborns have functioning B cells, but there is little antibody synthesis *in utero*. Postnatally, the B cells make antibodies to protein antigens but respond poorly to polysaccharide antigens, including the bacterial capsular polysaccharides of group B streptococcus (GBS) and *Haemophilus influenzae*. In the first weeks of life, the newborn depends on passively transferred maternal antibody and the repertoire of antibodies received depends on maternal exposure. Because placental transfer of antibody occurs in the third trimester, infants born at <34 weeks have low levels of immunoglobulin G antibody.

The newborn has a high total T-lymphocytic count, but phenotypic surface markers differ from those in the older child. Cytotoxic T-cell activity is decreased, as is T-cell helper function. The T-cell-dependent antigen-specific response is delayed, and there is limited production of several cytokines. These maturational defects in T cell function enhance the susceptibility of the newborn to intracellular pathogens such as *Listeria, Toxoplasma,* and *Salmonella*. Natural killer cell activity, important in control of herpes group viral infections, is also decreased.

Reduced numbers and activity of alveolar macrophages in the lungs of term and preterm infants increase the risk for pulmonary infection. The newborn has a decreased granulocyte storage pool and defective neutrophil and monocyte chemotaxis. Neutrophil phagocytosis and antimicrobial activity are largely intact but may be decreased when bacterial density is high or when opsonins are limited. Although production of complement proteins begins early in gestation, mature activity of the complement system may be delayed until 6 to 10 months of age.

Sources of Infectious Agents and Modes of Transmission

The newborn may develop infection as a result of exposure to maternal flora during labor or delivery, or postpartum from maternal, hospital, or community sources. Postnatally, the hands of healthcare workers are the most common vehicles for transmission of potential pathogens in neonatal units *(26,27)*. Nursery outbreaks of *Staphylococcus aureus*, enterococcus, a variety of gram-negative bacilli, and viruses have been attributed to hand transmission *(1,28–35)*. In one study, gram-negative bacilli were found on the hands of 75% of NICU personnel *(36)*. Usually, hands are transiently contaminated, and hand washing removes the microorganisms and interrupts transmission *(37)*. A few outbreaks have been linked to microbial contamination of hand washing agents *(38,39)*.

Occasionally, personnel who are persistent carriers of potential pathogens such as *S. aureus* or group A *Streptococcus* (GAS) have been implicated in nursery outbreaks *(40,41)*. Artificial fingernails may lead to increased hand carriage of gram-negative microorganisms, and healthcare workers with artificial nails have been linked to transmission of *Pseudomonas aeruginosa (29,30)* and *Klebsiella pneumoniae (42)*.

Patient care equipment may also serve as a vehicle for transmission. Multiple outbreaks have been associated with contaminated respiratory care equipment including ventilator circuits *(43,44)* laryngoscopes *(45)*, balloons used for manual ventilation *(46)* and suction devices *(47–49)*. Inadequate disinfection of rectal thermometers contributed to nursery outbreaks of *Salmonella eimsbuettel (50)* and *Enterobacter cloace (51)*.

Infusion of contaminated intravenous fluids, including total parental nutrition solutions and lipid emulsions, may result in bacteremia or meningitis *(52–60)*. Exposure to contaminated topical preparations and medications, including contaminated eyewash *(61)*, umbilical cord wash *(62)*, and glycerin *(63)* may also result in invasive infections. Use of contaminated ultrasound gel resulted in an outbreak of pyoderma in hospitalized neonates *(64)*, while bathing practices have been linked in clusters of listeriosis *(65)* and *Stenotrophomonas* infections *(66)*.

Blood transfusions may be a source of viruses such as hepatitis A virus, hepatitis B virus (HBV), and hepatitis C virus (HCV) *(67–69)*. Before current screening practices, blood products were also a source for perinatal cytomegalovirus (CMV) transmission *(70,71)*. Neonatal transfusion-acquired malaria has been rarely reported *(72,73)*.

Hospitalized neonates are at risk for food-borne infection. Powdered formula is not sterile, and feeding of reconstituted formula has been associated with gram-negative

bacteremia and meningitis *(74)*. Expressed breast milk may be contaminated during collection *(75–77)* and both breast milk *(78–80)* and formula *(81,82)* may be contaminated during storage and handling. Feeding practices may also contribute to infection. Pathogens may be acquired during insertion or handling of nasogastric tubes used for feeding *(35,83,84)*. Feedings administered though nasogastric tubes by continuous infusion remain at room temperature for several hours, creating the potential for microbes to proliferate in the reservoir or tubing during infusion *(77)*.

Infected personnel and visitors may introduce pathogens into the nursery, especially during community outbreaks of viral infections *(85)*. Both symptomatic healthcare providers *(86)* and visitors have been the source of healthcare-associated pertussis in the NICU.

Environment

Infection rates in the NICU increase with overcrowding and understaffing. In one report, a 16-fold increase in outbreaks of *S. aureus* infection was observed when the infant-to-nurse ratio exceeded 7 and there was a sevenfold increase when the nursery was crowded *(87)*. Increasing rates of endemic methicillin-resistant *S. aureus* (MRSA) were also linked to overcrowding and understaffing, with eradication of MRSA when these conditions improved *(88)*. An outbreak of *E. cloacae* infection was associated with understaffing and overcrowding in another report *(89)*.

Invasive Procedures

Any procedure that disrupts the normal barriers to infection may predispose the newborn to infection. Scalp electrodes, for example, provide a portal of entry for maternal genital microorganisms. Although infectious complications occur in <1% of infants and most are benign abscesses, occasionally severe cellulitis, bacteremia, osteomyelitis, and disseminated herpes simplex virus (HSV) occur *(90,91)*. Osteomyelitis has resulted from infected toe and heel punctures and femoral venipunctures. Surgical-site infections (SSIs), as well as device-associated infections including catheter-associated bacteremia, bladder catheter-associated urinary tract infection, and ventilator-associated pneumonia (VAP), are discussed in detail below.

INFECTIONS AT SPECIFIC SITES

Skin, Subcutaneous Tissues, Mouth, and Eyes

Pustules, cellulitis, subcutaneous abscesses, lymphadenitis, and infections at sites of percutaneous punctures are most often due to *S. aureus*, or less commonly to streptococci and gram-negative bacilli and other microorganisms *(92)*. Microbes causing infections at scalp monitor sites are more diverse and include maternal genital microorganisms such as HSV *(90,91)*.

Omphalitis is uncommon, occurring in 0.5% of term and 2% of preterm infants in one report *(93)*. The presentation varies from mild erythema or serous drainage to purulent discharge, cellulitis, and acute necrotizing fasciitis of the abdominal wall. *S. aureus* is most often isolated, but GAS, coagulase-negative staphylococci (CONS), enterococci, gram-negative rods, and anaerobes may also be involved *(94)*. A mortality rate of 7% was reported in a series, with fatalities associated with rapidly progressing cellulitis or necrotizing fasciitis *(95)*.

Mastitis, characterized by redness, swelling, or induration of the breast, is seen occasionally in term infants in the first 3 weeks of life *(96)*. *S. aureus* is the most common pathogen, although disease due to gram-negative microorganisms such as *Escherichia coli* and *Proteus mirabilis* is also reported *(97)*.

Circumcision is the most common surgical procedure performed in the newborn, although NHSN considers circumcision infections with skin and soft-tissue infections rather than with SSIs. Reported infection rates are low, at 0.06% to 0.4% *(98,99)*. Most are simple skin infections, but more serious complications, including necrotizing fasciitis, have occasionally been reported *(100)*. An outbreak of neonatal pustulosis due to a community-associated MRSA strain in one newborn nursery was attributed in part to circumcision practices *(101)*.

Healthcare-associated conjunctivitis is common in NICUs *(102,103)*. The conjunctivae of neonates may become colonized with nasopharyngeal and skin flora during routine care. The immature lacrimal system of preterm neonates facilitates pooling of bacteria and other debris on the surface of the eye, leading to conjunctival infection. The most common bacterial pathogens associated with healthcare-associated conjunctivitis include CONS, *S. aureus*, *Klebsiella* species, *Pseudomonas aeruoginosa*, *Serratia marscescens, H. influenzae,* and *E. coli (102)*. Viral conjunctivitis also occurs. Risk factors for conjunctivitis include low birth weight and the need for respiratory support, including nasal CPAP and mechanical ventilation. *P. aeruginosa* conjunctivitis in particular has been associated with contaminated resuscitation equipment *(47)*, and infection in intubated patients has been related to endotracheal tube colonization and eye contamination during suctioning *(104)*. Opthalmalogic exam for retinopathy of prematurity has been associated with the development of conjunctivitis, including outbreaks of adenoviral conjunctivitis *(105,106)*.

Bloodstream Infections

Bloodstream infections (BSIs) are the most common HAI in hospitalized neonates, and most are related to central venous catheters (CVCs) *(13*,14,*22)*. While there is significant variability in infection rates among NICUs, higher rates of device-associated bloodstream infection are consistently reported among the smallest, most premature infants (24). The pooled mean rates of umbilical catheter-associated BSIs in Level II/III NICUs that reported data to NHSN from 2006 to 2008 ranged from 1/1,000 catheter days in infants with birth weights of >2,500 g to 5.7/1,000 catheter/days in infants with birth weights ≤750 g. Central line–associated BSIs (CLABSIs) for the same time period ranged from 1.2/1,000 catheter days for the largest infants to 4.9/1,000 catheter days in infants in the smallest birthweight category. Even higher rates of catheter-associated BSIs are reported by NICUs in resource-limited settings *(107)*. NHSN does not further stratify CLABSIs by type of catheter, but some data suggest lower rates of infection with percutaneously inserted central catheters (PICCs) compared with tunneled catheters *(108)*, while a multicenter study showed no difference *(109)*.

Coagulase-negative staphylococci, *S. aureus*, enterococci and *Candida* species are the most common causes of CLABSIs *(110)*. Among neonates with PICCs, 75% of CLABSIs are caused by CONS (111), although differentiating true CONS bacteremia from culture contamination is challenging. Increasingly, *S. aureus* CLABSIs are due to MRSA. From 1998 to 2008, the rates of MRSA CLABSIs reported to NHSN rose 49% *(112)*.

In additional to low birth weight and gestational age, mechanical ventilation *(113,114)* and total parenteral nutrition *(114)* are risk factors for the development of CLABSIs. In one study involving 3,470 catheter days, sampling of blood through the central line and disconnection of the catheter increased the risk of CLABSIs *(115)*. The importance of catheter location on the incidence of infection remains controversial. One study identified a higher rate of catheter-related sepsis in VLBW infants with femoral PICCs compared to those with nonfemoral PICCs (22.5% vs. 12 or 10.9 vs. 6.8 episodes/1,000 catheter days) *(116)*. Another study found no difference in infection rates when PICCs placed in an upper extremity were compared to those placed in a lower extremity, although the pathogens associated with infections did vary by site *(117)*. Coagulase-negative staphylococcal infections were more common in infants with upper extremity catheters, while more gram-negative infections were diagnosed in children with lower extremity catheters.

Some (118) but not all studies have demonstrated that the risk of infection increases with the duration of catheter use. Umbilical catheterization for more than 5 days is recognized as an independent risk factor for sepsis *(113)*. In one study, catheter duration of 10 to 21 days was associated with a 40-fold risk of gram-negative BSIs in VLBW infants, while the risk was 90-fold with catheter duration of >21 days (119). In a retrospective cohort study in a single NICU, the incidence rate of CLABSIs increased by 14% by day during the first 18 days after PICC insertion. The trend reversed from days 19 to 35 after insertion, but after day 36, the incidence rate of CLABSIs increased by 33% per day.

Healthcare-associated BSIs can also occur in the absence of a central venous catheter. When all causes of late-onset sepsis are considered, the pathogens are similar to those observed with CLABSIs *(19,114)*. Although gram-positive infections still account for the majority of infections, the proportion of BSIs caused by gram-negative microorganisms is higher. In patients with short gut syndrome, enteric gram-negative bacilli and yeast predominate, probably because of translocation of bacteria from the gastrointestinal tract and subsequent seeding of the catheter *(120)*. Nasal cannula continuous positive pressure airway use and H_2 blocker/proton pump inhibitor therapy are also risk factors for gram-negative BSIs in VLBW infants (119).

Central Nervous System Infections

The burden of healthcare-associated meningitis in NICU infants is difficult to quantify, as not all infants with symptoms of infection undergo lumbar puncture. In a study of 9,641 VLBW infants born at NICHD Neonatal Research Network Centers, only 1.4% infants who survived at least 3 days developed meningitis, representing 5% of infants who underwent lumbar puncture (121). Notably, only half of the infants who had a blood culture obtained because of suspected sepsis also had a lumbar puncture performed, suggesting that some cases of meningitis could have been missed. One-third of infants with meningitis had negative blood cultures.

The most frequent pathogens isolated in VLBW infants with healthcare-associated meningitis include CONS (29%), *Candida* species (14%), and enterococci (13%). In the NICHD study, gram-negative microorganisms, including *E. coli*, *Klebsiella,* and *Serratia* species, accounted for 19% of episodes. Multiple NICU outbreaks of gram-negative meningitis have been reported *(56,122,123,124–127)*, some of which have been linked to feeding practices. A cluster of *Elizabethkingia meningosepticum* (formerly *Flavobacterium meningosepticum*) was linked to contamination of the formula preparation area and bottle stoppers *(128)*. Cases of *Chronobacter sakazakii* (formerly *Enterobacter sakazakii*) have been linked to contaminated powdered infant formula *(129)*.

Risk factors for gram-negative meningitis include underlying urinary tract anomalies and hydrocephalus *(130)*. Meningitis may also occur as a complication of ventricular drain and shunt placement *(131)*. In a study of shunt placement for hydrocephalus in newborns weighing <2,000 g, the shunt infection rate was 25% after primary placement and 36% after revision *(132)*. Common causes of shunt infection include CONS, *S. aureus,* and gram-negative bacilli *(133)*. Young age, prematurity, and the presence of intraventricular hemorrhage, a known complication of prematurity, are associated with an increased risk of shunt infection. In one study, prematurity increased the risk for shunt infection nearly fivefold. Proposed reasons for this increased infection risk may include a high density of CONS on the skin of preterm infants and colonization with more virulent CONS strains. Strategies for the prevention of ventriculoperitoneal (VP) shunt infections are similar to those proposed for the prevention of other SSIs. The use of antibiotic-impregnated shunt systems reduced infections in one small case series of premature infants and deserves further study *(133)*.

Respiratory Tract Infection

Early-onset pneumonia is usually related to intrapartum exposure and is most often due to GBS *(134)*. Maternally transmitted *Ureaplasma urealyticum* infection occasionally causes pneumonia or respiratory distress in VLBW, premature infants *(135)*.

Most cases of late-onset pneumonia are device-related *(134)*. VAP is common in preterm infants, many of whom require prolonged ventilatory support. In a prospective study, nearly 30% of infants born at <28 weeks of gestation developed VAP; infection was significantly associated with mortality (136). Not surprisingly, the rates of VAP reported through NHSN are consistently highest in infants of <1,000 g birth weight and are similar to those reported in pediatric intensive care units and adult medical intensive care units (24). Pooled mean rates of VAP for level II/III NICUs reporting data to NHSN from 2006 to 2008 ranged from 0.6/1,000 ventilator days in infants of >2,500 g birth weight to 2.7/1,000 ventilator days in infants of ≤ 750 g birth weight.

The true burden of VAP may not be known, because the diagnosis is difficult in NICU infants. While NHSN surveillance definitions for VAP include criteria for infants <1 year of

age, these definitions have not been validated in premature neonates. Comorbid conditions such as bronchopulmonary dysplasia may mimic the clinical and radiographic features of VAP *(137)*. Ultimately, many infants are treated empirically for presumed pulmonary infection.

Gram-negative microorganisms are thought to cause at least 30% of VAP episodes, but a specific microbiologic diagnosis is often difficult unless there is secondary bacteremia (14,*22*). Endotracheal cultures are rarely useful in the diagnosis of VAP because the respiratory tract of the intubated newborn rapidly becomes colonized with mixed gram-positive flora by the second week of mechanical ventilation, and gram-negative microorganisms after the fourth week *(138,139)*. The presence of purulence in a specimen suctioned from the endotracheal tube of a mechanically ventilated neonate has a poor positive predictive value for respiratory tract infection, including pneumonia and tracheitis *(139)*. Risk factors for VAP in NICU patients include duration of mechanical ventilation, reintubation, treatment with opiates, and endotracheal suctioning *(140)*. Other modes of assisted ventilation, including nasal continuous positive airway pressure, have been associated with the development of healthcare-associated pneumonia, albeit at lower rates than those associated with mechanical ventilation *(141)*.

Gastrointestinal Infections

Gastrointestinal infections account for ~1% of infections in NICUs. Microorganisms that cause community-associated outbreaks of gastrointestinal infection can also cause sporadic infections or clusters of infection in the NICU. Rotavirus is most commonly identified *(142)*, although outbreaks of norovirus and adenovirus have also been reported.

Outbreaks of bacterial enteritis are occasionally reported. *Salmonella* outbreaks in neonatal units may be prolonged, in part due to the prolonged incubation period of this microorganism, a high proportion of asymptomatic infants, and prolonged shedding by carriers *(143,144)*. Widespread contamination of the environment and equipment may also facilitate ongoing transmission *(145)*. The newborn with *Salmonella* gastroenteritis is at risk for bacteremia and focal infections are often seen. Symptomatic *Shigella* infection in the newborn is rare and transmission to other newborns is unusual; transmission to nursery personnel has been reported *(146)*. *Campylobacter jejuni* is an uncommon newborn pathogen and is usually of maternal origin, but healthcare-associated outbreaks have been described *(147,148)*.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) occurs in 1% to 8% of all NICU admissions *(149–151)*. It is a disease of prematurity, with preterm infants comprising 90% or more of all cases *(92)*. Rates of NEC are highest in infants born at 30 to 32 weeks of gestation and disease is most common in the second week of life *(152,153)*. The etiology of this disorder is not well understood but is thought to involve vascular compromise, bacterial invasion, and release of inflammatory mediators in the setting of a substrate such as enteral feedings.

While NEC is not strictly an infectious process, it is included in the CDC definitions of HAIs. Outbreaks in nurseries have been temporally associated with the isolation of a number of different microbes, including *Klebsiella* species; *Clostridia* species; *E. coli* species; *Serratia* species; *Pseudomonas* species; *Staphylococcus epidermidis*, *Salmonella* species, toxigenic *E. coli*, and *S. aureus* *(154–156)*. Because these microorganisms are commonly found in patients without NEC, proving a causal association has been difficult and association of specific microorganisms with clusters of NEC may reflect patterns of intestinal colonization rather than actual outbreaks of infection. The role of viruses in the pathogenesis of NEC is not well understood. Adenovirus *(157)*, norovirus *(158)*, coronavirus *(159)*, and rotavirus *(160,161)* have been recovered in infants with NEC but causality remains uncertain.

Prematurity is the principal risk factor for NEC, along with several factors related to infant feeding. The risk of NEC is 6 to 20 times higher in formula-fed infants than in breast milk-fed infants. While breast milk is generally protective, consumption of dry powdered human milk fortifier has been identified as a risk factor for NEC *(162,163)*. One study of >15,000 infants that utilized administrative data identified exposure to antenatal steroids as a risk factor for NEC independent of birth weight *(151)*.

A number of strategies have been evaluated for the prevention of NEC. Enteral probiotic supplementation reduces the risk of severe NEC and death in preterm infants with birth weights of at least 1,000 g *(164)*. In one study, oral immunoglobulin containing immunoglobulin A and immunoglobulin G was protective when fed to low-birth-weight infants for whom breast milk was not available *(165)*. Prophylactic oral vancomycin protected VLBW infants against NEC and may be indicated in specific situations, but routine use may increase the risk of colonization with resistant microorganisms *(166)*. Outbreaks of NEC, even those not temporally associated with isolation of a particular microbe, have been aborted with typical infection control interventions such as cohorting, environmental cleaning, and enhanced hand hygiene *(167)*.

Urinary Tract Infection

Some studies suggest that healthcare-associated urinary tract infections (HA-UTIs) are uncommon in NICU patients. In a national point prevalence survey of NICU HAIs in the United States, urinary tract infection occurred in only 10/827 patients (14). Most infections occurred in infants with birth weights of ≤1,000 g or >2,500 g. Similar rates were reported from a multicenter trial in Europe: only 0.3% of infants developed HA-UTIs *(13)*. Single center studies report rates of HA-UTIs ranging from 11.6 to 19/1,000 admissions *(168–170)*. Higher rates are reported in infants undergoing surgery *(170)* and in VLBW infants *(171)*. In a retrospective review of NICU infants weighing ≤1,500 g at birth, HA-UTIs developed in 8.1%.

The most common bacterial pathogens causing HA-UTIs in NICU patients include *E. coli*, *Enterobacter,* and *Klebsiella* species. In one 6-year retrospective study, *Candida* species were the most common cause of HA-UTIs *(169)*. Compared to bacterial UTIs, candidal UTIs occurred in less mature and younger (34 vs. 97 days) infants, and were more likely to be associated with bloodstream infection.

Most infants who develop HA-UTIs do not have underlying renal anomalies or vesicoureterial reflux. Exposure to

intermittent or indwelling urinary catheters is a well-described risk factor in pediatric patients *(168)*. Although catheters are used less frequently in newborns than in older children and adults, they carry a high risk of infection. This may be because of the use of feeding tubes, which are not well stabilized for bladder drainage rather than the balloon-tipped catheters used in older children *(172)*.

Surgical-Site Infections

Neonates are at increased risk for SSIs compared to children and adults *(173,174)*. In a study involving 1,094 neonates and 1,433 surgical procedures, 17% of patients developed a wound infection *(175)*. Staphylococci were most commonly isolated. Increased incision length, increased duration of surgery, and contamination of the operative site were all associated with an increased risk of infection but gestational age and birth weight were not. Rates of SSI are likely to vary by patient population, type of surgery, surgical site infection risk, severity of illness, and duration of operation. At present, NHSN does not provide risk-stratified, comparative data for neonates who develop SSIs, but such data are needed.

Guidelines for the prevention of SSI have been published. Although details of SSI prevention in pediatric surgical practice are not addressed in these guidelines, it is noted that SSI prevention measures effective in adult surgical care are indicated in pediatric surgical care *(176)*. Use of prophylactic antibiotics was associated with a lower infection rate after potentially contaminated surgery but not after clean surgery *(177)*. Unfortunately, there are few data on the efficacy of antibiotic prophylaxis for surgical procedures in the neonate *(175)* and detailed recommendations that address issues unique to this population are lacking. The current wound classification system used for determining the need for antibiotic prophylaxis (clean, clean contaminated, contaminated, and dirty or infected) was created based on adult surgeries, and it is unclear how these guidelines apply to neonatal operations *(178)*. The American Academy of Pediatrics (AAP) recommends systemic antibiotic prophylaxis "when the probability or morbidity of postoperative infection is high and the benefits of preventing wound infection outweigh potential risks for adverse drug reactions and emergence of resistant microorganisms" *(179)*. Specifically, prophylaxis is indicated for some clean wound surgeries and most clean contaminated wound surgeries (Table 52-1). Surgeries that involve contaminated wounds or dirty and infected wounds require treatment rather than prophylaxis. Ampicillin and gentamicin are recommended agents for surgical prophylaxis in all neonates <72 hours of age. For older neonates, prophylaxis is targeted to colonizing microorganisms, healthcare-associated microorganisms, and the operative site. Unfortunately, there is little consensus among pediatric surgeons about how these recommendations apply to specific neonatal surgical procedures, which agents should be used, and what duration of therapy is appropriate *(180)*.

Bone and Joint Infections

Neonatal osteomyelitis and septic arthritis are uncommon manifestations of HAI, with only one to three cases reported per 1,000 admissions to intensive care nurseries *(181)*. Both are usually hematogenous in origin and, as such, are most often caused by the same agents that cause neonatal sepsis, including GBS, *S. aureus,* a variety of gram-negative bacilli, and *Candida* species *(182)*. Osteomyelitis may also occur as a result of direct trauma related to heel puncture *(183)*, femoral venipuncture *(184)*, and fetal monitoring electrodes *(185)*. Most cases of bone and joint infection are sporadic, although outbreaks have been reported *(186)*.

TABLE 52-1

Indications for Surgical Antimicrobial Prophylaxis in Neonates

Clean wound surgeries[b]
Open heart surgery for repair of structural defects
Implantation of intravascular prosthetic material
Body cavity exploration in neonates
Neurosurgical procedures[a]
Clean-contaminated wound surgeries[b]
Gastrointestinal tract procedures involving obstruction
Gastrointestinal tract procedures when permanent foreign body in place
Biliary tract procedures involving obstruction
Urinary tract procedures in the setting of obstructive uropathy or bactiuria

[a]Most procedures.
[b]Includes but not limited to surgeries listed here.

INFECTIONS CAUSED BY SPECIFIC MICROORGANISMS

Staphylococcus aureus

S. aureus causes a wide spectrum of disease in neonates, from superficial skin infections to severe invasive disease including bacteremia, meningitis, osteomyelitis, and SSIs. Colonization is common; from 20% to 90% of newborns acquire the microorganism in the first week of life *(187)*. In NICUs, healthcare worker hands are implicated in transmission. In one study, 20/37 infants handled by a caregiver for 10 minutes through the portholes of incubators acquired that caregiver's strain of *S. aureus (27)*. Transmission may be reduced by hand washing *(26,188)*. Less commonly, outbreaks have been traced to nasal carriage by a healthcare worker, or the so-called cloud phenomenon *(40,41)*.

Increasingly, staphylococcal infections in NICUs are due to MRSA. According to data reported to NHSN, late-onset MRSA infection in US NICUs increased 300% from 1995 to 2004 (189). In units that conduct active surveillance, up to 40% of infants may be colonized *(190)*. Infants with MRSA colonization have a significantly higher rate of MRSA infection than those without colonization. In one study, the risk of infection in colonized infants was 26% versus 2% in non-colonized infants ($p < .001$; odds ratio 19.86). Other risk factors for infection include low birth weight and prematurity *(190,191)*.

The clinical manifestations of MRSA in neonates are similar to those seen with methicillin-susceptible *Staphylococcus*

aureus (MSSA). Bloodstream infections and skin and soft tissue infections (including postoperative wound infections) predominate, although in one report, infants with MRSA infections were younger at presentation than infants with MSSA infection (23 vs. 32 days, $p < .03$) *(192)*.

As with MSSA, transmission of MRSA within NICUs is most often ascribed to transient hand carriage on the unwashed hands of healthcare workers *(88,193,194)*. Overcrowding and understaffing may facilitate the MRSA spread *(87,195)*. Other sources include colonized or infected healthcare workers *(196)*, an infected or colonized family member *(197)*, or contaminated breast milk *(198)*. Rates of maternal vaginal or rectovaginal MRSA colonization in pregnant women range from 0% to 10% *(199–202)*. Nevertheless, maternal to child transmission with subsequent early-onset MRSA infection is rare *(200,201)*. Community-acquired MRSA chorioamniotitis with subsequent transmission to a premature neonate who developed MRSA sepsis has been described *(203)*.

MRSA has become endemic in some neonatal units, with ongoing introduction and transmission of multiple, distinct molecular strains over time *(204)*. Nevertheless, several centers have eradicated transmission using a multimodal approach to infection prevention (88,*205*,206,*207*). Active surveillance cultures, aggressive implementation of Contact Precautions with monitoring of compliance, cohorting, and decolonization of patients and healthcare workers eradicated MRSA from one 18-bed NICU in a community hospital for 2.5 years *(205)*. Creation of distinct nursing cohorts to care for MRSA-colonized or -infected infants, MRSA-exposed infants, and newly admitted infants contributed to the control of MRSA outbreaks in centers in the United States and France (206,*208*).

Decolonization of MRSA carriers, including colonized infants, is controversial. The optimal decolonization regimen remains unknown. In two, small observational studies, application of mupirocin to the anterior nares of colonized infants did not reliably eradicate colonization or prevent infection (206,*208*).

A working group composed of infection prevention experts at Chicago-area hospitals has published consensus recommendations for the control of MRSA in NICUs (209). Key features of the recommendations include ready availability of hand hygiene products with monitoring of hand hygiene compliance, cohorting and Contact Precautions for colonized or infected infants, periodic active surveillance culture of patients' anterior nares, molecular analysis of MRSA isolates, and communication between regional NICUs to prevent spread between institutions with patient transfers. Notably, screening of healthcare workers to detect MRSA colonization is recommended only to corroborate or refute epidemiologic data that link a particular HCW to transmission.

Coagulase-Negative Staphylococci

CONS are the most common cause of HAIs in NICU infants. They cause 35% of late-onset sepsis in neonates *(19,210)* and are a common cause of CLABSIs (14,111). A syndrome of persistent bacteremia accompanied by thrombocytopenia has been described in neonates, even in the absence of CVCs *(211)*. Endocarditis, abscesses, omphalitis, SSIs, and meningitis occur occasionally, and a mild form of NEC has been described. The role of CONS as a cause of neonatal pneumonia is suggested by the isolation of microorganisms in the blood of infants with pulmonary infiltrates. CONS are also the major cause of ventricular shunt and drain infections *(212)*. The virulence of these common skin commensals in neonates may relate in part to their ability to adhere to catheter surfaces and proliferate to form a multilayered biofilm *(213,214)*. Production of slime may also help the microorganism evade host defenses *(214a)*.

Low birth weight, low gestational age, and procedures that interfere with skin or mucosal integrity, including placement of intravascular catheters, endotracheal tubes, and feeding tubes, increase the risk for CONS infection *(19,215,216)*. Receipt of intravenous lipids is also a risk factor; lipids may enhance the growth of CONS in colonized catheters *(217,218)*. CONS infections prolong the hospital stay of infected newborns and increase healthcare costs but are not associated with increased mortality *(219,220)*.

Effective measures for the prevention of CONS infection include limiting the use of invasive devices and aseptic technique for insertion and handling of intravascular and other prosthetic devices. Addition of vancomycin to intravenous fluids has been shown to reduce the incidence of CONS bacteremia in neonates but is not recommended for routine use because of potential for inducing vancomycin resistance *(221)*. Transmission of CONS with heteroresistance to vancomycin in NICU has been reported *(222)*.

Group B Streptococci

GBS is a leading cause of neonatal sepsis and meningitis among newborns. Approximately 10% to 30% of pregnant women are colonized with GBS, 50% of these women will transmit the bacteria to their newborns, and 2% of colonized infants will develop disease. Early-onset disease usually presents on the first day of life with septic shock, pneumonia, and severe multiorgan failure. Intrapartum prophylaxis of GBS-colonized women has decreased the incidence of disease in infants in the first 72 hours of life *(223)*.

In contrast, late-onset disease is seen in infants up to 3 months of age or older and may manifest as bacteremia, meningitis, or focal infection such as osteomyelitis. The risk factors for late-onset disease are not well described, but only 50% of cases are attributable to maternal colonization *(224)*. Infection may result from a colonized healthcare worker or occasionally as a result of cross-transmission from other infants in the nursery. Healthcare-associated transmission has been reported, especially in crowded nurseries with a high rate of maternal colonization *(225)*.

Enterococci

Enterococci, including *Enterococcus faecalis* and *Enterococcus faecium*, are common commensals of the gastrointestinal tract and the vagina. Maternally acquired infection can result in sepsis during the first week of life, although symptoms are generally less severe than those observed with GBS *(226)*. Late-onset infection commonly manifests as bacteremia, often in the setting of NEC or other gastrointestinal tract pathology *(227)*. Bacteremia is often polymicrobial. Enterococci may also cause focal infections such as abscess, urinary tract infection, or meningitis.

Not long ago, vancomycin-resistant enterococci (VRE) were rarely encountered in hospitalized neonates (14), but

recent reports suggest that the incidence of VRE, like other MDRO, is increasing (228,*229*) Clinical cultures identify a minority of patients harboring VRE. In the setting of active surveillance cultures, the prevalence of colonization has ranged from 2% to >40% (228,*229*,*230*). Risk factors for VRE acquisition include low birth weight and exposure to antimicrobials *(229,230)*. Clonal spread in one NICU was linked to a contaminated electronic thermometer (228). Routine infection control measures, including Contact Precautions, cohorting, hand hygiene, and environmental cleaning, have been successful in terminating VRE outbreaks (228,*229*).

Group A Streptococci

GAS infections may be acquired vertically from colonized mothers or from colonized or infected healthcare personnel *(231–235)*. Most infants described in reports of nursery outbreaks developed mild, indolent omphalitis *(232–234)* although severe disease, including sepsis and necrotizing cellulitis, also occur *(235)*. Treatment of the umbilical stump with bacitracin *(233)*,triple dye *(234)*, or chlorhexidine *(236)* may reduce colonization and disease. Identification and treatment of GAS carriers is essential for the control of outbreaks. Administration of Penicillin G has been effective in some outbreaks. In other reports, eradication of colonization required clindamycin treatment *(235)*.

Other Gram-Positive Bacteria

Listeria is usually maternally acquired *(237)*. Maternal infection is food borne, and clusters of infection in newborns usually indicate community outbreaks. Early-onset disease, often associated with maternal symptoms, presents with pneumonia and rash and multisystem disease. Meningitis is the major form of late-onset disease. Control measures include advising pregnant women to avoid unpasteurized milk products and foods epidemiologically associated with an outbreak and diagnosing and treating infection in pregnancy. Nursery transmission is reported but rare *(238)*. Contaminated resuscitation equipment *(239)* and mineral oil used to bathe infants *(65)* have been implicated.

Streptococcus pneumoniae is an unusual cause of neonatal sepsis. Early-onset infection may be associated with maternal sepsis and has a poor prognosis *(240)*. Healthcare-associated transmission has been reported *(241)*.

Leuconostoc species may cause sepsis and meningitis in premature infants *(242)*. Case reports describe underlying gastrointestinal tract disease and central venous catheter use in infants diagnosed with this uncommon, vancomycin-resistant pathogen.

From 2% to 70% of infants may be asymptomatically colonized with *Clostridum difficile*, including toxigenic strains *(243,244)*. Rates of colonization decrease with age, falling in the second year of age to 6%. Rates of colonization in children >2 years of age are similar to those in adults (~3%).

Infants may acquire colonization early in the first week of life *(245)*. Studies examining the risk factors for *C. difficile* have failed to show a consistent association between acquisition of the organism and the mode of delivery or receipt of formula versus breast milk. However, healthcare acquisition of the microorganism is well described in NICUs and *C. difficile* contamination of the NICU environment has been demonstrated *(246)*.

Most studies have failed to show an epidemiologic association between colonization and disease in infants <1 year of age, including NICU patients. *C. difficile* toxin was recovered from the stools of 55% of patients in one NICU, but signs of enteric disease, including NEC, occurred with equal frequency in both toxin-positive and toxin-negative infants *(247)*. Data from neonatal rabbits suggest that the lack of disease in colonized infants may be related to the absence of a receptor for toxin A in immature enterocytes *(248)*.

Sporadic case reports suggest that severe *C. difficile* infection occasionally occurs in infants, especially those with underlying intestinal pathology. For example, *C. difficile* pseudomembranous colitis has been identified at autopsy in infants with Hirshprung's disease *(249)*. Fatal *C. difficile*–associated pseudomembranous colitis has also been described in a premature infant with NEC *(250)*. The impact of the emergence of the BI/NAP1 strain of *C. difficile* on disease in neonates is not yet known.

Enterobacteriaceae

The Enterobacteriaceae, including *E. coli, Enterobacter, Klebsiella* and *Citrobacter* species, and *Serratia marcescens*, are increasingly recognized as important causes of endemic and epidemic HAI in NICUs *(22,251)*. Transmission is usually person to person via hands, although contaminated patient care items have also been involved.

Early-onset *E. coli* disease is usually of maternal origin, but neonates may rapidly acquire nursery strains of *E. coli (252)*. Healthcare-associated *E. coli* infections commonly manifest as bacteremia, SSI, or infection of the gastrointestinal or urinary tracts *(22)*. Some reports suggest that cases of late-onset *E. coli* sepsis are increasing *(253)*. Prolonged NICU stay is a risk factor for the acquisition of extended-spectrum beta-lactamase (ESBL)-producing strains *(254)*.

Hospitalized newborns readily become colonized with *Klebsiella* species; the gastrointestinal tract is the major reservoir *(255)*. These microorganisms are the most commonly reported cause of outbreaks in NICUs; the mortality associated with *Klebsiella* outbreaks exceeds 11% *(251)*. Commonly identified sources include enteral feeding *(83)* and infusion therapy practices *(256)*. Increasingly, outbreaks associated with ESBL-producing strains are reported *(132*,*257*,*258*,*259*).

Like *Klebsiella* species, *Enterobacter* species are commonly in the fecal flora of hospitalized infants. Low birth weight and prematurity *(59)*, as well as prolonged hospital stay, are risk factors for the acquisition of *Enterobacter* colonization. Receipt of total parental nutrition and bladder catheterization are risk factors for the development of bacteremia *(260)*. Outbreaks have typically been associated with intravenous fluids *(52*,*59*).

Citrobacter koseri (previously *C. diversus*) is part of the normal gastrointestinal flora. Infection in the newborn most often manifests as meningitis, ventriculitis, and focal brain abscess *(261,262)*. Non–central nervous system infection is rare, although neonatal septic arthritis and osteomyelitis have been reported *(263)*. Most cases of *C. koseri* infection are sporadic, but outbreaks have been recognized in normal newborn nurseries as well as NICUs *(127,261,264*,). Outbreaks are characterized by large numbers of colonized infants with small numbers of symptomatic infants over extended periods *(*127,*264)*. Single strains differing from one hospital to another may be implicated *(264)*, or

several strains may be present in one outbreak, suggesting multiple introductions *(261)*. Hand or gastrointestinal carriage in healthcare workers has been implicated in transmission. Infants infected by vertical transmission are more likely to be premature than infants infected by horizontal transmission in the NICU *(265)*.

Long considered a commensal with little pathogenic potential, *S. marcescens* is now recognized as a frequent and often devastating cause of infection in NICU infants *(266)*. In a multicenter European study, 15% of HAIs in neonates were caused by *S. marcescens,* including 5% of BSIs. Other manifestations of *Serratia* infection include sepsis *(267)*, meningitis *(267,268)*, brain abscess *(269)*, and conjunctivitis *(39)*.

Sources of *Serratia* outbreaks include contaminated intravenous fluids *(56)*, delivery room equipment *(48)*, laryngoscopes *(270)*, breast pumps *(76)*, prepared infant formula, and soap *(39)*. Transient hand carriage of the microorganism has been considered a likely mode of transmission in outbreaks in which no point source has been identified (271). Infants with asymptomatic gastrointestinal tract colonization may act as reservoirs, facilitating both endemic and epidemic transmission *(272)*.

Other Gram-Negative Bacilli

Chronobacter sakazakii (formerly *Enterobacter sakazakii*) is a coliform that causes sepsis and meningitis often complicated by ventriculitis, brain abscess, and cerebral infarcts *(273,274)*. The microorganism has also been linked to NEC *(275)*. Mortality rates as high as 80% have been reported; 94% of meningitis survivors experience neurologic sequelae.

Prematurity, low birth weight, and age <28 days have been identified as risk factors for *C. sakazakii* infection *(276–278)*. Powdered infant formula has been implicated as the source of infection in both sporadic cases and clusters of disease. Intrinsic contamination resulting in manufacturers' recall of powdered formula *(279)* and extrinsic contamination of blenders *(82)* used in formula preparation have been reported. Strategies for the prevention of *C. sakazakii* infection have focused on infant feeding practices.

Carriage of *P. aeruginosa* has become endemic in some NICUs, with nearly 25% of infants colonized *(280)*. This microorganism is ubiquitous in the environment and proliferates in water *(281)*. It readily colonizes skin, gastrointestinal tract, and respiratory tract, especially when antibiotics are used *(47)*. Clinical manifestations of infection include sepsis, pneumonia, and urinary tract infection *(29,280, 282*). It is also an important cause of healthcare-associated conjunctivitis *(47,104)* and the leading cause of neonatal endophthalmitis *(283)*. Outbreaks have been associated with contaminated equipment *(282)*. Low-birth-weight infants are particularly at risk, and the case fatality rate is high *(284). Burkholderia cepacia (285)*, *Ralstonia pickettii (286),* and *Stenotrophomonas maltophilia (66)* may also be acquired from environmental water sources. A national outbreak of *Ralstonia mannitolytica* infection/colonization that involved primarily premature infants was epidemiologically linked to contamination of a respiratory gas humidification device *(287)*. Although the cause of the contamination was not identified with certainty, water was used to manufacture the device and its filter cartridge. The outbreak resulted in a national recall of the device and changes in the recommended procedures for cleaning and reprocessing. Outbreaks of neonatal meningitis caused by *B. cepacia (125)* and sepsis and meningitis caused by *S. maltophilia (123,288)* have been described.

Acinetobacter (Ab) species, including *A. baumannii*, *A. cacloaceticus*, and *A. lwoffii*, inhabit soil and water and frequently colonize the skin and the gastrointestinal tracts of adults. Ab species are common causes of HAIs, particularly bacteremia and VAP, in intensive care units and burn units (289). Outbreaks of bacteremia *(31,58,290,291)*, meningitis *(126)*, and pneumonia *(43)* have been described in NICUs. Most infections have occurred in low birth weight neonates.

Because Ab species can survive for prolonged periods on dry surfaces, contaminated environmental surfaces have been implicated in healthcare-associated spread. Healthcare-associated transmission has been linked to inadequate hand hygiene by healthcare workers, intravenous catheters, contaminated hydroscopic bandages used to secure endotracheal tubes and umbilical catheters, contaminated aerosols from an air conditioning unit, contaminated suction catheters, and contamination of the humidification chamber of ventilatory devices *(292,293)*.

Multidrug-resistant (MDR) Ab (MDR-Ab) is increasingly described as a cause of HAIs in adults and is emerging as a pathogen in neonates *(294,295)*. Simmods et al. described a clonal NICU outbreak of MDR-Ab that involved seven infants *(295)*. Three infants had bacteremia, and one had a positive pleural fluid culture. All infected or colonized infants were born at <26 weeks of gestation, weighed <750 g at birth, and had a positive culture in the first 7 days of life, leading the authors to speculate that invasive Ab has an affinity for damaged or nonkeratinized immature skin. Effective control measures were similar to those employed for other MDR microorganisms and included cohorting, reinforcement of Standard and Contact Precautions, and the use of dedicated personnel and equipment for colonized or infected infants.

Pertussis is an unusual HAI in the newborn, but when it occurs, it is often severe. Newborns may acquire the disease from visitors *(296)* or personnel *(8,297)* with unrecognized infection.

Only sporadic cases of *Legionella* infections have been described in neonates, but reported cases are usually healthcare-associated *(298)*. Infection has been linked to water used in an oxygen nebulizer and for heating feeding bottles and to postoperative contamination of a sternal incision with tap water *(299)*. Pneumonia has been reported after water birth *(300)*. Risk factors for infection include prematurity, immune deficiency, or congenital heart or lung disease *(301)*.

Mycobacteria

Congenital or perinatal tuberculosis may be acquired from an infected mother. It is rare, and diagnosis may be delayed. Infants are unlikely to transmit infection by coughing, but suctioning may generate infectious aerosols. Tuberculin skin test conversions have occurred in healthcare workers exposed to infected neonates *(302,303)*.

Candida

Candida species, most commonly *C. albicans* and *C. parapsilosis* (304,*305*,*306*), are important causes of HAIs in NICU infants. In a national point prevalence study conducted by

the Pediatric Prevention Network, *Candida* species were identified as the third most common cause of healthcare-associated bloodstream infection in NICU infants (14). Disseminated *Candida* infection also occurs and most commonly involves the kidneys; the heart, lungs, central nervous system, eyes, liver, spleen, bones, or joints may also be affected *(307)*. Although there is evidence that the incidence of infections due to *Candida* in NICUs is decreasing (304), invasive candidiasis remains an important cause of morbidity and mortality. The attributable mortality of invasive candidiasis is 11.9% in extremely low birth weight (ELBW) infants, and disease increases length of stay and hospital charges in older infants *(308)*. Neurodevelopmental impairment occurs in more than 50% of ELBW infants who survive an episode of candidemia *(309)*.

The highest rates of invasive candidiasis are in the smallest infants, and rates decline with increasing birth weight *(310)*. In a study of 4,579 infants, 11.4% of ELBW infants (birth weight 401–750 g) developed *Candida* infection *(309)*. Higher rates of disease are also seen in infants with gastrointestinal tract pathology, including congenital anomalies and NEC *(311)*. Central venous catheter use, intubation, and hyperalimentation are risk factors for invasive candidiasis *(306,312,313)*. Medications that increase the risk of *Candida* infection include third- and fourth-generation cephalosporins *(306,314,315)*, carbapenems (315), histamine-2 blocking agents *(306)*, and intravenous hydrocortisone *(316)*. Petrolatum ointment skin care increased the risk of invasive disease in neonates with birth weight of <1,000 g *(317)*. *Candida* colonization typically precedes disease. Endotracheal colonization in the first week of life identified VLBW infants at high risk to develop systemic disease *(318)*. While most *Candida* infections in NICUs are sporadic, common-source outbreaks have been associated with contaminated pressure transducers *(319,320)*, syringes *(57)*, and glycerin suppositories *(63)*.

Prevention of *Candida* infection in the NICU is a challenge. Antibiotic therapy is one modifiable risk factor, yet it is often impossible to withhold empiric antibiotic therapy in sick premature infants when bacterial infection cannot be excluded. Fluconazole prophylaxis decreases the rates of invasive candidiasis in premature infants. In one randomized, controlled trial, 100 infants of <1,000 g birth weight were randomized to fluconazole prophylaxis or placebo. Fluconazole was dosed at 3 mg/kg every third day for 2 weeks, every other day during weeks 3 and 4, and daily during weeks 5 and 6. Fungal infections decreased from 20% in the placebo group to 0 in the treatment group ($p = .008$) *(321)*. Similar results were achieved in a multicenter study that compared fluconazole dosing regimens to placebo. In infants weighing <1,000 g at birth, the incidence of invasive fungal infections was 2.7% in infants dosed with 6 mg/kg of fluconazole, 3.8% in infants dosed with 3 mg/kg of fluconazole, and 13.2% in placebo recipients (322). Individual centers have successfully implemented fluconazole prophylaxis for infants weighing <1,000 g at birth, reducing the incidence of *Candida* infections and essentially eliminating *Candida*-related mortality *(323)*. Recently published guidelines from the Infectious Diseases Society of America recommend that fluconazole prophylaxis be considered for neonates with birth weights of <1,000 g in nurseries with high rates of invasive candidiasis *(324)*. Although "high rates" are not specifically defined, it is noted that the incidence of invasive candidiasis in most NICUs is <5% in infants weighing <1,000 g, and ~1% in infants weighing 1,000 to 1,500 g.

Malassezia Species

Malassezia furfur, a dimorphic lipophilic yeast that causes tinea versicolor in older children, is an uncommon cause of fungemia in the NICU *(325)*. Receipt of intravenous lipids is the primary risk factor for invasive disease as lipids serve as a growth factor for this microorganism.

Malassezia pachydermatis, an animal pathogen, can also colonize infants in the NICU and cause fungemia in association with intravenous administration of lipids. Disease is generally mild *(326)*, but meningitis has been reported *(327)*. One NICU outbreak was associated with healthcare workers' pet dogs *(327)*.

Filamentous Fungi

Invasive infections with filamentous fungi are rare in the newborn, but sporadic cases of aspergillosis and zygomycosis have been reported. Spores may be inhaled as a result of environmental contamination with dust containing fungal spores such as may occur during hospital renovation or with faulty cleaning practices *(328)*. Alternately, puncture sites or wounds may be inoculated with the microorganisms. Contamination of nonsterile medical equipment, including adhesive tape and wooden tongue depressors used as splints to stabilize intravenous catheters, has been implicated *(329,330)*. Aspergillus infections in neonates present as cutaneous or disseminated disease. Gastrointestinal infections account for more than 50% of reported cases of zygomycosis in neonates; some cases mimic NEC, although pneumatosis intestinalis is absent *(331)*. Cutaneous and disseminated infections also occur. Extreme prematurity, acidosis, renal failure, and treatment with steroids are risk factors for invasive mold infections. Mortality rates are high, and diagnosis is often made only at autopsy.

Neonatal infection with dermatophytes is also rare. Healthcare providers with unrecognized infections were the sources of two nursery outbreaks of *Microsporum canis* skin infection *(332)*. In another outbreak, nurses were infected by contact with an infected newborn *(333)*.

Viral Infections

Up to 6% of all HAIs in the NICU are caused by viruses (334,*335*). In one prospective study, 1% of all NICU patients developed a viral infection (334). Outbreaks tend to reflect viral activity in the community. As with bacterial infections, vertical transmission may occur from an infected mother and contact with an infected healthcare worker, a visitor, or another infant may result in horizontal transmission. The symptoms of healthcare-associated viral infections can mimic those seen with bacterial sepsis. Symptoms include apnea, lethargy, feeding difficulties, and pulmonary infiltrates on chest radiograph.

Respiratory syncytial virus (RSV) outbreaks are common and have sometimes included large numbers of infants *(336–340)*. In one outbreak, 35% of newborns in the NICU for more than 6 days and 34% of the staff were infected *(336)* and in another, infections occurred in 84% of newborns in

the NICU for more than 3 weeks *(340)*. Pseudo-outbreaks have also been reported. The use of a rapid immunoassay led to an erroneous diagnosis of RSV in seven premature infants in one NICU, highlighting the need to employ confirmatory tests when viral outbreaks are suspected in a population expected to have low disease prevalence *(341)*. The false-positive results were attributed to cross-reactivity between the immunoassay and pulmonary surfactant that had been administered prophylactically at birth.

Concurrent outbreaks of RSV and rhinovirus *(337)* and RSV and parainfluenza virus *(339)* have been described. There is significant overlap in the symptoms seen with these three viruses, making respiratory virus testing important in the investigation and management of outbreaks. Crowding and understaffing may contribute to outbreaks of respiratory illness *(342,343)*, with attack rates of 63% in infants and 25% in personnel *(343)*.

Healthcare-associated influenza infections in neonates also occur. As with RSV, symptoms may be mild or may resemble bacterial sepsis. In two reported outbreaks, attack rates in neonates were 35% and 32% *(344,345)*. Low influenza immunization rates among healthcare providers may have contributed to the outbreaks. In one report, most nursery personnel had not received influenza vaccine, and 16% were symptomatic *(344)*. Immunization of healthcare personnel is an effective strategy for the prevention of disease in hospitalized neonates.

Healthcare-associated adenovirus infections may present as mild respiratory tract infections, conjunctivitis and gastroenteritis, or as severe pneumonia, sepsis syndrome, and death (334,*346*,*347*). Symptomatic maternal infection may result in severe neonatal disease, presumably because the newborn lacks passively transferred maternal antibody *(346)*. An outbreak of conjunctivitis and pulmonary disease was associated with ophthalmologic examination *(106)*. Healthcare-associated respiratory adenoviral infections may contribute to the development of bronchopulmonary dysplasia in premature infants *(347)*.

Enteroviruses

Neonatal enteroviral infections, including echovirus and Coxsackie B virus infections, occur in both newborn nurseries and NICUs and are commonly associated with community outbreaks *(348)*. Maternal infection may result in perinatal transmission. During a community outbreak, 3.4% of mothers were shedding enterovirus in the stool at delivery and reported transmission rates from mother to infant have ranged from 29% to 57%. Horizontal transmission occurs in the nursery by fecal–oral contamination.

Infants may be symptomatic within the first day of life. Personnel may also become infected and contribute to horizontal spread. Mild febrile illness and aseptic meningitis are the most frequent presentations, but disease may resemble bacterial sepsis. Severe hepatic necrosis or myocarditis may also occur.

Rotavirus

Rotavirus infections are common in hospitalized neonates. During a 25-month-long surveillance period, 12% of neonates hospitalized in six Brazilian special care nurseries were found to have rotavirus infection *(349)*. Viral excretion varied by season, with infection rates rising to 21% during "epidemic" periods. In another study, 53% of infants hospitalized in a special care nursery were found to excrete rotavirus; stools from more than half had detectable virus by the fifth day of life *(350)*. Others have demonstrated neonatal infection by 48 hours of life, suggesting a role for perinatal infection *(351–353)*.

The spectrum of disease associated with rotavirus infection in hospitalized neonates ranges from asymptomatic excretion of virus to severe, hemorrhagic diarrhea with dehydration *(354)*. Fever may occur with or without typical gastroenteritis symptoms *(355)*. Symptomatic disease is more common in infants who develop disease after 7 days of age *(355)*. Preterm infants infected with rotavirus are less likely than term infants to experience watery diarrhea and more likely to exhibit bloody mucoid stools, abdominal distention, and intestinal dilation *(356)*. Rotavirus has also been associated with an attenuated form of NEC *(356)*.

Hospital outbreaks of rotavirus are well described *(357)*. Rotavirus can survive on hands for at least 4 hours and on environmental surfaces for many days, factors that facilitate healthcare transmission *(358,359)*. Improved hand hygiene by healthcare personnel has been shown to decrease healthcare-associated transmission of rotavirus in children *(360)*.

Herpes Simplex Virus

The frequency of neonatal HSV infection varies from 1/12,500 to 1/6,000 live births *(361)*. Most infections result from exposure to the virus in the maternal genital tract at the time of delivery, with 50% to 80% of infected infants born to mothers with newly acquired disease *(362,363)*. The use of fetal scalp monitors may increase the risk of transmission.

Transmission of HSV in the nursery is rare, but small outbreaks have been described *(364)*. Infection has been transmitted to an infant suctioned by a healthcare worker with orolabial lesions *(365)* and during ritual circumcision that involves oral suctioning of the wound *(366)*.

Varicella-Zoster Virus

Varicella is transmitted by the airborne route, and transmission may occur before onset of the rash. Fortunately, varicella is rare in newborns, because most adults are immune and most infants are protected by maternal antibody. The newborn is at risk for severe perinatal disease when acquired from a mother who has onset of varicella lesions from 5 days before to 2 days after delivery, presumably because virus but no antibody is transmitted to the fetus *(367,368)*. Prophylactic varicella-zoster immune globulin or intravenous immune globulin (IVIG) is recommended for these newborns. Varicella may still occur despite the administration of prophylaxis. Airborne and Contact Precautions are recommended for infants born to mothers with acute varicella and should be continued for hospitalized infants for 21 days (or 28 days if varicella immune globulin or IVIG is given). Infants with varicella embryopathy from *in utero* exposure to varicella zoster virus do not require isolation unless they have active lesions.

Varicella may be introduced into the nursery by mothers, employees, or visitors with unrecognized infection *(369,370)* or by an infant with perinatal varicella *(371)*.

Hospitalized premature infants exposed to varicella are at risk for severe disease. Prophylaxis with varicella immune globulin or IVIG is recommended for exposed infants born at ≥28 weeks of gestation to mothers who lack a reliable history of chickenpox or serologic evidence of protection against varicella, and for all infants born at <28 weeks of gestation or with birth weights of <1,000 g (*367*,*368*). Airborne and Contact Precautions are indicated from 8 to 21 days after exposure; when varicella-zoster immune globulin or IVIG is given, precautions are continued for 28 days.

Parents and healthcare workers who receive live-attenuated varicella vaccine need not be excluded from the newborn nursery or NICU unless a rash develops after immunization. Transmission of vaccine-associated virus is rare and has occurred only when the immunized individual developed a rash *(367)*.

Cytomegalovirus

Approximately 1% of all newborns are infected with CMV *in utero*, but 85% to 90% are asymptomatic at birth *(372)*. Severe disease occurs when the mother has primary CMV infection in pregnancy *(373)*. Perinatal transmission of CMV, either as a result of exposure to the virus in maternal cervical secretions at the time of delivery or through receipt of CMV-containing breast milk, is usually asymptomatic. Some infants present with mild self-limited pneumonia or hepatitis at 1 to 4 months of age *(374)*. Severe disease may occur in premature infants with birth weight of <1,500 g, presumably because they receive little maternal antibody (*375*,376).

Severe disease in low birth weigh infants was described with transfusion-related CMV. Infants developed a sepsis-like syndrome with hepatomegaly, respiratory deterioration, and atypical lymphocytosis, and some died *(70)*. Transfusion-related CMV is of historical interest, but unlikely when leukoreduced or CMV-negative blood products are used. Transmission of CMV between infants in the NICU has been reported *(377)* but is extremely rare *(378)*.

Hospitalized infants with congenital or perinatal CMV infection are managed with Standard Precautions *(367)*. Transmission of CMV to healthcare personnel is unlikely if hand hygiene is performed after contact with urine or saliva.

Human Immunodeficiency Virus

Mother-to-child transmission of human immunodeficiency virus infection may occur *in utero*, at delivery, or postnatally through breast milk. A comprehensive strategy to reduce transmission, including universal HIV testing of all pregnant women, prophylaxis of infected women during pregnancy, labor, and delivery, prophylaxis of exposed infants during the first 6 weeks of life, elective cesarean section for women with viral loads of >1,000 copies/mL, and complete avoidance of breast-feeding, may reduce mother-to-child transmission from 25% to 30% to <2% *(379)*. Unfortunately, transmission continues to occur, even in locales with the infrastructure and resources to implement these strategies *(380)*.

In countries with resources for antiretroviral treatment, screening for HIV should be part of routine prenatal care, and all pregnant women with HIV infection should be offered antiretroviral therapy. All normal newborn and special care nurseries should have protocols in place to identify HIV-exposed infants, even if the mother's HIV infection was unrecognized prior to delivery *(381)*. For neonates born to mothers whose HIV serostatus is unknown, rapid HIV antibody tests should be performed on the mother or the infant so that antiretroviral prophylaxis may be provided to HIV-exposed infants within 12 hours of birth. Consent for such testing should be obtained in accordance with local laws. Prophylaxis is continued for 6 weeks, during which time infants should be monitored for drug-related, hematologic toxicities. Mothers known to be HIV-infected should not breast-feed if safe alternatives to breast milk are available.

Hepatitis B and C

The newborn may acquire HBV from a mother with chronic or acute infection in pregnancy. Infection is almost always asymptomatic at birth, but 90% of infants infected perinatally develop chronic HBV infection and are at risk for the development of hepatocellular carcinoma or cirrhosis. Administration of hepatitis B hyperimmune globulin and vaccine at birth prevents infection in the newborn, and neonatal units should have procedures in placed to ensure that all exposed newborns receive appropriate prophylaxis *(367)*.

Approximately 5% of infants born to women seropositive for HCV acquire infection *(367)*. Whether transmission occurs *in utero* or intrapartum is not known, but increased rates of transmission have been associated with increased maternal HCV viral load and coinfection with HIV. Although HCV has been detected in colostrum, breast-feeding does not appear to increase the risk of transmission. Infection in the newborn is usually asymptomatic, but 50% to 60% develop persistent infection. Prophylaxis for HCV exposure is not available *(367)*.

PREVENTION AND CONTROL OF INFECTIONS

The foundation of an infection prevention program in the NICU is similar to those for other at-risk patients. The program will identify infection risks through active surveillance, implement evidence-based practice to mitigate those risks, and monitor compliance. Appropriate infrastructure, encompassing both physical design and staffing, is crucial. Routine care practices for the neonate should promote healthy growth and development while minimizing the acquisition of pathogenic microorganisms.

Elements of an Infection Control Program

Surveillance Surveillance for HAIs is essential for infection prevention. Surveillance permits early detection of infection trends and clusters and identification of new risks, provides information on which to base empiric antibiotic therapy, and is one measure of quality of care (382). Targeted surveillance is generally more feasible and potentially of greater value than surveillance for all infections. A risk-assessment provides useful information to guide targeted surveillance.

Surveillance in the normal newborn nursery should concentrate on infections likely to be associated with

nursery outbreaks such as staphylococcal or streptococcal skin infections, gastroenteritis, and other viral infections. Because many of these infections manifest only after discharge, communication with community healthcare providers is essential. In intensive care settings, targeted surveillance may include device-associated infections such as CLABSIs or VAP, rates of colonization or infection with MDR microorganisms such as MRSA or VRE, or cases of healthcare-associated viral transmission. The use of standard definitions, such as those endorsed by NHSN, allows for accurate comparison of rates over time and benchmarking with similar institutions. Effective surveillance requires collection of appropriate denominators, including device utilization days and patient days stratified by birth weight.

Routine surface cultures from the skin and mucous membranes of hospitalized neonates are generally not helpful, because colonization is not a good positive predictor of infection and correlation of isolates from surveillance cultures and invasive infections has been poor *(138,383,384)*. Targeted surveillance for MDR microorganisms such as MRSA may be helpful when routine infection control procedures fail to control transmission *(385)*. Screening cultures of all intensive care unit patients to detect MRSA colonization is now required by law in some states *(386)*. In outbreaks, surveillance cultures may be indicated to identify colonized infants for purposes of cohorting or isolation or for assessment of risk factors for acquisition of the microorganism (382).

Hand Hygiene Hand hygiene before and after each patient contact reduces the incidence of HAIs in NICUs and other settings *(387)*. Compliance, however, is difficult to monitor and enforce, and studies show poor compliance with this procedure in the NICU *(388–391)*.

Guidelines for Hand Hygiene in Healthcare Settings were published in 2002 by the Healthcare Infection Control Practices Advisory Committee at the CDC (392). Additional recommendations for hand hygiene are included in the Guidelines for Perinatal Care published by the AAP and the American College of Obstetricians and Gynecologists. Before handling neonates for the first time on a work shift, personnel should scrub their hands and arms to above the elbows with an antiseptic soap. Hands should be rinsed thoroughly after washing and dried on paper towels. Watches, rings, and bracelets should be removed. Nails should be trimmed short, and no false fingernails should be worn (382,392). The Guidelines for Perinatal Care recommend a 10-second wash with soap and vigorous scrubbing before and after each patient contact and after touching objects in the patient's environment, while Healthcare Infection Control Practices Advisory Committee guidelines recommend use of an alcohol-based hand rub unless hands are visibly soiled. Use of alcohol-based products has been associated with increased hand hygiene compliance in neonatal units *(391)*. Neonatal units should have a program in place to monitor healthcare provider compliance with hand hygiene, and provide feedback to personnel.

Isolation Precautions Revised guidelines for isolation precautions for hospitalized patients were published by CDC in 2007 and are discussed in detail in Chapter 90 *(393)*. These guidelines include a comprehensive review and detailed recommendations for the prevention of infections due to MDR microorganisms in healthcare settings including NICUs *(385)*. Standard Precautions refer to precautions to be taken with all patients to reduce transmission from recognized and unrecognized sources of infection. Additional transmission-based precautions (Airborne, Droplet, and Contact) are used when caring for patients infected or colonized with microorganisms transmitted by these routes. Implementation of isolation precautions in neonatal units may pose unique challenges.

Although single rooms are recommended with Droplet and Contact Precautions, they are not mandatory and may not be available in all NICUs. Separate isolation rooms are not considered to be necessary for newborns if the following conditions are met: (a) the infection is not transmitted by the airborne route, (b) there is sufficient space for a 4- to 6-ft aisle between infant stations, (c) there are an adequate number of nursing and medical personnel and they have sufficient time for hand hygiene, (d) an adequate number of sinks are available for hand washing, and (e) continuing instruction is given to personnel about the ways that infections are spread (382). When multiple infants require isolation precautions for the same symptoms or colonization with the same MDR microorganism, an isolation area can be defined in the nursery or NICU by curtains, partitions, or other markers. Infants on Droplet Precautions should be separated from one another by at least 3 ft. A closed incubator may be helpful in maintaining barrier precautions, but because incubator surfaces and entry ports readily become contaminated with the microorganisms carried by the infant, the outside of the incubator should be considered contaminated and the boundaries of the isolation area should extend beyond the incubator itself. Forced-air incubators cannot be substituted for isolation rooms when Airborne Precautions are required, because of the discharge of unfiltered air into the nursery. Infants with suspected measles, varicella, or tuberculosis should be cared for in a negative pressure isolation room.

The necessary duration of Contact Precautions for infants colonized with MDR microorganisms such as MRSA and ESBL-producing gram-negative bacilli remains unknown. Some infants remain hospitalized for months to >1 year, and the potential adverse effects of prolonged isolation have not been studied in this population. Close contact between infants and their parents, as well as other caregivers, promotes bonding and is important for normal infant development. The need for parents to wear personal protective equipment when interacting with infants on isolation precautions is an unresolved issue and requires further study *(393)*.

Antimicrobial Stewardship Because hospitalized neonates are at risk for HAIs, they are frequently exposed to both empiric and therapeutic courses of broad-spectrum antibiotics *(394,395)*. In one point-prevalence study involving 29 US NICUs, 43% of NICU patients were receiving antimicrobials with a median number of two agents. While few studies have assessed the appropriateness of antimicrobial prescribing in this population, a study involving four NICUs characterized 25% of antibiotic courses and antibiotic days as inappropriate based on CDC guidelines. Inappropriate use of both vancomycin and carbapenems was noted (396).

Antibiotic exposure is a risk factor for colonization and infection with *Candida* and MDR bacteria. Antimicrobial stewardship interventions are needed to improve antimicrobial prescribing for NICU patients and reduce the emergence of MDR microorganisms (see also Chapters 86 and 87).

Prevention of Device-Associated Infections

Technologic advancements in neonatal care have given rise to new and sometimes unexpected infection risks. As a general principle, whenever a new invasive procedure or device is introduced, the potential risk for HAI should be considered, protocols established to minimize this risk, and surveillance initiated to monitor for infection. Exposure to an invasive device is a prerequisite for a device-associated infection. The need for any invasive device should be assessed daily, and use should be discontinued promptly when no longer essential. Bundled implementation of evidence-based infection prevention strategies is thought to be more effective than implementation of any single intervention.

Central Line–Associated Bloodstream Infections Guidelines have been published for the prevention of CLABSIs in adults and children *(397,398)*. Recommended strategies include (a) education and training for healthcare personnel who insert and maintain catheters; (b) use of maximal sterile barrier precautions during central venous catheter insertion and use of an insertion checklist; (c) 2% chlorhexidine gluconate (CHG) for skin antisepsis before catheter insertion in infants at least 2 months of age; (d) replacement of administration sets not used for blood products, lipids or propofol no more frequently than every 96 hours but at least every 7 days; and (e) avoidance of routine catheter replacement as an infection prevention strategy. Additional recommendations for the management of umbilical arterial and venous catheters, devices used exclusively in neonates, are listed in Table 52-2. The use of "bundled" strategies for catheter insertion and maintenance is emphasized, although the recommended components of such bundles are not provided.

Modifications to these recommendations may be indicated for NICU patients. Evidence-based guidelines recommend CHG-based products for skin antisepsis before central line insertion and with dressing changes. Notably, use of CHG as part of an insertion bundle has been demonstrated to reduce CLABSI rates in adults *(399)*. However, CHG is not currently approved by the U.S. Food and Drug Administration (FDA) for use in children <2 months of age, because safety and efficacy data are lacking in this population.

Modified strategies may be needed for NICU patients. For example, use of chlorhexidine gluconate (CHG) as part of an insertion bundle has been demonstrated to reduce CLABSI rates in adults *(399)*, and evidence-based guidelines recommend CHG-based products for skin antisepsis before central line insertion and with dressing changes. However, the U.S. Food and Drug Administration has not approved CHG for use in children <2 months of age, because safety and efficacy data are lacking in this population.

The Association of Women's Health, Obstetric Nurses and Neonatal Nurses (AWHONN) has acknowledged the benefits of CHG for skin antisepsis and has suggested that it can be used in neonates if applied judiciously, without splashing or excess solution and if removed after the procedure is complete *(400)*. Because of concerns about skin irritation, AWHONN skin care guidelines recommend aqueous CHG rather than an alcohol-containing preparation for infants <34 weeks of gestation.

Published data about CHG use for central venous catheter care in neonates are limited. In one study, 48 infants ≥1,500 g birth weight (BW) and at least 7 days of age were randomized to 2% CHG or 10% povidone-iodine for preparation of catheter insertion sites and for use with dressing changes *(400a)*. Severe dermatitis did not occur in the CHG group. Cutaneous absorption of CHG was documented but was not associated with systemic toxicity. This small study was underpowered to show a difference in CLABSI or clinical sepsis. The enrolled infants were relatively mature (mean BW of 2,000 g and 32–33 weeks of gestation) and whether the results can be generalized to younger or more premature infants is unknown.

A study in less mature neonates did demonstrate CHG-related dermatitis. When an Australian NICU employed 2% aqueous CHG for central line insertion and maintenance, 4/26 infants <1,000 g BW and <48 hours of age developed severe skin irritation (redness = 3; skin breakdown = 1) *(401)*. Use of a chlorhexidine-impregnated dressing has been associated with dermatitis in low birth weight neonates *(402)*.

Nevertheless, a recent survey of neonatology training program directors confirms that off-label use of CHG is common in NICUs. Sixty-one percent of survey respondents reported using CHG in their NICUs *(403)*. Prospective trials are needed to identify the safest CHG preparation for neonates as well as the optimal application technique. CHG

TABLE 52-2

Recommendations for the Management of Umbilical Artery Catheters

Remove and do not replace umbilical artery catheters if any of the following are present:
CLABSIs
Vascular insufficiency in lower extremities
Thrombosis
Remove and do not replace umbilical vein catheters if either of the following are present:
CLABSIs
Thrombosis
Replace umbilical venous catheters only in the setting of catheter malfunction
Cleanse umbilical insertion site with antiseptic before catheter insertion
Avoid tincture of iodine because of the potential effect on the neonatal thyroid
Avoid topical antibiotics or creams at the catheter insertion site
Add low doses of heparin (0.25–1 U/mL) to fluids infused through umbilical artery catheters
Remove umbilical artery catheters after 5 d (or sooner if they are no longer needed)
Remove umbilical vein catheters after 14 d (or sooner if they are no longer or have not been managed aseptically)

is applied to the skin of older children and adults, using a scrubbing motion, but this may not be ideal for neonates because of their fragile skin.

Individual centers and statewide collaborative groups *(404)* have reported decreases in NICU CLABSI rates coincident with adoption of central catheter insertion and maintenance bundles. Although variation exists in the components of these bundles, core strategies were similar to those implemented by a group of 22 NICUs in California (Table 52-3). This collaborative also developed auditing tools for monitoring critical processes such as central line set-up and entry and investigated all possible CLABSIs concurrently with bedside interviews and observation. CLABSI rates fell 25% during the first year of the project.

When rates of CLABSIs remain elevated despite consistent, documented compliance with evidence-based practices for catheter insertion and maintenance, additional interventions may prove beneficial. Lock therapy is a promising strategy for the prevention of CLABSIs. Filling the lumen of a catheter with a supraphysiologic concentration of an antibiotic or agent such as ethanol may prevent or eliminate the bacterial colonization that ultimately results in CLABSIs. Current guidelines suggest that lock therapy could be useful in certain high-risk patients or those with recurrent infections. However, few studies have evaluated lock therapy in neonates.

TABLE 52-3

Sample Insertion and Maintenance Bundles for the Prevention of Central Line-Associated Bloodstream Infections in the NICU

Insertion
Maximal sterile barrier precautions
Skin disinfection with chlorhexidine or povidone–iodine
Dedicated team for catheter placement and maintenance
Availability of all supplies at the bedside at start of procedure
Hand hygiene standards met
Insertion checklist used
Staff empowered to stop nonemergent procedure if sterile technique is not followed
Maintenance
Daily assessment and documentation of catheter need[a]
Daily review of dressing integrity, cleanliness
Closed systems for infusion, blood draws, and medication administration
Infusion tubing assembled and connected aseptically or sterilely
Scrub of needless connecters with friction for at least 15 s before line entry[b]
Clean for all line entries (hand hygiene before and after glove use)
Use of prefilled, flush-containing syringes when feasible

[a]When catheter used primarily for nutritional purposes, catheter removal considered when infant receiving ≥120 mL/kg/d enteral nutrition; discontinuation of intravenous lipids considered when infant receiving >2.5 g/kg/d enteral fat.
[b]Alcohol or chlorhexidine used.

Vancomycin–heparin locks were studied in a prospective randomized double-blind trial in NICU patients. When definite and probable BSIs were considered, there were significantly fewer infections in the lock group (2.3 vs. 17.8/1,000 catheter days; relative risk 0.13: 95% confidence interval: 0.01–0.57) (111). Similar results were observed in an Italian trial of a fusidic acid–heparin lock in neonates *(405)*. To date, however, few centers employ antibiotic lock therapy for primary prevention of CLABSIs in NICU patients.

Ventilator-Associated Pneumonia Recommendations for the prevention of VAP in children and adults have been published, although not all of the recommended strategies are applicable for NICU patients *(406)*. For example, elevation of the head of the bed to 30 to 45 degrees is not feasible in a 1,000-g infant. Moreover, the optimal products and regimens for oral care in ventilated newborns are not known.

Few published data inform VAP prevention strategies in neonates. A closed endotracheal suction system did not prevent the development of VAP or bacterial airway colonization in a study of 133 ventilated NICU patients. However, the majority of nurses involved in the study (40/44) found the system easier to use than an open suction system and better tolerated by infants *(139)*. In a study involving 60 relatively mature infants (mean birth weight 2,100 g), mechanically ventilated patients were randomized to supine or lateral positioning. Although rates of VAP *per se* were not reported, infants positioned on their sides were less likely to have new or persistent infiltrates on chest radiographs (20% vs. 67%; $p < .01$) or positive endotracheal tube cultures after 5 days of mechanical ventilation (30% vs. 87%; $p < .01$) *(407)*. In one NICU with high rates of VAP, increasing hand hygiene compliance before and after patient contact was temporally associated with a decrease in infections from 16.9/1,000 ventilator days to 6.4/1,000 ventilator/days ($p = .37$) (408). The Institute for Healthcare Improvement has made recommendations for the prevention of VAP in pediatric patients (409). An example of a VAP bundle for neonates is presented in Table 52-4.

Infrastructure

Design Nursery design should provide adequate space for appropriate care of the infant and for the necessary equipment and sufficient numbers of strategically placed sinks. Specific recommendations include a space of 30 net square feet per neonate with at least 3 ft between bassinets in the normal newborn nursery *(410,411)*.

For continuing care of low-birth-weight infants who are not ill but require more nursing hours than term infants, 50 square feet per infant with 4 ft between bassinets is recommended. Intermediate-care nurseries should have 120 square feet per patient station if subspecialty care is required, with at least 4 ft between incubators or bassinets. Five-foot-wide aisles are recommended in multiple bed rooms and 8-foot-wide aisles in single patient rooms, or fixed-cubicle partitions should have 150 square feet per infant with at least 6 ft between incubators and 8-foot-wide aisles. There should be one sink for every six to eight patients in the normal newborn nursery and one sink for every three or four patients in intermediate- and intensive-care nurseries. Each nursery should have access to at least one negative pressure

TABLE 52-4

Sample Bundle for Ventilation-Associated Pneumonia Prevention in the NICU

Elevate the head of the bed 15 to 30 degrees to prevent aspiration
Age-appropriate comprehensive mouth care
Meticulous hand hygiene before handling ventilator circuit
Drainage of ventilator circuit condensate away from patient every 2–4 h
Daily assessment of extubation readiness
Use heated ventilator circuits
Change ventilator circuits and in-line suction devices only when soiled
Store oral suction devices in clean, nonsealed plastic bag

isolation room, with exhaust air vented to the outside, to accommodate newborns with airborne infections (382,*411*).

Nursery design has the potential to impact rates of HAI. One NICU noted a decrease in catheter-associated BSIs (10.1/1,000 device days to 3.3/1,000 device days) coincident with the adoption of single patient rooms for the care of critically ill neonates *(412)*.

Staffing Staffing should be sufficient to allow for adequate care of infants with sufficient time for hand hygiene between patient contacts. For normal newborn nurseries, recommendations are one nurse for every six to eight infants or for every three to four mother–infant pairs. A ratio of one nurse for every two to three patients is recommended in intermediate-care units and of one nurse for every one to two patients in NICUs *(410)*. Understaffing has been linked to increased rates of BSIs, as well as the transmission of MRSA and gram-negative pathogens *(413)*.

Employee Health Healthcare personnel can serve as sources of infection for infants in newborn and neonatal intensive care nurseries *(410)*. At hire, personnel should be screened for immunity to rubella, measles, mumps, varicella, and HBV *(414)*. Susceptible workers should be offered vaccination. Annual influenza vaccine is indicated for all healthcare providers and either inactivated, injectable vaccine or live-attenuated, intranasal vaccine is appropriate for personnel who work with neonates. Tuberculin reactivity should be determined on employment and periodically; the frequency of testing is based on local epidemiologic data *(414)*. Because adults including healthcare workers can transmit pertussis to susceptible infants, a single dose of tetanus–diphtheria–acellular pertussis vaccine is recommended for all healthcare workers *(415)*. Although Tdap vaccines are licensed for individuals <65 years of age, in January 2011, the ACIP recommended a single dose of Tdap for all adults 65 years and older, including healthcare providers, who anticipate having close contact with an infant <12 months of age *(415a)*.

It is important that employees understand the risks of transmitting infections to newborns and report acute infections for assessment. Employee health policies should encourage reporting of symptoms and not penalize workers who stay away from work because of illness.

Decisions to furlough workers should be made on an individual basis, taking into consideration the mode of transmission of the particular infection and the ability of the employee to comply with preventive measures.

Individuals with active tuberculosis should be excluded from patient care until adequate treatment is completed and the noninfectious status has been verified. Employees with exudative or herpetic hand lesions should not have direct patient contact or handle patient care equipment. Personnel with herpes labialis are unlikely to transmit infection but should avoid touching the lesions during patient care and cover any external lesions (382). Nonimmune persons exposed to varicella, measles, or rubella should not work during the latter part of the incubation period, because these diseases may be transmitted for a few days before eruption of the rash *(367)*.

Personnel should take precautions to minimize the risk of potential infection with blood-borne viruses and should be familiar with hospital protocols for postexposure prophylaxis after occupational exposures to blood (382) (see also Chapters 73 and 74).

Special Attire In general, special attire is not required for routine care of most infants in newborn nurseries or intensive care units. Most nurseries provide scrub suits or dresses that are laundered by the hospital for personnel spending most of the day in the nursery. This practice may prevent soiling of personal clothing and may be reassuring to parents in providing easy recognition of personnel but should not be considered an infection control measure. Several studies have shown that wearing of cover gowns over scrubs suits or street clothes has no effect on colonization or infection rates in the newborn nursery or the NICU *(389,416–419)* and does not improve hand hygiene compliance. Cover gowns need not be worn for entry to the NICU or for provision of routine care unless an infant is on Contact Precautions. Additional recommendations from the AAP are for a long-sleeved gown to be worn by personnel holding newborns outside of the bassinet or incubator (382).

Decontamination and Cleaning The nursery should be kept clean and dust free by daily cleaning using cleaning methods that minimize dust dispersal. Quaternary ammonium, chlorine, and phenolic compounds are satisfactory low-level disinfectants for nursery cleaning (382). These do not sterilize but reduce the concentration of microbes to an acceptable level. Phenolic compounds should be used with caution, because inappropriate use has been associated with absorption by the newborn resulting in hyperbilirubinemia *(420)*.

NICU equipment should be maintained free of dust, because fungal spores from dust may result in serious infections. Responsibility for the cleaning of delicate equipment, especially monitoring equipment, radiant heaters, or infant care units in constant use, must be clearly assigned, because these items are often not handled by the regular cleaning personnel *(20)*. Incubators, open care units, and bassinets should be cleaned between infants and changed and cleaned periodically for those infants with prolonged stay (382).

Humidifier reservoirs in incubators are potential sources of *Pseudomonas, Legionella,* and other water-borne microorganisms. During periods when the incubator humidifier is in use, the reservoir should be drained, cleaned, and refilled with sterile water every 24 hours (382). When humidification is required, use of a humidifier external to the incubator may facilitate appropriate cleaning.

Nebulizers and attached tubing and water traps should be replaced regularly with equipment that is sterile or has undergone high-level disinfection (382). Only sterile water should be used in these devices, and residual water should be discarded when they are refilled.

New garments and linens should be laundered before use. Linen for newborns does not need to be autoclaved as this has not been shown to reduce infections in hospitalized neonates (382). Clean linen should be transported to the nursery or NICU in covered carts and stored in closed cabinets to prevent dust contamination. Used linen should be handled as little as possible to avoid hand contamination and aerosolization of microorganisms.

Care of the Hospitalized Neonate

Skin and Cord Care Once the newborn's temperature has stabilized, blood and meconium should be removed with sterile cotton sponges (not gauze) and warm water. Alternately, the newborn can be bathed with a mild, nonmedicated soap followed by careful rinsing with water. Soap should be supplied in a single-use container or reserved for use with one infant. Because of potential exposure to blood-borne viruses, personnel should wear gloves when handling the neonate until this has been done (382). Localized skin care using warm water and a mild soap for the diaper area and other soiled areas may be sufficient throughout the nursery stay. Whole-body bathing and antiseptic agents are not necessary for routine newborn care but may be indicated in outbreaks if the benefits outweigh the risks. In the 1970s, bathing infants with hexachlorophene effectively reduced staphylococcal disease in some settings *(421)* but reports of neurotoxicity led to a discontinuation of this practice *(422)*.

Care should be taken to avoid damage to the newborn skin from excessive drying, manipulation, exposure to irritating chemicals, or other trauma *(423)* The skin of the premature infant is especially fragile, and minor trauma such as removal of adhesive tape or oxygen probes may remove the outer layer of the epidermis. Prophylactic application of topical ointments to the skin of neonates to improve barrier function has been shown to increase the risk of coagulase-negative staphylococcal infection as well as any HAI *(424)*. Routine use of topical ointments is not recommended.

The optimal regimen for umbilical cord care remains controversial. A recent Cochrane review examined the use of topical antibiotics and antiseptics for umbilical cord care *(425)*. Twenty-one studies involving 8,959 participants were included, the majority of which were from high-income countries. Neither the use of antibiotics nor antiseptics for cord care reduced the incidence of local infection, although there was a trend to reduced colonization with antibiotics. Antiseptics prolonged the time to cord separation.

Eye Care The eyes of the neonate should be cleaned with sterile cotton to remove secretions and debris. Topical prophylaxis against gonococcal opthalmia neonatorum is mandatory for all infants immediately after birth. Acceptable agents include 0.5% erythromycin ophthalmic ointment or 1% tetracycline opthalmic ointment; either agent causes less chemical irritation than silver nitrate *(179)*. Single-dose containers should be provided. Topical prophylaxis appears to be ineffective against neonatal *Chlamydia* conjunctivitis. Strategies for the prevention of healthcare-associated conjunctivitis include scrupulous hand hygiene, protection of the eyes of infants during respiratory care, proper disinfection of ophthalmologic instruments, and use of eye drops only from single-dose vials whenever feasible *(102)*.

Infant Feeding Human milk is optimal for infant feeding *(426)*. Human milk provides immunologic and nutritional benefits and has been reported to reduce the risk of sepsis in premature infants *(427,428)*. When the sick newborn cannot suck, the mother may express and store breast milk. Routine microbiologic monitoring of milk expressed by a mother for her infant is not necessary or cost-effective *(410)*. Nevertheless, improper expression or storage of milk can result in contamination with a variety of bacteria, including *S. aureus* and gram-negative bacilli. Mothers should therefore be instructed about proper collection technique, including the performance of hand hygiene, to minimize bacterial contamination. Milk should be expressed into sterile containers and if a breast pump is used, part components in contact with milk should be washed with hot soapy water, rinsed thoroughly, and allowed to dry after each use *(444)*.

Freshly expressed milk should be refrigerated promptly and used or frozen within 48 hours. Fortified human milk should be used within 24 hours. Milk stored in the freezer compartment of a refrigerator should be used within 3 months; milk stored in a deep freeze at –20°C can be stored for 6 to 12 months. Frozen milk should be thawed in the refrigerator or quickly under running or fresh warm water, because standing water may become contaminated. Milk should not be subjected to excessive heat from hot water or a microwave oven. Thawed milk should be used promptly or stored in the refrigerator for up to 24 hours. Human milk is not sterile and bacterial growth can occur when expressed milk is held for several hours at room temperature, as occurs with continuous feeding. The hang time for human milk should not exceed 4 hours and continuous feeding is employed, the syringe and tubing must be changed every 4 hours. There is no evidence that any healthcare worker has acquired a viral infection from handling human milk and as such, the Occupational Health and Safety Administration does not consider unprotected contact with human milk to be an occupational exposure. Nevertheless, many experts recommend that healthcare workers wear gloves when handling human milk.

Not all mothers are willing or able to provide breast milk for their infants. Banked human milk is an acceptable alternative provided that donors are appropriately selected and screened and donated milk is carefully collected, processed, and stored. Donor milk banks that belong to the Human Milk Banking Association of North America voluntarily follow guidelines drafted in consultation with the CDC and the FDA. Donors are screened for hepatitis B surface antigen (HbsAg) and

antibodies to HIV-1, HIV-2, human T-lymphotrophic virus 1 (HTLV-1), HTLV-2, hepatitis C, and syphilis. Donated milk is heat treated at 62.5°C (144.5°F) for 30 minutes and is released only if bacterial cultures yield no pathogenic microorganisms. Fresh human milk from unscreened donors is not recommended because of the risk of transmission of infectious agents.

Inadvertent administration of stored breast milk to the wrong infant occasionally occurs and may result in exposure to infectious agents *(429,430)*. Therefore, accidental exposure to breast milk is treated in the same manner as accidental exposure to other potentially infectious body fluids. Counseling is necessary for both the mother who provided the milk (donor mother) and the mother of the infant who mistakenly received the milk (recipient mother). Confidentiality must be maintained for both families. Both should be screened for hepatitis B and HIV; some experts would also test for HTLV. Evaluation and treatment of the exposed infant must be individualized based on the results of this screening *(431)* (Table 52-5). Processes and procedures that reduce medication errors may have applicability to the prevention of human milk misadministration *(432)*.

Detailed guidelines for aseptic preparation of infant formula have been published by the American Dietetic Association *(433)*. Powdered infant formula is not sterile and should be avoided in infants at high risk for invasive disease *(129)*. Since powdered formulas are not sterile, they should be used only when no commercially sterile liquid products are available. Formula made from liquid concentrates or powders must be prepared with chilled, commercially sterile water using aseptic technique. If commercially sterile water is not available, water may be boiled for 1 to 2 minutes and then cooled before use. Because blenders may be difficult to clean, the use of stainless steel mixing bowls and electric beaters or whisks are preferred for formula preparation. Formula should be bottled in quantities for individual feeds or for 4 hours continuous feeding, refrigerated for a maximum of 24 hours, and used within

TABLE 52-5

Sample Plan for Managing Inadvertent Exposure to Hepatitis B and HIV through Human Milk[a]

Donor Mother[b]	*Recipient Mother*	*Treatment of Infant Recipient*
Management of Potential Hepatitis B Exposure		
Hepatitis B surface antigen negative	Hepatitis B surface antigen negative	Hepatitis B vaccine given according to the routine infant immunization schedule
	Hepatitis B surface antigen positive	Administer hepatitis B vaccine and hepatitis B immune globulin (HBIG) if not yet given
Hepatitis B surface antigen positive	Hepatitis B surface antigen negative	Administer hepatitis B vaccine (if not yet given) and HBIG
Hepatitis B surface antigen positive	Hepatitis B surface antigen positive	Administer hepatitis B vaccine and HBIG if not yet given
Management of Potential HIV Exposure		
Negative	Negative	Standard infant care
	Positive	If receiving AZT and standard therapy for infants born to HIV-positive mother, no additional therapy
Positive by ELISA with Western Blot confirmatory test	Negative	No standard for AZT prophylaxis but could be considered in high-risk situations. Consultation with expert in HIV care recommended
	Positive	Standard prophylactic treatment for infant born to HIV-positive mother. Consultation with expert in HIV care recommended

[a]Treatment options should be discussed with the family and care individualized.
[b]When the donor mother refuses or is not available for testing, treatment with hepatitis B vaccine is given. Some experts would treat with HBIG.
(Compiled from recommendations by the Human Milk Banking Association of North America. *Best practices for expressing, storing and handling human milk in hospitals, homes and child care settings*, 2005; and American Dietetic Association. *Infant feedings: guidelines for preparation of formula and breast milk in health care facilities*, 2005. Readers may wish to consult the latest ADA Guidelines: Pediatric Nutrition Practice Group. Infant feedings: Guidelines for the preparation of human milk and formula in health care facilities, second edition. Robbins ST, Meyers R, eds. Chicago, IL: American Dietetic Association, 2011.)

4 hours of opening. Any formula remaining after the 4-hour "hang time" should be discarded. The American Dietetic Association recommends that tubing and feeding reservoirs also be changed every 4 hours. Formulas containing probiotics should not be feed by continuous infusion.

All facilities should have a Hazard Analysis and Critical Control Point (HACCP) plan for human milk, infant formula and enteral feeding. This plan should include all aspects of the feeding process, including preparation, storage, delivery and administration, and be integrated into a facility's overall performance improvement program.

Blood Development of guidelines for administration of blood products to hospitalized neonates and strict adherence to these guidelines in order to limit exposure to blood products is the best way to prevent transmission of bloodborne pathogens. Nevertheless, many premature or ill newborns receive blood products *(434,435)*. All cellular blood products given to low-birth-weight infants should be from CMV-seronegative donors or leukoreduced to remove CMV. Some centers use these products for all newborns.

Family-Centered Care The family-centered care model recognizes the importance of parents and families in the care of sick newborns. Active engagement and participation in care is encouraged, and while a number of benefits have been described, the associated infection risks have not been well studied.

The kangaroo care model was initially described in Colombia in the 1970s as a model for home care of low-birth-weight infants. The key components include 24-hour skin-to skin contact with the infant positioned upright on the mother's chest, and exclusive or nearly exclusive breast-feeding. The original model is still employed in resource-limited settings, and several studies have suggested a benefit for infant outcomes, including decreased infections *(436)*. In more affluent settings, kangaroo care has been implemented as skin to skin contact that lasts at least 1 hour per day, is thought to promote bonding and improved physiologic and is not typically associated with an increased risk of infection *(437)*. In one small study in Japan, kangaroo care increased the risk of developing an MRSA infection (odds ratio 3.82; $p = .033$) *(191)*.

Even when kangaroo care is not employed, most neonatal units promote physical contact between mothers and their infants. Transmission of maternal flora to the newborn usually occurs during delivery, and postpartum separation of the mother and the newborn is rarely desirable or necessary, even when the mother has an active infection. Most maternal postpartum infections are urinary or gynecologic infections that arise from endogenous flora. The mother with a communicable infection should perform hand hygiene before handling the infant and take measures to prevent contact of the infant with potentially contaminated clothing, bedclothes, tissues, and other fomites (382).

When a mother has untreated pulmonary tuberculosis, separation is necessary until both mother and baby are receiving antituberculous therapy. When MDR tuberculosis is suspected, the infant should be separated from the mother and neonatal immunization with Bacille Calmette-Guérin vaccine should be considered. The newborn who has received varicella immune globulin or IVIG may remain with the mother with varicella infection (382). Separation should be considered if a mother has extensive *S. aureus* infection with drainage not contained by dressings or if a mother has a GAS infection until she has received antibiotic therapy and the infection is no longer communicable (382). Rooming-in has traditionally been encouraged for infants born to mothers with acute seasonal influenza infection, although when mothers and infants are not interacting, infants should be placed in isolettes positioned at least 3 ft from the mother's bed. Mothers are advised to wear a surgical mask and to perform hand hygiene before each feeding or other contact with the infant for at least 5 days after the onset of infection *(438)*. Concerns about the virulence of a novel H1N1 influenza virus that circulated in 2009 and 2010 prompted more stringent recommendations for postpartum women known or suspected to be infected with this virus. Temporary separation of the mother and the infant was recommended until the mother had been treated with antiviral medication for at least 48 hours, was afebrile without antipyretics for at least 24 hours, and could control her cough and secretions *(439)*. The efficacy of this strategy relative to the one usually employed with seasonal influenza is unknown.

There are relatively few infection-related contraindications to breast-feeding. Human immunodeficiency virus can be transmitted via breast milk; in the United States and in other settings where safe, affordable, and sustainable alternatives to breast milk are available, HIV-infected mothers should not breast-feed their infants *(445)*. Likewise, mothers in the United States known to be seropositive for HTLV-1 and HTLV-2 should not breast-feed. Women with tuberculosis who have been treated with at least 2 weeks of antituberculous therapy and who are not considered contagious may breast-feed. Breast-feeding by HSV-infected mothers is permissible as long as there are no lesions on the breast and other cutaneous lesions can be covered. Although HBsAg has been detected in the milk of women infected with HBV, breast-feeding does not increase the risk of transmission to the infant. Hepatitis B vaccine and hepatitis B immune globulin are recommended for all infants born to HbsAg-positive mothers, including those who will be breast-fed. Although hepatitis C RNA has been detected in human milk, transmission of hepatitis C by breast-feeding has not been documented. Although HCV infection is not a contraindication to breast-feeding, infected mothers should be counseled about the theoretical risk of transmission and counseled not to breast-feed with cracked or bleeding nipples.

Cytomegalovirus can be transmitted by breast milk, although clinically significant disease is uncommon in term and near-term infants. Conversely, severe CMV disease has been associated with breast milk transmission in infants born at less than 28 to 30 weeks of gestation (*375,440)*. CMV-seropositive mothers who deliver VLBW infants should be counseled about the potential risks and benefits of breast-feeding. Pasteurization of milk may be considered. Freezing milk at -20°C (-4°F) decreases but does not reliably eliminate CMV.

Mothers with mastitis may continue to breast-feed. Conversely, breast abscesses may rupture into the ductal system and release large numbers of pathogenic bacteria into the milk. Interruption of breastfeeding on the affected breast for 24 to 48 hours after surgical drainage and appro-

priate antimicrobial therapy has been suggested *(441)*. Breast-feeding may continue on the unaffected breast.

Co-bedding is the practice of placing multiples (i.e., twins) in the same crib or isolette. Proposed physiologic advantages include improved weight gain and decreased episodes of central apnea *(442,443)*. The infection risks associated with this practice have not been well studied, although in one randomized study of 82 infants, the incidence of HAI and NEC were similar in co-bedded infants and controls *(443)*. Infants in the co-bedded group who developed infections did not transmit infections to their twin.

The AAP encourages sibling visits for both healthy and sick newborns, including those in NICUs *(444,445)*. The benefits of visitation are thought to outweigh the risk that a sibling may harbor and transmit an infectious disease in the NICU. Few studies have systematically evaluated sibling visitation in NICUs, but limited data suggest that neonatal colonization and infection are not increased with such visits *(446)*.

In the normal newborn nursery, visiting in the mother's room or a special visiting room reduces the exposure of other newborns. NICUs should establish policies that minimize infectious risks associated with sibling visitation (Table 52-6). Some facilities restrict sibling visitation during community outbreaks of RSV and other respiratory viral illnesses, but this is not necessarily evidence-based.

Immunizations Premature infants generally respond well to protein antigens *(447)*. All infants with birth weights of at least 2,000 g should receive monovalent hepatitis B vaccine at birth. Newborns remaining in the NICU should receive diphtheria, tetanus, acellular pertussis, *H. influenzae* B conjugate, pneumococcal conjugate, and inactivated polio vaccines, as well as subsequent doses of hepatitis B vaccine, at full dose at the usual chronologic age *(448)*. Diminished immune responses to hepatitis B vaccine have been noted in infants weighing <2,000 g who are vaccinated before 1 month of age. The immunization strategy for these infants depends on the HBsAg status of the mother. When the maternal HBsAg status is positive or unknown, hepatitis B vaccine is administered within 12 hours of birth, but this dose is not counted in the three-dose series. Routine hepatitis B immunization should begin at 1 month of age. For infants <2,000 g born to HBsAg-negative mothers, the first dose of hepatitis B vaccine is postponed until 1 month of age or hospital discharge.

Premature infants are at increased risk of hospitalization for rotavirus gastroenteritis during the first year of life and should be immunized with live-attenuated rotavirus vaccine. However, because vaccine virus is shed in the stools of immunized infants and a theoretical risk exists for transmission to other infants who are acutely ill, the vaccine should be administered only at or after discharge from the nursery or NICU *(449)*. If an infant immunized with rotavirus vaccine requires readmission to the NICU within 2 weeks after receipt of vaccine, Contact Precautions should be implemented and maintained for 2 to 3 weeks after vaccine administration.

Infants should receive inactivated influenza vaccine at 6 months of age *(450)*. Influenza vaccine is also recommended for all pregnant women. In a randomized study in Bangladesh, administration of trivalent, inactivated influenza vaccine to pregnant women reduced proven influenza infection in their infants by 63% for up to 6 months of age *(451)*. Immunization during pregnancy to protect the newborn against other pathogens is an approach that is being explored *(452)*.

A "cocoon strategy" has been advocated for the protection of young infants against vaccine preventable diseases. Vaccinating an infant's close contacts against diseases such as influenza and pertussis may, in fact, protect the infant who is too young to be immunized himself. Both the Advisory Committee on Immunization Practices and the AAP recommend influenza vaccine for all household and other close contacts of infants <6 months of age, but compliance with the recommendation is low. One NICU was able to vaccinate 95% of NICU parents by offering education and free vaccine at the infants' bedsides *(453)*.

Similarly, tetanus–diphtheria–acellular pertussis vaccine is recommended for contacts of infants <12 months of age to protect infants against pertussis *(415)*. Routine immunization of postpartum women before hospital discharge is recommended and standing order protocols may result in immunization of most women *(454)*. Immunization of both mothers and fathers may be achieved by offering the vaccine in the NICU *(455)*.

Immunotherapeutic Agents Prophylactic administration of IVIG to preterm or low birth weight infants results in modest decreases in sepsis and other serious infections but does not decrease mortality *(456)*. Routine use of IVIG as an infection prevention measure is not recommended. Immunoglobulin preparations with sufficient concentrations of antibodies against common neonatal pathogens may be more effective. Monoclonal anti-RSV antibody (palivizumab) protects against RSV disease and is recommended for selected high-risk infants at hospital discharge to prevent community-acquired RSV disease *(457)*. However, routine use in hospitalized infants is not recommended nor is its use recommended in the setting of nursery outbreaks of RSV. Several antistaphylococcal immunoglobulin preparations have been developed but to date, these have not been more effective than placebo in reducing staphylococcal infections in preterm and VLBW infants and their use is not recommended *(458)*.

TABLE 52-6

Guidance for Sibling Visitation

Prepare child in advance of visit
Perform screening health interview for each sibling outside the unit
Document screening results in patient record
Verify that immunizations are current, including influenza vaccine
Defer visitation for any child with fever, symptoms of acute illness, or recent exposure to communicable disease[a]
Teach and observe compliance with recommended hand hygiene practices
Prohibit visitation with any patient other than child's own sibling
Require supervision of child by parents or other responsible adult

[a]Aymptomatic siblings who have recently been exposed to varicella but have been previously immunized are considered immune and may visit.

Lactoferrin, the major whey protein in mammalian milk, exhibits antimicrobial activity and is thought to play an important role in innate immune host defenses. In one randomized, placebo-controlled trial, orally administered bovine lactoferrin given with or without the probiotic *Lactobacillus rhamnosus GG* reduced the incidence of a first episode of neonatal sepsis in infants with birth weights of <1,000 g *(459)*. Further advances in the understanding of immune function in the newborn may lead to new strategies to strengthen neonatal defenses.

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CHAPTER 53

Healthcare-Associated Infections Acquired in Childcare Facilities

Andi L. Shane and Larry K. Pickering

Group childcare facilities continue to be a major source of care for almost 10 million preschool aged children who spend at least 10 hours per week in one of these settings. According to the National Association of Childcare Resource and Referral Agencies (NACCRA), there were 119,174 childcare centers and 238,103 home-based childcare programs in the United States in 2008 (http://www.naccrra.org/randd/docs/2008_Child_Care_Capacity.pdf). Of the 9.6 million (40%) children from birth through 4 years of age in (nonrelative) childcare identified in the 2007 National Survey of Children's Health, 11% received childcare in their own home, 22% received childcare in someone else's home, and 72% were enrolled in center-based childcare. Children in out-of-home childcare tend to have higher rates of infectious diseases and antimicrobial use than children cared for at home, and their illnesses were transmitted to their care providers and family members. The burden of illness associated with group childcare depends on the age, developmental stage, immunization, and immune status of childcare enrollees, as well as environmental characteristics of the facility where care is provided as well as seasonal factors. Adult providers and school-aged siblings also may have an impact on the direct and indirect introduction and propagation of infectious microorganisms to children in group childcare. A reduction in antimicrobial use due to an increased awareness of appropriate use by providers with a corresponding emergence of antimicrobial resistant pathogens has influenced the epidemiology of many common childhood infectious diseases (1,*2*).

While funding for childcare-associated activities has increased over the past decade, the majority of these resources have been directed toward policy development and regulatory compliance activities. Support for understanding transmission of infectious microorganisms and for assessing the effectiveness of interventions to reduce infections has declined, without a corresponding decline in the incidence of childcare-associated outbreaks. The threat of propagation of infectious pathogens, accentuated by the 2009 novel H1N1 influenza pandemic, resulted in numerous discussions by policy makers and healthcare providers regarding efforts to contain and reduce transmission of infections. Although pandemic response planning focused on all members of communities, preschool aged children in group settings inherently pose a risk for transmission of respiratory and enteric pathogens due to the frequent contact of secretions directly with other children and indirectly through exposure to contaminated environmental surfaces and toys. Guidance for childcare and early childhood programs during outbreaks of novel H1N1 and seasonal influenza were outlined as part of a community response (www.cdc.gov/h1n1flu/childcare/technical.htm). Universal immunization of eligible people with influenza vaccination, decreasing exposure of ill and well attendees and staff, age-appropriate hand hygiene and respiratory etiquette, medical evaluation and treatment, and consideration of selective program closures were strategies proposed in the technical report. Consideration of a pandemic and response of childcare providers heightened awareness of the role of group childcare for preschool aged children in the containment of a community outbreak.

The national interest in promoting better childcare has been augmented by the planned publication of the third edition of *Caring for Our Children: National Health and Safety Performance Standards: Guidelines for Out-of-Home Childcare* by the American Academy of Pediatrics (AAP), the American Public Health Association (APHA), and the Health Resources and Services Administration (HRSA) (3), (*http://www.nrckids.org/*). As with previous editions, this comprehensive document is a compendium of best practices and policies developed by committees of experts in childcare and childcare health and safety.

TYPES OF CHILDCARE SETTINGS

Definitions

The U.S. Census Bureau classifies regular preschool childcare arrangements by provider (relative vs. nonrelative) and location of care. Nonrelative care may be further divided into provision of care in an organized care facility or childcare center and into other nonrelative care in the child's home or in the provider's home, (*http://www.census.gov/population/www/socdemo/child/ppl-2005.html*) *(4)*. Types of facilities also may be classified by size of enrollment, age of enrollees, and environmental characteristics of the facility. Grouping of children by age varies by setting but in organized care facilities infants and children usually are separated by age into infants

(6 weeks through 12 months), toddlers (13 through 35 months), preschool (36 months through 59 months), and school-aged children (5 through 12 years). The classification of group childcare settings has relevance to infectious disease epidemiology with regard to regulation and monitoring. Most nonrelative care provided in an organized care facility is subject to state licensing and regulation, whereas relative care in a child or provider's home may not be subject to state regulations and monitoring. The terms *caregiver* and *childcare provider* are used interchangeably to identify people providing direct care to children.

Alternative Childcare Arrangements

Employer-Sponsored Childcare Employer-sponsored childcare and onsite childcare have become prevalent and are often selected as an option for families who are unable to utilize relative or other forms of nonrelative childcare. An advantage of employer-sponsored or onsite childcare is that the child or the children are located in close physical proximity to the parent. For young infants, this proximity may facilitate breastfeeding, and for older children, transportation to and from work/ childcare activities as well as proximity to after school activities offer opportunities for increased parent–child interactions. Financial benefits including direct payroll deduction and increased productivity by parents who may be able to devote time saved to their jobs. Additionally, an employed parent may be less likely to be absent if he or she is in close proximity to a mildly ill child in an employer-based childcare arrangement. Accessibility and observation of a child in employer-based care may be an incentive to keep the child in the employer-based care arrangement and continue with employee obligations.

Ill Childcare Ill childcare is defined as the provision of care for a child who is mildly ill and who does not meet criteria for exclusion from childcare. However, some childcare facilities may not be able to accommodate a mildly ill child, translating into parental absences, ranging from 5 to 29 days annually and a corresponding cost to employees ranging from $2 to $12 billion annually (*http://nascd.com/index.htm*). Following a 1998 needs assessment for ill childcare, a collaboration of childcare providers formed the National Association for Sick Child Daycare (NASCD), a nonprofit educational organization that serves as a resource for ill childcare programs. Arrangement for the provision of ill childcare may vary with the needs and the structure of the center. Considerations affecting the choice of an appropriate alternative include the need to ensure the child's health and well-being, increased costs of alternative arrangements, the desire to reduce parental absenteeism from work, disruption of the child's routine, and the potential for spread of infection to children or adults in the alternative setting *(5)*.

Models include temporary or permanent arrangements for the care of ill children and dedicated locations within a facility or a separate facility in which ill care is provided. Temporary arrangements may best be suited for a local or community outbreak of a communicable disease, while a permanent ill childcare location may serve the needs of a higher volume facility or a community where ill childcare cannot be provided effectively within an existing childcare center.

Although ill childcare raises concerns about children's emotional and medical needs and the risk of transmission among children in such settings *(6)*, few studies have addressed these issues. A comparison of 118 children who attended a center providing short-term care for children with mild illnesses with an age-matched cohort of ill children who received care from a home care provider in their own homes indicated no increased risk of subsequent illness in the former group *(7)*. The provision of ill childcare may require additional training of staff including availability of facilities to maintain segregation of children with a variety of illnesses. Providers of care for ill children should be well versed in strategies to prevent transmission of potentially infectious microorganisms, both among attendees and staff, and should be able to maintain vigilance for changes in conditions of children who are mildly ill. Hospitals that provide employer-based childcare may be uniquely situated to provide ill childcare and may provide a sense of reassurance to parents due to their proximity to the availability of medical care services, if needed. While these facilities are not intended to replace evaluation by a healthcare provider, childcare providers with training and experience related to provision of care for mildly ill children may result in appropriate care for mildly ill children.

Backup Childcare Care of children who receive care from an individual provider may be interrupted when the provider becomes ill or is unable to provide care for another reason. In these situations, availability of backup childcare is beneficial. One of the challenges to providers of intermittent care is that the need for these services is variable and the care provided is frequently transient, lasting only for the duration of the incapability of a regular provider. Although backup childcare arrangements facilitate continuation of care for children and sustainability of employment for parents, settings that provide urgent childcare should be evaluated prior to their need to ensure that they meet local licensing requirements.

Sibling Childcare When children are hospitalized for acute and chronic conditions, a need has developed to provide care for their siblings while their parents spend time with the hospitalized child. In certain inpatient units, such as intensive care or transplant units, age and developmental limitations may not be conducive to sibling visits. Additionally, care for well siblings of hospitalized children may be a challenge for families who reside at significant distances from the hospital. Therefore, the provision of childcare for well siblings of hospitalized children provides a service to families of pediatric inpatients and optimizes compliance with visitation policies. Hospitals or medical centers that provide employer-based care could extend care of employee children to that of temporary care for siblings of hospitalized children.

MAGNITUDE OF CHILDCARE HEALTH ISSUES

Children attending out-of-home childcare generally have higher rates of infectious diseases and antibiotic use than children in home care. Among preschool children

in the United States, 9% to 11% of all upper respiratory tract infections (URIs), 10% to 14% of all otitis media episodes, and 19% of all clinic visits for diarrheal disease are attributable to childcare attendance *(8–10)*. Despite variations in study methods and definitions, the increased burden of illness associated with childcare compared with illness among children in home care has been demonstrated fairly consistently. In a study of children enrolled in a Memphis healthcare maintenance organization, children in out-of-home childcare had 2.5 to 3.1 physician-diagnosed infections during a 7-month study period compared with 2.0 infections among children in home care *(11)*. These differences were statistically significant. Results from the National Institute of Child Health and Human Development Study of Early Childcare suggest that these differences still exist for children younger than 2 years of age but by 3 years of age, illness experiences among children in out-of-home childcare are comparable to illness episodes in children cared for at home (12).

The risk of illness associated with family childcare usually has been found generally to be intermediate between the risks associated with center care and risks associated with home care *(11–21)*. However, some studies have indicated that provider-reported illness rates in children attending childcare homes were greater than those among children in centers *(22,23)*. As many previous studies obtained data through retrospective telephone interviews with parents, these differences in results suggest that comparisons of illness rates from various types of childcare facilities may be influenced by the information source.

In 1989, childcare-associated illnesses were estimated to cost the U.S. economy at least $1.8 billion annually *(24)*. Two-thirds of that cost was due to lost employee time due to parental care of an ill child. In one survey conducted in 1990, almost 18% of mothers interviewed had missed an average of 2.2 days of work during the month before the study interview to care for an ill child *(25)*. During a similar period, the mean monthly costs of medical care incurred by children in home care and center care in Memphis, TN, were $19.78 and $32.94, respectively *(11)*. After including lost income for parents who missed work, the mean monthly cost of illnesses ranged from $29.50 for families with children in home care to $61.64 for families with children in center care. Total parental- and societal-adjusted average costs for illness among toddlers in Quebec childcare facilities over a 6-month period were U.S. $260.70. The costs of medical care ($47.47 for medication and $49.10 consultation) may have underestimated actual costs. However, this assessment included an estimate of $35.68 for a previously overlooked cost of care by family members *(26)*.

By amplifying the prevalence of pathogens already present in the community, childcare patterns have influenced the epidemiology of a number of illnesses, including cytomegalovirus (CMV) infection, hepatitis A, shigellosis, giardiasis, and cryptosporidiosis. A concerning issue is the widespread use of antimicrobial agents among children attending childcare and the increased likelihood of isolation of antibiotic-resistant bacteria from children in out-of-home childcare (*27*,*28*,29,*30–35*,36,*37–42*).

INFECTION CONTROL CONSIDERATIONS

The concept of infection control, as applied in the hospital or other healthcare venues, can serve as a model for understanding the epidemiology of infectious diseases in the childcare setting. Although differences between the childcare and inpatient settings are significant, some common elements can be found. Very young children, like hospitalized patients, have an increased susceptibility to infections. Like many patients in hospitals and nursing homes, young children depend on care providers for the most basic functions, including nourishment and personal hygiene. Care providers inadvertently may transmit microorganisms between children and are themselves at risk for contracting infections through occupational exposures. Prevention methods focus on increased recognition of the risks of transmission and on interrupting the chain of transmission within the institutional setting *(43–49)*.

EPIDEMIOLOGY OF INFECTIOUS DISEASES IN CHILDCARE

The incidence of illness within a childcare facility is determined by factors influencing both the rate of introduction of pathogens into a facility and the rate of transmission once a pathogen has been introduced *(50)*. Aspects influencing the rate of introduction are often beyond the control of the facility and include the prevalence of the illness in the community, the age and health status of children served by the facility, and facility size (usually expressed as the total number of children enrolled). One model suggests that the geographic distribution of the homes of children attending the facility may influence morbidity and that facilities with more widely distributed homes of attendees were less likely to experience major epidemics than those with clustering of homes *(50,51)*.

Characteristics influencing the rate of transmission once a pathogen has been introduced can often be addressed and modified. These factors include practices and policies concerning hygiene and disinfection, including hand hygiene, staffing patterns and education of staff, isolation or exclusion of ill children, mixing of children of various ages in the same classroom, and diaper type and use of overclothing with diapers. A simple scheme depicting the mode of spread of enteric bacteria within childcare centers has been devised *(49)*. This model has been developed further and probably applies, with some modification, to nonenteric pathogens as well *(52)* (Table 53-1).

Factors Related to Increased Transmission among Children

Young children have an increased susceptibility and high age-specific attack rates for numerous diseases. Infections in childcare settings are transmitted primarily by person-to-person spread of pathogens through body substances, including feces, saliva, nasal secretions, and urine; through direct contact; or by hands of children and care providers. Children, especially toddlers, in childcare have frequent person-to-person contact and often have poor personal hygiene with regard to contact with and disposal

TABLE 53-1

Modes of Transmission of Organisms in Childcare Settings

Usual Route of Transmission[a]	*Bacteria*	*Viruses*	*Other*[b]
Fecal–oral	*Campylobacter* organisms, *Clostridium difficile*, *Escherichia coli* O157:H7, *Salmonella* organisms, *Shigella* organisms	Astrovirus, norovirus, enteric adenovirus, enteroviruses, hepatitis A virus, rotaviruses	*Cryptosporidium species*, *Enterobius vermicularis*, *Giardia intestinalis*
Respiratory	*Bordetella pertussis*, *Haemophilus influenzae* type b, *Mycobacterium tuberculosis*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, group A *Streptococcus*, *Kingella kingae*	Adenovirus, influenza virus, human metapneumovirus, measles virus, mumps virus, parainfluenza virus, parvovirus B19, respiratory syncytial virus, rhinovirus, rubella virus, varicella-zoster virus	—
Person-to-person contact	Group A *Streptococcus*, *Staphylococcus aureus*	Herpes simplex virus, varicella-zoster virus	Agents causing pediculosis, scabies, and ringworm[c]
Contact with blood, urine, and/or saliva	—	Cytomegalovirus, herpes simplex virus	—
Blood-borne	—	Hepatitis B virus	—

(Used with permission of the American Academy of Pediatrics. Children in out of home care. In: Pickering LK, Baker CJ, Kimberlin DW, et al., eds. *Red Book: 2009 report of the committee on infectious diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics.)
[a]The potential for transmission of microorganisms in the childcare setting by food and animals also exists (see Appendix IX, Clinical Syndromes Associated With Foodborne Diseases, p 860, and Appendix X, Diseases Transmitted by Animals, p 864, and Diseases Transmitted by Animals [Zoonoses]: Household Pets, Including Nontraditional Pets, and Exposure to Animals in Public Settings, p 198).
[b]Parasites, fungi, mites, and lice.
[c]Transmission also may occur from contact with objects in the environment.

of potentially infectious body substances (*43,46*,53,*54*). Frequent hands-on contact by staff, often in hectic circumstances, provides additional opportunity for person-to-person spread via the care providers' hands both to other children and to other care providers *(49,52,55,56)*. The lack of fecal continence in children who are not toilet trained and the tendency for children to explore their environment with their hands and mouths lead to frequent sharing of oral secretions and fecal–oral spread of infection *(46,52,54,57–59)*.

Children also share secretions and excretions via fomites; contaminated toys and environmental surfaces are important in the epidemiology of childcare-associated infections. These areas, especially surfaces in classrooms of non–toilet-trained children, are often contaminated with enteric microorganisms *(52,59–63)*. Many microorganisms associated with childcare related infections can survive on environmental surfaces for considerable periods of time. Some, including CMV, rotavirus, and *Giardia*, have been isolated from environmental surfaces in childcare facilities *(58,64–66)*. The concentration of microorganisms recovered from surfaces and air samples in childcare center classrooms is inversely related to the age of the children in the room *(67)*. Environmental levels of fecal coliforms in childcare classrooms often increase during outbreaks of diarrheal illness *(49)*. Group A *Streptococcus* was isolated from plastic toy food during an investigation of two cases of invasive GAS infections in a childcare facility *(68)*. Although mouthing behavior is uncommon among children 3 and 4 years of age, such as the children involved in this outbreak, food replica toys encourage mouthing behavior and are examples of the types of fomites that contribute to transmission.

Airborne transmission also contributes to spread of pathogens. Respiratory tract infections, transmitted through respiratory aerosols and droplets, are the most common infections associated with childcare attendance (12,*19,22,23,48*,69). Studies in crowded homes and childcare settings have shown that risk of respiratory tract infections, including otitis media, increases as the number of children per room increases *(8,70,71)*. Results from a series of longitudinal studies suggest that a positive association exists between frequency of respiratory tract illness and childcare among preschool children. These results also suggest that this association is related to the number of children in the group, may be moderated by length of time in childcare, and is reversed to a protective effect in school-aged children, with the differences disappearing by 13 years of age (12,*72*).

Common source and food-borne transmission rarely are reported causes of outbreaks in childcare settings *(73–77)*. However, unhygienic food-handling practices have been shown to be a risk factor for illness spread by fecal–oral transmission in childcare facilities *(14,55)*, and clinicians may not have recognized fully the significance of food-borne transmission in this setting.

Other Persons and Groups at Risk

Childcare Providers Childcare providers, like healthcare providers, are at risk of occupational exposure to infectious microorganisms *(78,79)*. The majority of childcare providers are women; many of whom are of childbearing age *(80–82)*. Childcare providers have an increased endemic risk for a number of infections including CMV, parvovirus B19, and *Giardia* and an increased epidemic risk for infections with other agents such as *Shigella*, hepatitis A, and *Cryptosporidium*. Infections caused by pathogens, such as varicella, parvovirus B19, and CMV, which are common in childcare settings, pose a significant risk of adverse consequences for pregnancy outcomes. However, few studies have focused on infections among childcare providers, and the actual risk of maternal or fetal infection or of specific adverse pregnancy outcomes as a result of these likely exposures has not been well defined.

Childcare providers experience annual rates of CMV seroconversion ranging between 8% and 20%, compared with hospital employees who experience annual rates of seroconversion of 2% (*58,80,83*,84,*85,86*). During community outbreaks of erythema infectiosum, childcare providers were found to be among the most affected occupational groups, with seroconversion rates ranging from 9% to 31% *(87–90)*. In a prevalence study of hepatitis A antibodies among childcare providers employed in 37 randomly selected childcare centers in Israel during 1997, 90% (402 of 446) of the childcare providers had antibodies to hepatitis A. The authors concluded that childcare providers are at high risk of occupational exposure to hepatitis A, and postulated that seronegative employees may have a twofold chance of acquiring hepatitis A *(91)*. Since the recommendation for universal immunization of children over 12 months of age in 1995, the risk for infection with hepatitis A after occupational exposure in a childcare setting may be reduced. However, the risk of exposure to unimmunized children and international adoptees may warrant hepatitis A immunization of childcare providers *(92)*.

Childcare providers compared with nonproviders have a significantly higher risk of at least one infectious disease and lose more work days due to infectious diseases *(79,93,94)*. Childcare providers should receive all immunizations routinely recommended for adults, as shown on the adult immunization schedule, which is updated annually (*www.cdc.gov/vaccines*).

During outbreaks of diarrhea in childcare centers, 40% of care providers developed diarrhea *(95)*. During a multicommunity outbreak of shigellosis, the overall median attack rate among employed staff of childcare centers was 6%, with a range of 0% to 17% *(96)*. In outbreaks of group A streptococcal (GAS) infection and echovirus 30 infection *(97,98)* in childcare centers, both microorganisms have been shown to infect and cause disease in adult providers and parents. A cross-sectional study of 477 childcare staff revealed a seroprevalence for parvovirus B19 IgG antibodies of 70%. Seropositivity was associated with age, and among staff <40 years of age, with length of group childcare contact *(89)*. A concern is that an infected pregnant woman could transmit the virus transplacentally, leading to fetal hydrops, intrauterine growth retardation, isolated pleural and pericardial effusion, and death, but congenital malformations have not been linked to prenatal parvovirus B19 infection. Estimates of the risk of fetal loss when a pregnant woman of unknown antibody status is exposed are 2.5% for fetal death after household exposure and 1.5% after occupational exposure in a school *(87)*.

Family Members Family members of both providers and children may be infected by pathogens transmitted in childcare settings. Parents of children who attend a childcare facility and persons who provide care to these children have increased risk of acquiring infections such as CMV (*58,80,82,83*,84,*86,99*), parvovirus B19 *(87–90)*, hepatitis A virus (HAV) *(91,93)*, and diarrhea *(95,96,100)*. Mothers of children in childcare are at increased risk of acquiring childcare-associated infections *(83,87,101–103)*. Preschool children often introduce infections into their families *(9,54,87,101,102,104)*. Secondary attack rates among household contacts are often high (53,*74,79,103,105*), especially for highly communicable diseases such as shigellosis. In the case of hepatitis A, clinical illness among older household contacts may be the first indication of transmission within a childcare facility *(101)*. Older siblings, secondarily infected at home, may spread infections to other children through school and play contact.

The Community Childcare-associated infections generally reflect agents circulating in the community. Transmission within childcare facilities amplifies the prevalence of pathogens in the community, including *Giardia*, *Cryptosporidium*, *Shigella*, hepatitis A, and CMV. Interrupting disease transmission in childcare settings may lead to a reduction in the disease burden within the community and to a reduction in expenditures associated with infectious diseases outbreaks.

The economic burden of illness associated with group childcare was estimated at $1.5 billion annually adjusted to 2005 U.S. dollars *(106)*. Precise mechanisms for estimating illness burden and for evaluating effectiveness of infection control interventions are rare due to challenges associated with performing such assessments (107). Economic evaluations of outbreaks occurring in the school setting and modeling of vaccine prevention efficacies have been described frequently in the literature, but few economic analyses of outbreaks of infections associated with group childcare have been published. In order to perform an economic analysis, information required for the analysis must often be collected concomitantly with an outbreak investigation. Due to numerous variables, computerized models must often be created to perform these evaluations. Attributing an outbreak to group childcare is challenging, because although these settings may promote transmission of infection, childcare attendees and staff interact with household contacts external to the childcare arrangement, thus facilitating secondary spread. An economic analysis of a childcare-associated outbreak of *Shigella sonnei* in southwestern Ohio in 2001 incurred an overall cost of $821,725 to contain the outbreak of over 1,600 infections, which was the equivalent of $514 per culture confirmed case *(96)*. A prospective evaluation of 208 families with at least one childcare enrollee, conducted from November 2000 to May 2001 in the Boston area, documented 2,072 viral illnesses over 105,352 person days. Among the 834 subjects,

1,683 URIs and 389 gastrointestinal tract illnesses (GI) were reported during the study period with a total mean cost of $49 per URI and $56 per GI episode. Decreased parental productivity during missed days of work to care for a child who was not in childcare accounted for a significant proportion of the nonmedical costs *(106)*.

Future investigations of outbreaks of illness associated with group childcare could utilize computerized models and paradigms to assess the economic impact of outbreaks. In an era of limited funding, an understanding of expenses and allocation of resources will be important information to justify utility of interventions.

Antimicrobial Resistance and Antimicrobial Use

Emergence of antimicrobial-resistant strains of bacteria resulting from inappropriate use of antimicrobial agents is a serious public health issue. While antimicrobial use among all preschool aged children is notable, children enrolled in out of home childcare generally receive more antimicrobial treatments than children in home care *(21,34,41,108)*. During an 8-week period of observation of 270 children, antimicrobial agents were used by 36% of children in childcare centers compared to 7% and 8% of children in childcare homes or in home care, respectively ($p < .001$). The mean duration of antimicrobial therapy prescribed for children in childcare centers (20 days) differed significantly ($p < .001$) from children in childcare homes (4 days) and children in home care (5 days). The estimated annual rates of antimicrobial treatment ranged from 2.4 to 3.6 times higher for children in childcare when compared with children in home care *(41)*.

As a result of this increase in antimicrobial use, an association of childcare center attendance with colonization or infection with resistant bacteria has been documented. Outbreaks of illness due to resistant *Streptococcus pneumoniae* (29,*30,40,109–115*,116,*117–120*) and *S. sonnei (96,121,122)*, as well as colonization due to resistant *Haemophilus influenza (123)*, *Escherichia coli (42,94,124)*, and methicillin-resistant *Staphylococcus aureus (32,37)* have been described. In a written survey of 135 licensed childcare directors in Pennsylvania in 2007 to assess opinions of antimicrobial use for childhood illnesses, approximately one-half (52%) of respondents agreed that children are prescribed antimicrobial agents unnecessarily and 89% believed that parents pressure physicians to prescribe unnecessary antimicrobial agents. However, policies requiring receipt of antibiotics prior to returning to the childcare center were notable. Most directors reported that children with conjunctivitis with white or yellow discharge, conjunctivitis with watery discharge, or diarrhea were excluded from the childcare center until antibiotics were prescribed. Although receipt of antibiotics prior to the child's return to a childcare center was not always required in other scenarios, including clear rhinorrhea and afebrile cough, directors frequently reported that antibiotics were sometimes required. In centers with larger enrollments, directors were more likely to exclude children with ear pain until the child receives antibiotics (125). Educational campaigns including the AAP's Healthy Childcare America (HCCA) Campaign, (*http://www.healthychildcare.org/index.html*) and the Centers for Disease Control and Prevention's (CDC's) Get Smart Campaign, (*http://www.cdc.gov/getsmart/*) provide targeted information to parents, childcare, and healthcare providers to assist with choices for judicious use of antimicrobial agents. Efforts should disseminate information that most illnesses acquired in the childcare setting are attributable to viruses, for which supportive care is optimal and for which antimicrobial therapy is economically and scientifically disadvantageous. Additionally, immunization against common viral and bacterial pathogens is an effective means of reducing the prevalence and severity of infections with these microorganisms *(126)*. The current recommended immunization schedule for children can be found at www.cdc.gov/vaccines. This schedule is updated annually in January.

EPIDEMIOLOGY, ETIOLOGY, AND PREVENTION OF DISEASE SYNDROMES

Respiratory Tract Infections

Upper and Lower Respiratory Tract Infections Infections of the upper respiratory tract are the most common illnesses involving children in both home and childcare settings *(127)*. Studies have documented the association between childcare attendance and increased risk of URIs especially in children <3 years of age *(127)*. Using different methods, the risk of contracting a respiratory tract infection was found to be 2 to 3 times higher among children cared for at home *(8,127,128–130)*.

Respiratory tract symptoms were involved in 45% to 85% of illness episodes reported among children attending childcare facilities in various geographic locations *(19,22,23)*.

Respiratory tract infections that have been studied in the childcare setting include pharyngitis, sinusitis, otitis media, the common cold, bronchiolitis, and pneumonia *(20,131–133)*. Microorganisms responsible for illness in the childcare settings are similar to microorganisms that circulate in the community. Depending on the season, these microorganisms include parainfluenza, influenza, respiratory syncytial virus, adenovirus, rhinovirus, coronavirus, metapneumovirus, parvovirus B19, and *S. pneumoniae*. Infections due to *Haemophilus influenzae* b and pertussis have experienced dramatic declines in the United States although cases and outbreaks continue to occur *(134)*. In a group childcare setting, adolescents or adults may serve as the index case for pertussis outbreaks or tuberculosis infections *(135–140)*, particularly when children or adults are not appropriately immunized against pertussis *(134,135)*.

Person-to-person transmission of *Chlamydophila pneumoniae* among children in the childcare setting has been reported without occurrence of disease *(141)*. *Kingella kingae* colonizes the oropharynx and respiratory tracts of young children and has been associated with invasive disease *(142–146)*. Invasive *K. kingae* osteomyelitis/septic arthritis has been reported in two children in a childcare center with nine other children in the same class found to be colonized. Matching pulse-field gel electrophoresis (PFGE) patterns supported child-to-child transmission *(142)*. GAS infection among children and adult staff in the childcare setting has been reported *(68,147)* but is not common *(68,147)*. Following a fatal case of invasive disease, 25% of 258 children and 8% of 25 providers had GAS isolated from throat cultures *(147)*. In Israel, a study

conducted in childcare centers showed the prevalence of GAS to be 3% in infants and 8% in toddlers. Carriage was not associated with respiratory tract symptoms *(148)*.

Respiratory tract infections contribute to the burden of otitis media, antibiotic use, and absenteeism experienced by children in out-of-home childcare. Approximately 29% of respiratory tract infections among young children are complicated by otitis media *(20)*. Children with respiratory tract infections in Seattle childcare facilities were absent for an average of 0.9 days per illness episode; these infections accounted for 3,558 days of absence, representing almost half of the total 7,635 days of illness-related absences among these children *(22)*. Among children in San Diego childcare facilities, illness episodes involving rhinitis accounted for 2,335 days of absence (1.6 days per child year), an average of 0.3 days absent per illness episode *(23)*.

Children who have been enrolled in group childcare for some time may have no greater risk of respiratory tract infections than their same-aged peers who stay at home (*9*,12,*44,149*). Results from the National Institute of Child Health and Human Development Study of Early Childcare support this finding and suggest that, although childcare was associated with increased illness in children younger than 2 years of age, the difference was negligible by 3 years of age (12). Children who first entered out-of-home childcare after 3 years of age experience more illness than their classmates who were in childcare before 3 years of age *(150)*. However, the excess respiratory tract illness among children in childcare centers may protect those children against respiratory infections during the early school years *(72)*.

Although results of the few studies assessing the impact of childcare attendance on lower respiratory tract infections are not definitive, they suggest an increased risk among children in childcare *(151–155)*. After other risk factors were controlled, children hospitalized with lower respiratory tract infections at one of four Atlanta area hospitals were more likely than control patients to have been in out-of-home childcare *(152)*. Center care posed a greater risk for hospitalization than care in a childcare home. However, other studies have found no association between lower respiratory tract illnesses and childcare *(108,155)*.

Most authorities agree that children with mild to moderate symptoms of viral upper respiratory infection, such as rhinitis, cough, pharyngitis, or otitis media, may continue in their usual childcare arrangement unless they meet other criteria for exclusion (3,*43*,156). Care should be taken to clean objects, including toys, and surfaces contaminated with oral or nasal secretions. Tissues, towels, or other material used to wipe children's noses and mouths should be handled as contaminated items (3,*43,48,158*). Hand hygiene protocols must be followed carefully (3,*43,48*,156,159).

Immunization of healthy people 6 months of age and older, including adults, with influenza vaccine is encouraged to reduce the impact of influenza on the health of both the children and their contacts (156,*160*). Influenza and other respiratory tract infections predispose children to otitis media. Immunization against influenza may provide some protection against otitis among vaccines and may even reduce respiratory illness among household contacts *(161–164)*.

Invasive Bacterial Infections The risk of developing invasive bacterial infections, especially meningitis and bacteremia caused by *H. influenzae* type b (Hib) before routine use of Hib vaccine in the United States, was higher among children attending childcare centers than in children cared for at home *(109,165)*. The incorporation of conjugated Hib vaccine into the routine immunization schedule to prevent invasive Hib disease has dramatically decreased the frequency of invasive Hib infections. Since use of conjugated Hib vaccine in infants beginning at 2 months of age in October 1990 *(166,167)*, the average annual rate of invasive Hib infections has declined from over 20,000 cases per year to <100 cases of known serotype b *H. influenzae* per year from 2003 through 2008 *(168)*. The prevention of invasive Hib infections in childcare settings today requires ensuring appropriate immunization of all enrolled children, complete reporting to allow the characterization of suspect vaccine failures, standardized serotyping procedures, and serotype tracking for all invasive *H. influenzae* infections *(169)*.

Household contacts of people with *Neisseria meningitidis* infections are at increased risk of disease, but the magnitude of risk for childcare contacts is uncertain. Reports from outbreaks suggest that childcare contacts of cases are at increased risk *(170–172)*. However, from 1998 to 2008, the incidence of invasive meningococcal disease has reached a historic low in the United States *(173)*. From 1993 to 2001 in the Netherlands, clustering of *N. meningitidis* cases beyond chance occurred at a rate of 3% (CI: 2–4%) and concluded that this rate was likely the result of direct transmission *(174)*. Childcare center attendance was reported as the likely exposure for 8/40 (20%) of clusters, accounting for 13/82 (16%) cases of invasive disease with multiple serotypes. Childcare attendees who develop clinical disease while enrolled in group care often result in the need for administration of chemoprophylaxis to family and childcare centers.

In the event of a case of invasive *N. meningitidis* disease in a facility, rifampin prophylaxis generally should be given to childcare contacts (both children and adults) (3,*43*,156,*165*). It is often not necessary to administer rifampin to all center attendees as they may not have had at-risk contact with the case. Public health authorities and healthcare providers should be involved in evaluating the significance of exposure on an individual basis. Routine immunization of healthy preschool aged children with a meningitis vaccine is not recommended unless the child is 2 years of age or older and has an underlying, predisposing condition, anatomical or functional asplenia, persistent complement deficiencies or human immunodeficiency virus (HIV), or plans to travel to a country with highly endemic or epidemic disease (156,175). Immunization may be useful in controlling outbreaks caused by serogroups to which the vaccine confers immunity.

Childcare attendance was shown to be a risk factor for primary invasive pneumococcal disease *(111,112,120)*, for nasopharyngeal carriage of *S. pneumoniae*, and for carriage of antibiotic-resistant strains for children in childcare centers (29,*30,110,112,114,115,120,176–178)*. Secondary spread of *S. pneumoniae* in the childcare setting has been reported, but the exact risks are not known *(40,111,112)*.

Incorporation of a conjugated pneumococcal vaccine into the routine childhood immunization schedule in the United States in 2000 has resulted in a dramatic reduction in the frequency of invasive pneumococcal disease *(179)*. With expansion of coverage of pneumococcal serotypes by six with the recommendation for routine use of PCV13, further disease reduction may occur *(177,178)*.

The emergence of antibiotic-resistant strains of pneumococci is a matter of both clinical and public health concern. Israeli investigators reported that the risk of resistant pneumococcal infections in children who attended childcare centers and who had received at least one course of antimicrobial treatment in the previous 3 months was 12.9 times that of children who had neither of these risk factors *(180)*. In studies among children attending four Houston childcare centers, *S. pneumoniae* was recovered from 40% of 140 children younger than 3 years *(181)*. Intermediate penicillin resistance was found in 11% of isolates; none was highly resistant. During a 7-year prospective study, upper respiratory tract cultures were collected monthly from 72 children *(39)*. Each child had an average of 2.1 episodes of *S. pneumoniae* colonization; 68% had resistant pneumococci isolated at least once. In another study, multiply resistant strains were isolated from nasopharyngeal cultures from 9 of 47 children in a center attended by two toddlers hospitalized with invasive pneumococcal infections *(40)*. After isolation of resistant *S. pneumoniae* from the middle ear fluid of a child with otitis media, researchers found that 52 of 250 exposed children were carriers of a resistant pneumococcus *(118)*. Carriage was associated with receipt of antimicrobial agents, especially at prophylactic doses. This association has been demonstrated previously *(110,182)*. Studies in an Omaha childcare center suggest that decreasing antibiotic use may control the spread of resistant pneumococci *(110)*. Resistant pneumococci may persist among children in centers. Although treatment with rifampin or rifampin and clindamycin can reduce the prevalence of carriage temporarily *(112)*, it may not eliminate carriage or reduce spread *(40,181)* and is not recommended.

Group A Streptococcal Infections Outbreaks of GAS infections among children and adult staff in the childcare setting have been reported *(39,147,183)*. A study of prevalence of GAS in a childcare center after a fatal case of invasive disease showed that 25% of 258 children and 8% of 25 providers had GAS isolated from throat cultures *(147)*. Risk of carriage was similar in children housed in the same room as the index case. GAS infection associated with varicella also has been reported *(68)* as has an outbreak associated with toxic shock *(184)*. A program of aggressive intervention that involves culturing and treating symptomatic contacts and environmental sanitation measures has been recommended for outbreaks of symptomatic GAS disease with a high attack rate *(185)*. However, the relative benefits of this approach in comparison to less aggressive interventions have not been evaluated *(131,132)*.

Tuberculosis The principal risk of tuberculosis in the childcare setting is transmission from infected adolescents or adults to children *(137,140,186,187)*. Child-to-child transmission occurs infrequently. Transmission of tuberculosis in childcare is uncommon and generally results in multiple cases. In England, a community outbreak involving 12 children in a play group was traced to one child's infected mother. Investigators were unable to identify a source of infection for two infected children in a Kentucky childcare center *(186)*. In an outbreak of tuberculosis associated with a private home childcare facility, 9 of 11 outbreak cases occurred in children <7 years of age, all of whom had extensive contact with the private-home childcare facility where the adult index case was present for long periods of time *(137)*. Transmission of tuberculosis has been reported to occur in an adult day care facility *(187)*.

Current recommendations call for preemployment screening of all childcare providers with a tuberculin skin test or an interferon-gamma release blood assay and chest radiograph follow-up of all positive reactors. Because the risk of transmission from infected children to other children is low, children do not need routine screening before entry into childcare.

Care providers or children with active disease who are infectious should be excluded from childcare and treated in accordance with the appropriate protocols. After initiation of therapy, public health authorities should determine that the patient is noninfectious before the caregiver or child is readmitted (156).

Otitis Media Otitis media is associated with viral respiratory tract infections and respiratory tract colonization or infection with bacteria including *H. influenzae* or *S. pneumoniae (129,183)*. Childcare attendance, with increased risks of both respiratory tract infections and exposure to pathogenic bacteria, also is associated with an increased incidence of otitis media *(19,20,129,133,183,188–193)*.

Children 6 to 24 months of age in Swedish childcare centers and family childcare homes (caring for one to four children) had 2.5 to 3 times the mean number of episodes of otitis media per child compared with children in home care *(18)*. Older children in childcare were not at increased risk of otitis media. Neither the facility's policy concerning exclusion of ill children nor the number of children enrolled in the facility influenced the risk of illness. A telephone survey of families of 575 children in Atlanta found that children in full-time childcare (>40 hours per week) had 3.8 times the risk of developing an ear infection compared with children in home care *(8)*. The risk was greatest among children younger than 36 months. For children younger than 2 years of age with URIs, attending childcare for at least 20 hours per week resulted in a 1.6- to 1.7-times higher likelihood that the URI would be complicated by an episode of otitis media. The risk was not increased significantly among children older than 2 years of age *(194)*.

Other studies have suggested that the incidence of otitis media among children in out-of-home childcare increases as the number of children present in that setting increases (e.g., in a childcare center rather than family childcare home) and decreases with increasing age at entry into childcare *(11,71,195–197)*. Results from the Child Health Survey of the National Health Interview Survey suggest that children in childcare have 1.5 times the risk of repeated ear infections compared with children in home care *(71)*. Attending a facility with more than six children significantly increases the risk of repeated otitis media in children younger than

3 years of age. Childcare attendance also is associated with an increased risk of recurrent and more severe otitis media, including persistent effusion and complications such as a need for tympanostomy tube placement *(71,191,196–198)*. Otitis media is responsible for most antibiotic use in children younger than 3 years of age in the childcare settings.

Enteric Infections

The childcare setting has been associated with infection caused by a wide variety of enteric pathogens, including *Shigella (14,55,96,100,199–205)*, *Salmonella (75,76,206,207)*, *E. coli (208–217)*, *Campylobacter (55,100,202,218–220)*, *Clostridium difficile (221)*, *Aeromonas (221,222)*, rotavirus *(55,100,223–232)*, coxsackievirus *(233,234)*, calicivirus *(235–237)*, astrovirus *(238–242)*, adenovirus *(238,243,244)*, *Giardia (245–256)*, *Cryptosporidium (234,257–260)*, *Dientamoeba fragilis (251)*, and *Blastocystis hominis (261)*. A study of childcare-associated diarrhea in Maricopa County, Arizona, showed that specific pathogens could be identified from stools of 18% of sporadic cases and 26% of outbreak-associated cases *(55)*. Other investigators have obtained similar results *(74,247,262)*. During outbreak investigations, multiple pathogens frequently are recovered from stools *(55,204,205,253,254)*, suggesting that diarrhea caused by one agent may facilitate transmission of other pathogens.

The risk of diarrhea among children in childcare centers is 1.6 to 3.5 times that of children in homecare settings *(13,55)*. The risk may be much greater for certain pathogens such as *Shigella*, *Giardia*, rotavirus, and *Cryptosporidium* with a low infectious dose, and among subgroups of children, such as infants or toddlers in diapers *(74,95,202)* or those recently enrolled in the facility *(55,262,263)*. Studies based on clinic visits or information from parents have suggested that children in childcare homes have a lower risk of diarrhea than those in centers *(10,13,14)*. However, results of studies comparing illness incidence in childcare homes and centers may be biased by the source of information. Data obtained from childcare providers in Seattle and San Diego showed that the incidence of illness (including diarrhea) among children in childcare homes was greater than that among children in centers *(22,23)*.

Rotavirus, *Giardia*, *Cryptosporidium*, and *Shigella* appear to be the most common causes of diarrhea in childcare settings. Rotavirus appears to cause disease more commonly in infants, and *Giardia* and *Cryptosporidium* appear to cause disease more commonly in toddlers *(55,100,262)*. *Shigella* infections generally occur in outbreaks and are more likely to involve adults and children older than those at greatest risk for the other three common infections *(100,202,203)*. *Giardia*, *Cryptosporidium*, rotavirus, and *Shigella* are more frequent causes of infectious diarrhea in childcare settings because of their low infectious dose *(74,202)*. Outbreaks of these infections are often associated with high rates of asymptomatic infection and prolonged excretion by both asymptomatic and convalescent people who no longer have diarrhea *(40,204,205,223,253)*. These people may pose difficulties in management including exclusion and cohorting to control transmission.

Secondary attack rates are often quite high among family members of children with childcare-associated diarrheal illness. These rates have ranged from 12% to 47% for *Giardia*, 24% to 62% for *Cryptosporidium*, 17% to 79% for rotavirus, and 22% to 29% for *Shigella (74,100,202,205,247,258,259)*. Childcare-associated outbreaks, especially cases of shigellosis, may spread beyond the center and play an important role in the epidemiology of community-acquired infections.

Outbreaks of diarrheal disease occur primarily among children who are incontinent. Other risk factors associated with an increased incidence of diarrheal disease in childcare settings include age of child, duration of attendance in a particular childcare facility, type of setting, and levels of environmental sanitation and adherence to good hygienic practices *(49,55,56,263)*.

Children who are incontinent generally have the highest attack rates during childcare center outbreaks of many diarrheal agents, including *Cryptosporidium*, *Giardia*, and rotavirus *(100,105)*. In a 2-year prospective study of diarrheal illness among children in Houston childcare facilities, the risk of diarrheal illness in children younger than 3 years was 17 times that of children 3 through 5 years of age; the mean incidence of diarrheal illness in facilities that accepted children in diapers was significantly greater than in facilities that did not *(95)*.

The principal means by which enteric diseases spread in childcare facilities is by the fecal–oral route, direct interactions between toddlers, or contamination of caregiver hands or the environment *(43,48,74)*. Low scores on assessments of hygiene and environmental sanitation in Maricopa County, Arizona, childcare facilities were associated with an increased risk of outbreaks of diarrheal illness *(55)*. Practices linked to outbreaks included inadequate hand hygiene, especially by staff with diaper-changing and food-handling responsibilities *(55,56,95)*. Studies in Atlanta childcare centers have shown that a rigorously monitored hand washing program can reduce the incidence of diarrheal illness, especially among children aged 6 through 18 months *(263)*. However, training of childcare staff, without monitoring compliance, has been shown to be ineffective in reducing diarrheal incidence *(264)*. The impact of even subtle reinforcement of hand hygiene protocols is suggested by decreases in both diarrhea and environmental contamination rates among facilities participating in research projects *(61,263)*.

Levels of environmental contamination with fecal coliforms are associated with the incidence of diarrheal illness *(49,52)*. The proportion of cultures from hands and environmental surfaces positive for fecal coliforms increases when cases of diarrhea occur in a classroom *(49,52,62,63)*. One study demonstrated an association between the incidence of diarrhea and the recovery of fecal coliforms from hands of children and staff and from moist environmental surfaces, including sinks and faucet handles *(52)*. Because many enteric pathogens are relatively stable in the environment and some, such as *Cryptosporidium*, are resistant to many commonly used disinfectants, addressing this potential environmental link in the transmission of enteric diseases requires careful adherence to cleaning and disinfection protocols *(58,59,265)*.

Children newly enrolled in childcare centers have a greater incidence of diarrheal illness than those who have attended for at least 3 months *(55,262,263)*. This was first recognized during a hand hygiene intervention study where

researchers noted a peak incidence in diarrhea among children enrolled in centers for 2 to 4 weeks. Although the peak was somewhat smaller in intervention facilities with handhygiene programs than in control facilities, it was present in both groups *(263)*. Children enrolled in Phoenix childcare centers for <3 weeks not only had an increased risk of sporadic diarrhea but were also significantly more likely to be ill during an outbreak of diarrhea than other children *(55)*. Children with a previous history of group childcare attendance who were newly enrolled in Houston childcare centers had an incidence of diarrheal illness comparable to that of newly enrolled children with no previous history of group childcare attendance *(262)*. This phenomenon, coupled with the large influx of children into childcare facilities in the early fall, may explain the increased incidence of *Giardia* and *Cryptosporidium* infections during the late fall and winter months.

Strategies for controlling diarrheal illness focus on preventing fecal–oral transmission (*43,48*,156). Childcare providers should ensure that their own hands and the child's hands are washed after diapers are changed (3,*63*,156). Diapers should be of a type that contains feces without leaking; clothing should be worn over diapers (3,*63*,156). Appropriate environmental sanitation must be maintained, especially in places likely to be contaminated with feces, such as diaper-changing areas. Proper handling of soiled diapers and other contaminated items such as disposable wipes must be ensured (3,*43*). Exclusion of children with diarrhea is controversial. Some authorities maintain that incontinent, symptomatic children need to be excluded (3,156). Readmission criteria for asymptomatic persons excreting enteropathogens depend on the pathogen (3,156,*204,266,267*). As public health laws frequently call for isolation of people with enteric diseases, local health authorities should be contacted regarding criteria for readmission.

Hepatitis A Hepatitis A is spread principally by the fecal–oral route. Therefore, childcare settings offer many opportunities to spread this virus. Several childcare-associated outbreaks of hepatitis A have been reported; some of these may have led to community-wide epidemics *(50,101,268–276)*. The early recognition of outbreaks in childcare facilities is complicated by the high proportion of asymptomatic or mild infections among young children. In a follow-up study of 28 outbreaks of hepatitis A in Maricopa County childcare centers, 84% of cases in children 1 through 2 years of age were asymptomatic, compared with 50% of cases in children aged 3 and 4 years and 20% in older children *(273)*. Children with hepatitis A infections who are symptomatic may be only mildly ill and these infections may not be accurately diagnosed; fewer than 10% show evidence of jaundice *(274,276)*. Outbreaks are usually recognized when cases begin to appear among the children's adult contacts *(101)*. In one study of a community-wide outbreak, household contacts of children in Maricopa County childcare facilities accounted for the largest number of outbreak-associated hepatitis A cases (204 of 342 cases) reported to the health department *(101)*. The attack rate among childcare workers (12%) was greater than that among household contacts (4%). The remainder of reported cases involved the children themselves and other adult contacts such as child sitters. Similar patterns have been reported in other outbreaks associated with childcare facilities *(275,276)*.

The distinction between factors influencing introduction of pathogens into a facility and those influencing transmission within the facility after introduction was first applied to hepatitis A *(50,275)*. Increasing hours of operation and enrollment was associated with hepatitis A introduction. Once hepatitis A is introduced, its transmission is more likely in centers that enroll younger incontinent children. Infection appears to be spread by contact between children and possibly by contamination of care providers' hands *(50,273,275,276)*. Fomites and environmental contamination may also play a role; the virus is relatively stable and can survive on environmental surfaces for up to 1 month *(265)*.

The principles for preventing hepatitis A infections in childcare facilities are similar to those for other infections transmitted through the fecal–oral route and include hand hygiene, environmental sanitation, and exclusion of ill children *(43,273)*. Universal hepatitis A immunization of children ≥1 year of age will decrease acquisition and transmission among childcare attendees and their providers and is recommended by the Advisory Committee on Immunization Practices (ACIP), *(277)*. Hepatitis A vaccine is also the preferred postexposure prophylaxis for vaccine-eligible children and adults 1 through 40 years of age who have been exposed to hepatitis A due to the longer-term protection and availability compared with hepatitis A immunoglobulin. Passive prophylaxis with immunoglobulin should be administered to individuals in whom hepatitis A vaccine is contraindicated and children and adults outside the recommended age range for postexposure prophylaxis *(278)*. Decisions to administer immune globulin and/or hepatitis A vaccine should be made in conjunction with local health authorities and the children's and care providers' physicians (3,*43*).

Blood-Borne Infections

Hepatitis B The transmission of hepatitis B virus (HBV) between people in close daily contact, such as in households and facilities for the developmentally disabled, has raised concern about transmission in childcare settings *(273,275,279,280)*. Suspected potential routes of transmission include bites and inoculation of infectious blood or body fluids onto mucous membranes or broken skin *(273,275,281)*.

Reports of HBV transmission in childcare settings in the United States are rare *(273)*. A case of apparent child-to-child transmission in a center has been reported; no specific exposure episode could be identified in that case *(281)*. In another report, a childcare provider was infected after exposure to the blood of an infected child *(282)*. Other cases of apparent transmission related to childcare have been reported from outside the United States. In Japan, where HBV is endemic, 15 of 269 children younger than 5 years who attended a nursery school were hepatitis B surface antigen (HBsAg) positive in the absence of any apparent household exposure, suggesting that transmission may have occurred in the school *(283)*. However, two different studies of separate instances in which a HBsAg-positive and hepatitis B e antigen-positive child was attending a childcare facility showed that the mere attendance of such children does not necessarily result in transmission

of infection *(281,284)*. In each instance, the child had been in the facility for more than a year before the infection was recognized and no special infection control precautions had been taken. Contact screening showed no transmission to other children or staff. Reviews of national surveillance data have not demonstrated an excess proportion of cases linked to childcare exposure *(273,281)*. Although HBV transmission can occur in childcare settings and appropriate precautions must be observed, the risk appears to be very low. Widespread compliance with recommendations for universal infant HBV immunization has significantly reduced the risk of transmission *(280,285)*.

Current guidelines recommend that children who are chronic HBV carriers may be admitted to a childcare facility if they have no behavioral or medical conditions that could facilitate transmission of HBV (3,156), including aggressive behavior (e.g., biting or scratching), dermatitis, bleeding problems, or open skin lesions that cannot be appropriately covered (3,156,*273*).

The decision to admit or not admit a child with the previously mentioned risk factors who is a chronic carrier of HBV should be made in conjunction with the child's healthcare provider, the facility's health consultant, and local public health authorities (3,*273*). Information regarding a child's HBV carrier status should be available to care providers who regularly provide care to the child; however, the confidentiality of the child and the child's family must be respected and this information must be appropriately limited to those persons who need to know to protect the child's health and the health of others (3,*273*). The child should be observed for development of any behaviors that could increase the likelihood of transmission. If a bite or other exposure places a susceptible staff member or child at risk, the exposed person should be promptly referred to his or her healthcare provider and to the health department for evaluation of the need for post exposure prophylaxis (3,156,*273*).

As symptomatic undiagnosed HBV carriers may be enrolled in childcare, all staff members should be appropriately trained and educated regarding specific precautions to avoid exposure to potentially contaminated blood and body fluids *(280,285,286)*. Asymptomatic staff members infected with HBV may be allowed to work as long as they are without dermatologic conditions that may facilitate transmission, have received necessary training, and are compliant with methods to prevent transmission of HBV (3,156).

The ACIP recommends universal immunization of infants, nonimmune children and care providers in the childcare setting with the hepatitis B vaccines series *(280,285)*.

Human Immunodeficiency Virus Initial concerns regarding the presence of children and providers with HIV in childcare facilities have not been supported. The possibility that HIV-infected individuals may be susceptible to more severe manifestations of infections transmitted in the group childcare setting and the transmission of HIV infection to others has not been observed *(287–289)*. Although immunosuppressed children may be at increased risk for severe complications from infections, including those caused by varicella, herpes simplex, CMV, *H. influenzae*, *Mycobacterium tuberculosis*, *Cryptosporidium*, and measles, information is limited on the risk that any one child with HIV will acquire a specific infection. In one study, the prevalence of intestinal parasites among children attending a hospital-affiliated childcare center for HIV-infected children was lower than the prevalence typically reported in other childcare facilities *(290)*. Rigorous prevention procedures were followed; by nature of the location, resources available to this center may have been greater than those available to most childcare facilities.

Although HIV has been isolated from several body fluids, including saliva, urine, and tears, only blood, semen, cervicovaginal secretions, and human milk have been implicated in the transmission of infection *(287,291,292)*. Extensive studies of household contacts of HIV-infected children and adults indicate a very low risk of transmission *(287)*. Only a single case of child-to-child transmission (not involving percutaneous or intravenous exposure) among preschool-aged children living in the same home has been reported *(287,293,294)*.

Transmission of HIV in childcare settings via biting is rare and probably involves exposure to blood from the biter or bitten person rather than saliva *(294,295)*. Post exposure follow-up of both parties when biting results in blood exposure should occur (156,*295*).

Skin exposure resulting from spills of human milk or vomitus is unlikely to result in HIV transmission (156).

Children who enter childcare should not be required to be tested for HIV or to disclose their HIV status. Restriction of HIV-infected children without risk factors for transmission of blood-borne pathogens in childcare facilities is not indicated. Decisions regarding the attendance of a HIV-infected child should be made on a case-by-case basis by knowledgeable individuals, including the child's physician, the child's parents or guardian, public health authorities, and the childcare facility operator or director (3,156,*288,294–296*). As is true for any child exposed to a potentially serious infection, the child's parents or guardian should be notified promptly of exposure to communicable illnesses (156). Ongoing involvement of parents, childcare providers, the child's healthcare provider, and local health officials will help to ensure appropriate care. Immunization protocols for HIV-infected children have been published by the ACIP; compliance with these protocols should be ensured (*289*,297). Updates to the recommended childhood immunization schedule occur annually and can be found at *www.cdc.hov/vaccines*.

Asymptomatic HIV-infected care providers should be allowed to provide childcare if they are without conditions that might facilitate contact between potentially contaminated body fluids and children or other adults (3,156,*288*). The potential for and management of exposures of such care providers to other infectious diseases should be addressed as recommended for HIV-infected children (3,156,*288*).

Precautions that apply to the prevention of hepatitis B are relevant to HIV-infected children and care providers. Standard precautions, including careful attention to the handling of potentially contaminated body fluids in both everyday care and as a result of less common events (e.g., blood spills or injuries) should be implemented routinely (3,*79*,156,*286,295*).

Vaccine-Preventable Diseases

Routine immunization is recommended for children and adolescents against 15 infectious diseases: measles, mumps,

rubella, diphtheria, pertussis, tetanus, poliomyelitis, Hib, hepatitis A, hepatitis B, varicella, rotavirus, human papilloma virus, influenza, and pneumococcal infections. Both the adult and childhood immunization schedules are updated annually in January, *http://www.cdc.gov/vaccines/pubs/acip-list.htm* (175). Preschool-aged children continue to have the highest age-specific attack rates of measles, rubella, pertussis, and Hib infections and can suffer more severe sequelae than older children if they become infected *(54,298)*. Most states require immunization before attendance in licensed childcare facilities, which has resulted in more complete immunization histories than children not in licensed childcare establishments *http://nrckids.org/STATES/states.htm.* Children's attendance in out-of-home childcare offers healthcare providers and the public health system an opportunity to ensure that children have received appropriate immunization.

Other Infections

Cytomegalovirus CMV infection is the most common congenital infectious disease in the United States *(102,299)*. Most congenitally infected infants are asymptomatic at birth, but, within the first few years of life, 10% to 20% of these children will experience developmental delay, sensorineural hearing loss *(300)*, cerebral palsy, and visual impairment from chorioretinitis or optic atrophy*(102,299)*. Contact with children in childcare is a well-documented risk factor for adult infection with CMV; childcare providers and family members of children in childcare are at risk *(58,78,80,82,83,85,86,99,102,103,301–309)*. When the exposed adult is pregnant, the fetus may be at risk for congenital infection. Transmission of CMV among children in out-of-home childcare is common; virus excretion rates as high as 69% have been reported, compared with lower excretion rates of 8% among similarly aged children cared for at home *(83,103,302,303)*. Restriction endonuclease patterns of CMV DNA have demonstrated transmission between children in childcare settings; infected children in the same childcare facility have been shown to share identical CMV strains *(83,301,302)*.

Children enrolled in childcare before their first birthday are more likely to be infected; mixing children younger than 18 months with children older than 18 months also appears to increase the risk of transmission. The likelihood of excretion is age dependent, with the highest excretion rates in children between 1 and 3 years of age *(103,299,301,304,306)*. More than three quarters of children aged 12 through 18 months excreted CMV in saliva or urine at the time of assessment *(308)*. One cohort of uninfected children experienced an annual acquisition rate of 3% per year *(306)*. Excretion began between 11 and 59 months after entering childcare; the duration of excretion ranged from 3 through 28 months, with excretion in the urine lasting longer than excretion in the saliva *(306)*.

High rates of transmission and excretion among children in out-of-home childcare pose an infection risk for pregnant women contacts. Baseline rates of seropositivity of CMV antibody among childcare providers ranged from 38% to 63% in one surveillance study; annual seroconversion rates among initially seronegative workers are from 8% to 20% *(80,82,308)*. In comparison, the annual seroconversion rate among 229 seronegative female healthcare providers was 2% *(80)*. Seropositivity is associated with a history of contact with children younger than age 2 years *(80,308)*; seroconversion is associated with providing care for children younger than age 3 years *(80)*.

The risk of long-term sequelae from congenital CMV infection should be communicated as part of employee counseling and education to all providers who may be at risk (3,*43*,*79*). Care providers should be given information regarding prevention through the use of appropriate hygienic precautions (3,156).

Parvovirus B19 Parvovirus B19, the etiologic agent of erythema infectiosum (fifth disease), has been linked with several conditions, including fetal hydrops and fetal death, arising from intrauterine transmission and infection *(310)*. As with CMV, concern exists regarding the risk of exposure and infection of pregnant childcare providers and exposure of mothers of childcare enrollees. The seroprevalence of immunoglobulin G (IgG) antibodies to parvovirus B19 among 122 childcare providers in Virginia was 25%, whereas that among 68 mothers of children in childcare was 29% *(311)*. The annual seroconversion rate among providers and parents of children in childcare was 1.5%. Higher prevalence and incidence rates were reported from studies during a large outbreak in Connecticut in 1988 *(87,89)*. Teachers and childcare providers were assessed using serum immunoglobulin G (IgG) as a marker for preoutbreak seroprevalence and serum immunoglobulin M (IgM) as an indicator of recent infection. The preoutbreak seroprevalence (IgG) among 50 childcare providers was 68%; 5 of 16 (31%) susceptible providers exposed to children with erythema infectiosum showed evidence of recent infection (IgM). The number of classroom exposures to children with a rash was significantly correlated with risk of infection *(89)*. In a second study during the same outbreak, the highest rates of seroconversion were among teachers (16% of susceptible persons), childcare providers (9%), and homemakers (9%) *(89)*. Teachers and childcare providers who were exposed to erythema infectiosum at work and who also had children living in their homes had higher infection rates (13%) than occupationally exposed teachers and childcare providers who did not live with children (10%) (see also Chapter 51).

Herpes Simplex Virus By 5 years of age, 42 of 115 children (37%) attending a North Carolina childcare center had evidence of primary infection with herpes simplex virus *(312)*. Children 1 year of age had the highest incidence; 20.5 infections occurred per 100 children per year. During the 12-year study, most primary viral isolates (55%) were recovered during outbreaks.

Children with mild herpes simplex virus disease and good control of oral secretions may be admitted to childcare after consultation with their healthcare providers and after staff have been reminded of the importance of avoiding contact with infected secretions (3).

INFECTION CONTROL IN CHILDCARE FACILITIES

Several excellent sources of detailed recommendations on health and safety practices in out-of-home childcare include

publications from the HCCA program, coordinated by the AAP, Early Education and Childcare Initiatives (the Section on Early Education and Childcare), and partly funded by the Childcare Bureau (CCB), Office of Family Assistance (OFA), Administration for Children and Families (ACF), and the Maternal and Child Health Bureau, HRSA, U.S. Department of Health & Human Services, *http://www.healthychildcare.org/*. The National Association for Education of Young Children http://www.naeyc.org/ offers a selection of resources and guidance documents for providers of care to young children. The National Resource Center for Health and Safety in Childcare and Early Education publishes *Caring for Our Children: National Health and Safety Performance Standards: Guidelines for Out-of-Home Childcare*. The second edition, published in 2002 is accessible at *http://nrckids.org/CFOC/index.html*, and is currently undergoing revision with a third edition expected to be available in 2011. During the increase in 2009 novel H1N1 influenza infections, the CDC developed guidance for parents, childcare providers, and healthcare professionals to reduce the transmission of influenza in childcare and school settings, *http://www.cdc.gov/flu/professionals/infectioncontrol/childcaresettings.htm*.

In addition to these reference materials, childcare facilities should have access to a health consultant, usually a clinician with expertise in pediatrics, from whom care providers can obtain advice and assistance when making decisions on health issues (3,*313*). Public health authorities and infection preventionists (IPs) may serve as consultants to childcare facilities in the community and to those facilities managed by the IPs' healthcare institution *(314)*.

General Recommendations

Many general principles of infection control in childcare settings are similar to those in healthcare settings: interruption of transmission through hand hygiene and proper handling of contaminated material, management of the environment, surveillance, limitation of the potential for exposure of susceptible persons, and adherence to recommendations for immunization of children and adolescents. As in healthcare settings, hand hygiene is considered to be the single most important step in preventing and controlling infectious diseases in childcare settings (3,*43,47,48,57*,156,*157*,159,*263*). Careful attention by providers to hand hygiene practices, both their own and those of the children, can reduce the incidence of infectious diseases *(55,57,263)*. Guidelines stress both frequency and timing of hand hygiene and use of proper technique (3). The use of alcohol-based hand sanitizers widely used in healthcare settings (159) has the potential for use in childcare settings. The use of alcohol-based hand disinfection in addition to traditional hand washing significantly reduced the rate of absenteeism by 12% compared with a child using traditional hand washing only, in an evaluation in Swedish childcare centers *(315,316)*. In an observational prospective cohort study of families with ≥1 child enrolled in out of home childcare conducted in Boston, the use of alcohol-based hand gels was protective against respiratory virus transmission in the home setting *(317)*. A school-based, cluster-randomized controlled trial involving the use of alcohol-based hand sanitizers and quaternary ammonium wipes in classrooms of third through fifth graders for 8 weeks reduced absenteeism attributable to gastrointestinal illness in elementary school students *(318)*. The use of alcohol-based hand gels was shown to be safe without the absorption of significant amounts of alcohol, despite mouthing behaviors (319). Alcohol-based hand gels may have a role in prevention of outbreaks of infectious pathogens associated with childcare settings and among children involved in activities such as petting zoos where traditional hand washing with soap and water may be impractical *(320)*. Further evaluations of hand hygiene strategies, and educational interventions would assist with allocation of resources to the most effective prevention regimens.

Attention to environmental sanitation also is an important infection control measure in childcare settings, especially in facilities with incontinent or nearly continent children. Younger children often explore by mouthing objects in their environment, resulting in contamination with feces, saliva, and other body fluids. Several of the most common pathogens causing disease among children and providers have been found on environmental surfaces and objects in childcare settings (3,*42,52,58,59,61, 226,314,321*).

Food is often prepared and served in childcare settings. Written policies should enforce meticulous care involving storage, handling, and preparation of all enterally consumed items. Policies should specify procedures for sanitization of all food preparation areas. Adherence to segregation of location and staff involved in preparation and service of food and those involved in toileting activities should be maintained (3,156). The importance of hand hygiene before preparing and serving nutrition must be stressed in training, reinforced, and monitored to ensure compliance (3).

Surveillance of Childcare Infections

As in the hospital setting, effective surveillance is central to preventing and controlling communicable diseases in childcare facilities. Although the major purpose of surveillance is to detect potential problems or outbreaks within facilities, surveillance data also can contribute to the understanding of specific risk factors for infection. The information derived from surveillance can contribute to the design of prevention and control measures and can aid development and conduct of training programs for childcare providers and parents (3,*322*,*323*). Implementation of surveillance has been associated with decreases in diarrheal illness in childcare facilities *(264)*; surveillance in childcare settings can serve as a sentinel system for illness in the community *(314,322)*.

In addition to education of childcare providers, directors, and parents, a relationship with a healthcare consultant may facilitate surveillance activities as well as reporting of infections. Frequent positive interactions between public health officials and the childcare community in the form of training sessions and educational materials may reduce concerns about confidentiality and encourage a collaborative response to potential problems. Maintenance of current lists of licensed providers by public health authorities facilitates notification of reporting requirements and is invaluable in rapidly disseminating information to childcare facilities during public health emergencies. The National Resource Center for Health and Safety in Childcare and Early Education in collaboration with the AAP and APHA, developed a comprehensive source, *Caring for Our*

Children: National Health and Safety Performance Standards: Guidelines for Out-of-Home Childcare Programs that lists over 700 health and safety practices. Updates posted to an internet-based site, *http://nrckids.org/CFOC/updates.htm* are designed to keep providers up to date with the latest guidelines for quality childcare. Additionally, the AAP has appointed Chapter Childcare Contacts (CCCCs) in each of its State Chapters to provide a network of pediatric childcare experts who can mobilize efforts to improve the health and the safety of children in childcare and engage parents in discussions about quality care and their options. Each volunteer is a member of the Section on Early Education and Childcare and is appointed by the AAP Chapter to serve as a liaison between their chapter and stakeholders regarding early education/childcare topics and initiatives.

Role of the Health Department

State and local health departments play an important role in monitoring the health status of children in childcare. For example, they routinely ask about childcare contacts in case investigations of notifiable diseases and generally intervene quickly to interrupt transmission when they learn of an outbreak (3,*314,324,325*). Health departments are often a principal resource for information, training, and education for childcare providers and parents. Public health officials often serve as consultants to childcare licensing and regulatory agencies. Some communities have model programs in which health departments serve as a focus for developing community-wide programs for child health and safety (3,*314,324,325*).

Training and Education

Staff Training Successful childcare infection control programs require high levels of staff training and education. Childcare providers are less likely to receive infection control training than healthcare providers; however, when childcare providers understand the rationale for guidelines and practices, they are more likely to translate education into practice *(326)*. Studies have shown that care providers need and are interested in receiving training, independent of licensing requirements *(81,327)*. This curriculum should cover basic infection control principles, and providers should understand the potential risks of infections that may be acquired in childcare settings (3,*79*). Additional topics to address include techniques to control those risks, including hand hygiene, environmental sanitation, avoidance of exposures to blood and body fluids, and personal protection including immunizations *(55,60,81,86*,156,*326*). Educational efforts in which childcare providers may actively participate in are self-directed learning, and opportunities for periodic updates may be received and accepted with retention.

Health Education for Parents The childcare setting offers unique opportunities to provide health education to parents and to care providers (3). Tailored to the specific setting, educational programs could provide information about immunization, signs of illness requiring medical consultation, fluid replacement for diarrheal disease, proper use of antipyretics and judicious use of antimicrobial agents.

Exclusion and Inclusion

Among the more difficult problems in the childcare setting is establishing and implementing appropriate criteria for excluding ill children from the facility. Parents of excluded children must either seek alternative forms of childcare or miss work to care for an excluded child. Much of the economic burden of childcare-associated illness is due to parental absenteeism (Table 53-2).

TABLE 53-2

General Recommendations for Exclusion of Children in Out-of-Home Childcare

Symptom(s)	*Management*
Illness preventing participation in activities, as determined by childcare staff	Exclusion until illness resolves and able to participate in activities
Illness that requires a need for care that is greater than staff can provide without compromising health and safety of others	Exclusion or placement in care environment where appropriate care can be provided, without compromising care of others
Severe illness suggested by fever with behavior changes, lethargy, irritability, persistent crying, difficulty breathing, progressive rash	Medical evaluation and exclusion until symptoms have resolved
Rash with fever or behavioral change	Medical evaluation and exclusion until illness is determined not to be communicable
Persistent abdominal pain (2 h or more) or intermittent abdominal pain associated with fever, dehydration, or other systemic signs and symptoms	Medical evaluation and exclusion until symptoms have resolved
Vomiting two or more times in preceding 24 h	Exclusion until symptoms have resolved, unless vomiting is determined to be caused by a noncommunicable condition and child is able to remain hydrated and participate in activities
Diarrhea or stools containing blood or mucus	Medical evaluation and exclusion until symptoms have resolved
Oral lesions	Exclusion until child or staff member is considered to be noninfectious (lesions crusted and dry)

(Used with permission of the American Academy of Pediatrics. Children in out of home care. In: Pickering LK, Baker CJ, Kimberlin DW, et al., eds. *Red book: 2009 report of the committee on infectious diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics.)

Overly strict exclusion policies can create tension between parents and care providers and encourage parents to enroll, or "drop in," an ill child at other facilities without notifying the new facility of the child's health status; this may introduce an infection into a new group of susceptible children *(43)*. Failure to exclude ill children when it is appropriate to do so may increase the risk of transmission to other children in the facility, childcare providers, household contacts of enrollees, and thus the community at large. Ill childcare alternatives for conditions that do not require exclusion may offer parents an opportunity to maintain childcare while fulfilling their work obligation. Open communication between parents and providers will facilitate the provision of optimal care for a child and his or her contacts.

In a telephone survey evaluation of the rate of unnecessary exclusion decisions by childcare directors in a state that endorses AAP/APHA guidelines, directors reported that they would have unnecessarily excluded 57% of children. More than 62% of directors were unaware of AAP/APHA guidelines. Regression analysis demonstrated fewer exclusion decisions by experienced compared with less experienced directors and among larger enrollment centers compared with smaller enrollment centers. This evaluation supports the premise that focused initial and ongoing training of directors regarding AAP/APHA guidelines may help to reduce high rates of unnecessary exclusions (328).

Cohorting and Ill Childcare

In the event of an illness outbreak, the benefits of closing a facility to prevent additional spread of disease should be weighed against the possibility of infected children being sent to other facilities *(44,199,205)*. Cohorting—separating infected and uninfected children into different groups—has been proposed as an alternative to excluding children who are well enough to attend childcare but who may have a transmissible infectious disease. Although this strategy is feasible, it requires careful monitoring to determine which children are and are not infected and to ensure that this separation is maintained. Cohorting may be resource intensive for an individual childcare center, frequently requiring additional staffing and rearrangements of existing or additional physical space. Although the initial increased use or reallocation of resources may be significant, in certain situations, these efforts may interrupt transmission of an outbreak. Small centers with skeleton staff may not be able to accommodate the increased resources of cohorting *(203,267)*. The involvement of local and state health authorities may facilitate cohorting efforts by more than one childcare facility in a community promoting the sharing of resources and maintaining childcare arrangements.

Role of the Healthcare Provider

Guidelines for exclusion of infants and children from group childcare settings exhibiting signs and symptoms consider the prevalence of mild illness among children, frequent transmission of infection before recognized symptoms, and the infectious potential of asymptomatic children. Most children do not need to be excluded from childcare when they have mild respiratory tract illnesses. However, children in obvious discomfort, those whose symptoms interfere with their ability to participate comfortably in childcare activities, and those whose illness requires a level of attention by staff that may interfere with the care of other children, should be excluded from a group childcare setting (3,156). Most states have regulations requiring isolation of people with various types of communicable diseases, including those common among childcare attendees. These regulations vary by region and take precedence over recommendations from other entities. Local or state health departments should be contacted for information about these regulations, their interpretation, and enforcement.

Healthcare professionals may perform a significant service as advisors or consultants to childcare providers. In return, the professional will become more knowledgeable regarding the composition and structure of group childcare options. This partnership may be especially beneficial in situations involving cohorting or exclusion of children or staff in an outbreak setting. Furthermore, if a childcare center enrolls children or staff with special medical or social needs, the contributions of a childcare consultant may be instrumental to the childcare center's provision of care. In addition to providing advice regarding inclusion and exclusion criteria, childcare consultants may serve as sources for information on a range of topics including medication administration, immunization, and optimizing infection control practices. Furthermore, their input as educators for enrollees, staff, and parents may provide additional expertise based on their training. Additional resources for locating a childcare consultant may be found through the HCCA Campaign *www.healthychildcare.org* and the National Training Institute for Childcare Health Consultants, *http://nti.unc.edu/*.

Environmental Control

Disinfection An overriding principle in environmental control of infectious diseases is good physical cleaning using a detergent or detergent-germicide solution. Many difficulties in recommending the use of specific products or formulations for hospital disinfection also apply to the childcare environment *(265)*. In addition, because children crawl on the floor and mouth objects or furnishings, children in childcare, unlike hospitalized patients, are at risk for exposure to toxic substances used for cleaning and disinfection. Thus, disinfectants may need to be assessed in ways not always relevant to the hospital setting (e.g., the potential for chemical residue to remain on environmental surfaces such as floors, walls, and furniture and the risk that chemical agents may be accidentally ingested). The U.S. Environmental Protection Agency registers specific products as detergent-disinfectants for cleaning and disinfecting various settings and materials. The APHA/AAP standards recommend a diluted bleach solution for disinfection in childcare settings (3).

Physical Facilities The design of the environment in and around the facility can directly affect the risk of infectious diseases *(67)*. Ideally, areas for different activities that may affect health risks—diaper changing, play, and food preparation and handling—should be physically separated. Diaper-changing areas, accessories, and receptacles

should be arranged to facilitate appropriate hygiene while changing, handling, and disposing of soiled diapers (3). Sinks should be easily accessible, preferably within arm's reach of the changing area. Children of different age groups should be separated to decrease exposure of older children to environmental fecal contamination. Environmental surfaces, including furnishings and other objects in childcare facilities, should be easy to clean and disinfect (3,*67*). Toys that are shared by children should be cleaned and disinfected daily and removed from circulation when obviously contaminated with saliva or other body fluids (3).

Personnel Health Issues

All staff should have a health appraisal before initiation of childcare activities (3). This evaluation should include documentation of receipt of recommended immunizations or immunity to vaccine preventable diseases for adults, *www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm#print*, or for adolescent volunteers and providers, *www.cdc.gov/vaccines/recs/schedules/child-schedule.htm#printable*. All adolescents and adults with anticipated child contact should undergo tuberculosis screening and appropriate management if indicated before care-giving activities are initiated (3). Annual screening may be indicated based on the risk of acquiring a new infection and on local and state health department recommendations. Additionally, adolescents and adults who are not considered to be staff, but who spend a significant amount of time in a location where care is provided to infants and children, should undergo annual tuberculosis screening. All people over 6 months of age should receive influenza immunizations annually, unless contraindicated. Orientation and periodic refresher courses reinforcing strategies for prevention of infectious diseases, including hand and respiratory hygiene as well as effective diapering and food-handling practices should be provided to maintain competence. Although infections with pathogens including CMV, parvovirus B19, and novel H1N1 influenza may have implications for susceptible pregnant women, Standard Precautions should be routinely practiced despite a provider's or a child's infectious disease status. Childcare providers should practice the same criteria for inclusion and exclusion of themselves as for the children to whom they provide care.

Recommendations for Prevention of Specific Infections

The spread of infectious diseases in childcare settings is best prevented by careful adherence to routinely recommended precautions: hand hygiene; environmental sanitation; and care in handling potentially contaminated material such as tissues, diapers, eating utensils, and mouthed toys (3,*265*). Special care should be taken with exposures to blood or blood-containing body fluids. Children and care providers should be appropriately immunized, and access to immunization records should be available to the facility operator or director (156). Public health officials and parents should be notified if a child or caregiver is exposed to a communicable disease; exposed persons should be referred, as appropriate, to both the health department and healthcare providers for chemoprophylaxis or immunoprophylaxis. Persons who could transmit infection may need to be excluded from the childcare setting (3,156).

Vaccine-Preventable Diseases All children enrolling in childcare should have written documentation of age-appropriate immunizations (297). Depending on local public health and licensing regulations, unimmunized children may be allowed to attend childcare if the appropriate immunization series has been initiated within 1 month of enrollment and completed according to recommended schedules. Unimmunized children, or those who are exempt from routine childhood immunizations for medical or other reasons, should be excluded if the facility has cases of a vaccine-preventable disease to which they may be susceptible. These children may be permitted to return to the center after the risk of exposure no longer exists or they have been appropriately immunized.

THE NEED FOR ONGOING RESEARCH

The increasing number of infants and children enrolled in group childcare has resulted in an increased awareness of infections associated with these settings. Recommendations for practices with regard to transmission, inclusion and exclusion criteria, and personal hygiene are based on clinical and epidemiological studies performed in previous decades. A need to reevaluate the findings and recommendations from these studies is indicated. Updated recommendations based on evaluations using newly developed laboratory molecular techniques could improve our understanding of transmission as well as identification of pathogens. These evaluations would have clinical, social, and economic impact on the growing number of infants and children, parents, and providers who are stakeholders in group childcare. Resource allocation to perform innovative clinical and molecular epidemiological studies in childcare centers would facilitate practices with current guidelines and recommendations.

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SECTION VII

Epidemiology and Prevention of Healthcare-Associated Infections in Special Patient Populations

CHAPTER 54

Healthcare-Associated Infections in Dental, Oral, and Maxillofacial Surgery

Cynthia J. Whitener

Dental and oral surgical procedures are some of the most frequently performed minor surgical procedures in the United States. Because these procedures rarely occasion admission to hospital, either for the initial procedure or for the care of a complication, data on incidence rates for procedure-related infections in this setting are limited. Maxillofacial surgery is more commonly performed in an inpatient setting, especially surgery for reconstructive purposes after trauma or that involving major restructuring of bones for cosmetic surgical reasons. Therefore, more information exists concerning risks of procedure-related infection for maxillofacial procedures. Because of the recognition of human immunodeficiency virus (HIV) transmission in one dentist's practice, national attention has been focused on infection control practices in dentistry (1). This chapter discusses the infections seen in these settings, their recognition, and measures for their prevention.

MICROBIOLOGY

Infections after surgery to the gums or teeth or involving mucosal incisions made in the mouth are caused by a combination of the aerobic, facultatively anaerobic, and anaerobic microorganisms found in the saliva and the gingival crevices *(2,3)*.

The number and variety of bacteria found in the oral cavity of each person increase as he or she matures, the dentition erupts, and the flora of the gingival crevice establishes itself. Cross-sectional surveys have suggested that a few anaerobes are present in the mouth of young children before the eruption of their first deciduous teeth *(4,5)*. Older children have a microbial flora closely approximating that of the mature dentulous adult.

In recent years, the breadth of bacterial diversity in the mouth has been appreciated due to the availability of advanced molecular and bioinformatic tools. Numerous formerly uncultivable species have been recognized. Although it is likely that not all oral flora have been identified yet, well over 500 bacterial species are now thought to coexist in the mouth, of which an estimated 50% are uncultivable *(6–8)*. While the variety in any individual is less, studies suggest there still may be more than 50 to 70 species present *(6,9)*. The composition of the oral flora is dynamic, partly because of its connection with the external environment. The microbiome of the mouth is influenced by numerous factors, including genetics, illness, hospitalization, age, diet, hormones, medications, salivary gland secretions, chemotherapy, radiation, dentures, and artificial devices, and, importantly, by oral hygiene (*9*,10,*11*,*12*). Species that generally constitute >80% of the total cultivable oral flora are *Streptococcus, Peptostreptococcus, Veillonella, Lactobacillus, Corynebacterium*, and *Actinomyces* (10). Facultative gram-negative bacilli are infrequent in healthy adults but are common in hospitalized and seriously ill patients.

Within the mouth, bacterial biofilm microcosms are present on the mucosal surface of the tongue, buccal mucosa, tooth surfaces, gingival crevices, and artificial surfaces such as appliances and prostheses, each site with a unique constitution *(13)*. A group of 20 to 30 predominant species are found in each niche, though *Streptococcus* is the predominant species found in nearly all sites *(6)*. While

most studies have focused on bacterial biofilms, fungi, specifically *Candida albicans* and *Saccharomyces cerevisiae*, also can be found in some periodontal niches *(14)*. Most salivary flora are aerobic and facultatively anaerobic, whereas many microorganisms in the gingival crevice are anaerobic. In addition, there are generally many more microorganisms per gram in the latter location. There appears to be no relationship between the appearance of the tongue (presence of white coating or not) and salivary bacterial load *(15)*. Table 54-1 lists the predominant cultivable microorganisms in the saliva and gingival crevice of adults (10,*16–19*).

Using standard culture techniques, studies in the 1990s suggested that key periodontopathogens were eliminated after full teeth extraction. However, a more recent study utilizing qPCR methodology in nine patients before and 6 months after full mouth tooth extraction observed a reduction in, but not eradication, of potential pathogens. A 3-log reduction of *Porphyromonas gingivalis* and *Tannerella forsythia* and lesser reductions of *Aggregatibacter actinomycetemcomitans* and *Prevotella intermedia* were seen. It is unclear if residual lower concentrations have clinical relevance *(20)*.

Although no studies have documented transmission of oral flora from one patient to another in the dental operatory, Genco and Loos *(21)* reviewed several studies using molecular epidemiologic techniques to demonstrate the transmission of *Streptococcus mutans* by vertical transmission from mother to infant and intrafamilial transmission of *A. actinomycetemcomitans*. These studies are the first to document the spread of oral microorganisms and raise the possibility of whether oral bacteria can be transferred in a medical setting from one patient to another.

TABLE 54-1

Common Cultivable Flora of the Oral Cavity

Saliva	*Gingival Crevice/Plaque*
Streptococci	Streptococci
S. salivarius group	*S. mutans* group
S. mitis	*S. mitis*
S. sanguis	*S. sanguis*
Peptostreptococcus	*Peptostreptococcus*
Lactobacillus	*Lactobacillus*
Staphylococcus aureus	*Treponema*
Corynebacteria	*Eikenella corrodens*
Neisseria	*Neisseria*
Branhamella	*Branhamella*
	Actinomyces
	Eubacterium
Veillonella	*Veillonella*
	Leptotrichia
Herpes simplex	*Bacteroides*
Candida albicans	*Porphyromonas*
	Prevotella
Entamoeba gingivalis	*Capnocytophagia*
Trichomonas tenax	*Fusobacterium*
	Aggregatibacter actinomycetemcomitans

Many aerobic bacteria transiently colonize or infect the pharynx and posterior nasopharynx. Recognition of these agents depends either on characteristic clinical symptoms, such as the chancre of syphilis or the adherent membrane of diphtheria, or on culture to demonstrate the presence of group A β-hemolytic streptococci or *Neisseria meningitidis*.

The viruses frequently present in saliva are those agents causing latent infection, particularly the herpes group and less commonly hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV *(22)*. Herpes simplex virus (HSV) has been recovered from the saliva of approximately 1% of asymptomatic children and between 0.75% and 5% of asymptomatic adults. Serial sampling of the saliva from normal adults over time has demonstrated that HSV can be recovered from oral secretions in over 50% of adults in the absence of clinical lesions. More than 50% of seropositive patients undergoing organ transplantation will shed oral HSV asymptomatically *(23)*. Acyclovir prophylaxis results in a decreased incidence of viral excretion after bone marrow transplantation *(24)*. Not surprisingly, HSV is a recognized occupational hazard for dentists, oral surgeons, and dental technicians.

Cytomegalovirus (CMV) has been isolated from salivary glands, adenoid tissue, and pharyngeal secretions. The prevalence of antibody to CMV increases with age and is further increased among people from lower socioeconomic groups. In seroprevalence studies performed in the 1970s, between 40% and 80% of adults had serologic evidence of infection with CMV by the age of 40 *(25)*. CMV excretion is increased in the presence of transplantation and immunosuppression. No transmission to dental workers or medical staff has been shown *(26)*.

Epstein–Barr virus (EBV) is another herpes virus that causes acute infectious mononucleosis followed by a chronic infection of lymphocytes. It is also associated with oral hairy leukoplakia. The prevalence of infection as indicated by the presence of antibody is higher at early ages in the tropics and in underdeveloped countries. Prevalence progressively increases with age in developed countries *(27)*. Saliva is the primary vehicle for EBV transmission from person to person, though no transmission to dental workers or medical staff has been demonstrated. EBV has been implicated in the pathogenesis of periodontitis, but more studies are needed to determine its true significance *(28,29)*.

Herpesvirus 6, herpesvirus 7, and herpesvirus 8 have been identified in up to 29% of gingival biopsies of HIV-seronegative adults with periodontitis, suggesting that the periodontium might constitute a reservoir for these viruses *(30)*.

The blood-borne viruses, including HBV, HCV, and HIV, may be present in the saliva of persons with chronic infection. Small cuts and abrasions in the oral cavity, especially when made acutely during dental or intraoral surgery, serve as the primary sources for seeding the saliva with virus. These viruses are addressed in the epidemiology section of this chapter.

Many other viral agents can be recovered from oropharyngeal secretions during or after acute infection. These agents include polioviruses, coxsackieviruses and echoviruses, influenza viruses A and B, rhinoviruses, and coronaviruses. Despite the occasional isolation from saliva and nasal secretions of these viruses and the childhood

respiratory pathogens rubeola (measles), mumps, and rubella, no occupationally proven transmission of any of these viral agents to a dental worker has been documented, except one case of coxsackievirus infection *(22)*. However, seroprevalence studies have shown a higher prevalence of antibodies to influenza A and B viruses, respiratory syncytial virus, and adenovirus among dentists compared with controls *(31)*. Dental procedures should be avoided in patients suspected of having active severe acute respiratory syndrome, which is caused by a coronavirus and is likely transmitted by droplet and contact routes.

Yeasts and fungi also are part of the normal flora of the oral cavity. *C. albicans* can be isolated from the mouths of approximately 55% of healthy people. Many other species of *Candida* are found less frequently. The dorsum of the tongue has the greatest density of yeast. Carriage rates for yeast are increased among hospitalized patients, people with dentures, persons who are blood type O or nonsecretors, solid organ transplant recipients, and in HIV-positive populations *(32–35)*. Transient carriage of filamentous soil fungi such as *Aspergillus* spp. and zygomycetes can be shown.

Protozoa are also normal inhabitants of the mouth. *Entamoeba gingivalis* and *Trichomonas tenax* are the most common commensals recovered *(36)*.

TYPES OF INFECTIONS

Infections of the oral cavity and maxillofacial regions can be grouped loosely into the categories of localized infection, infection by direct extension, and distant infection.

Localized infections can be classified as dentoalveolar, periodontal, infections of the salivary glands or tonsils, and cellulitis from tissue injury. Dentoalveolar infections are also known as odontogenic infections and include carious teeth with resulting infections of the dental pulp and periapical dental abscess. Infections involving the gingiva, periodontal ligament, and other tissues supporting the teeth are known as periodontal infections. These infections include gingivitis and acute necrotizing ulcerative gingivitis (ANUG). Periodontal disease has been shown to be a risk factor or marker for coronary heart disease *(37,38)*. Parotitis and sialoadenitis are infections of glands.

Infections resulting from the direct extension of one or more of these localized infections include osteomyelitis of the mandible or maxilla, infection of the deep fascial spaces (e.g., submandibular, canine, and retropharyngeal), maxillary sinusitis, noma (necrotizing infection of the cheek), posterior mediastinal infection, and anaerobic pulmonary infection. The anatomy of the deep fascial spaces is beyond the scope of this discussion but is well treated in standard texts *(2,4,19)*.

Distant infections that may develop secondary to oral infection include cerebral, spinal, and liver abscesses, and septic arthritis *(39–44)*. Remote spread of bacteria from the oral cavity to implanted prosthetic devices via the bloodstream is well documented *(45,46)*. Herpetic gingivostomatitis is occasionally complicated by secondary bacteremia, and there are numerous reports of septicemia related to mucositis and/or gingivitis, particularly in immunocompromised patients *(47,48)*. The risk of bacteremia may rise with increasing severity of gingival inflammation.

PATHOGENESIS OF INFECTION

Localized Infection

Infection of the dental pulp may result from microbial penetration directly through the dentin secondary to dental caries, dental drilling, or tooth fracture or by hematogenous spread. The most common cause of pulpal infection is from dental caries that begins with the formation of dental plaque. Regular oral care is needed to prevent plaque buildup. Plaque is composed of a large number of bacteria ($>10^8$ colony-forming unit [CFU]/mm^3), including *S. mutans*, which firmly adhere to the enamel of the tooth. These bacteria secrete enzymes that progressively dissolve away the tooth enamel and dentin, permitting the bacteria to access the pulp *(49)*. Microbial infection of the pulp (pulpitis) results and manifests clinically with pain and temperature sensitivity in the tooth. If the infection is not recognized and treated, the bacteria may then migrate through the pulpal foramen at the apex of the tooth into the alveolar bone at the root of the tooth, forming a periapical abscess, or extend beyond into the medullary space of the mandible, resulting in osteomyelitis.

Gingivitis is a periodontal process. Mild inflammation of the gums is present in almost all adolescents and in most American adults *(50,51)*. Acute and chronic gingivitis begin with the formation of plaque below the gumline. Swelling and hyperemia of the free gum margin occurs, and the gums may bleed easily with brushing. Gingivitis is increased in frequency or severity in certain patient groups such as HIV-positive patients, cancer patients undergoing chemotherapy, and young patients with type 1 diabetes mellitus *(52)*. Cessation of dental oral hygiene results in the appearance of gingivitis within 10 to 21 days.

Periodontal infections usually begin with gingivitis. As the infection becomes chronic, it extends deeper into the junction between the tooth and gingiva. This leads to loss of the connective tissue attaching the tooth to the bone (the periodontal ligament) and resorption of the bone. The resulting periodontitis causes a pocket to form between the tooth and the gingiva. This space is ideal for the growth of anaerobes due to the very low reduction oxidation potential. Spirochetes, of many morphotypes, some uncultivable, appear to be one of the predominant bacteria in advanced lesions *(53,54)*. The chronic infection that occurs causes loosening and then loss of teeth. Periodontal abscesses result from infection of deep periodontal gingival pockets *(55,56)*. Needle aspiration and appropriate culture of pus from dentoalveolar abscesses reveal a polymicrobial flora with a predominance of facultatively anaerobic streptococci together with obligately anaerobic gram-positive cocci and gram-negative rods *(57)*. Over 60% of these infections include aerobic microorganisms, whereas approximately one third have purely anaerobic isolates. In an analysis of apical abscess aspirates from 42 persons using reverse capture checkerboard hybridization assay, the most prevalent microorganisms were *Fusobacterium nucleatum, Parvimonas micra, Porphyromonas endodontalis*, as well as streptococci, *Olsenella uli, Eikenella corrodens*, and other anaerobes such as *Prevotella (58)*.

The most extreme form of gingivitis is ANUG. ANUG represents tissue invasion and destruction by mixed anaerobes and facultatively anaerobic bacteria. Data suggest an important role for spirochetes and for *Fusobacterium* spp. *(59)*. In HIV-seropositive patients, yeasts and herpes viruses may also contribute *(60)*. ANUG manifests as a loss of the papillae between adjacent teeth and results in exposure of the roots of the tooth. There is bleeding of the gingivae with blunting and necrotic punched-out lesions of the interdental papillae. The disease is characterized by the sudden onset of pain and tenderness of the gums associated with increased salivation and a peculiar metallic taste, and it is accompanied by systemic symptoms. ANUG most frequently occurs in adolescents and young adults. Risk factors include poor oral hygiene, infrequent dental care, poor nutrition, and possibly diabetes *(61)*. Prevalence studies have demonstrated that 4% of students using dental services at Harvard University and 6.7% of 9,203 adolescents in Chile have this condition *(61,62)*. *Stenotrophomonas* bacteremia associated with ANUG in a young girl with leukemia has been reported *(63)*.

Acute suppurative parotitis is a healthcare-associated infection that occurs after surgery or in patients who are predisposed because of malnutrition, immunosuppression, or dehydration or in whom drugs have been used that decrease salivary flow *(64,65)*. Such drugs include anticholinergic agents, antihistamines, and tranquilizers. The pathogenesis of this infection is presumed to be retrograde movement of mouth microorganisms up the parotid duct in patients with diminished rates of salivary flow. The condition is unilateral in 80% to 90% of cases and presents clinically as the acute onset of unilateral facial swelling with pain. Physical examination demonstrates purulent fluid, which can be expressed from the parotid duct. The microbial causes reported in the older literature were *Staphylococcus aureus* in the vast majority *(64)*. Newer studies using proper anaerobic culture methods demonstrate anaerobes in most patients *(66)*. The microorganisms are the same as those recovered from the gingival sulcus. Methicillin-resistant *S. aureus* has been reported as the cause of one outbreak in a nursing home *(67)*.

Acute tonsillitis is rarely an institutionally related infection unless an outbreak of acute group A β-hemolytic streptococcal infection is spreading through the population. Although group A β-hemolytic *Streptococcus* is the most commonly recognized cause of tonsillitis, the significance of recovery of other microorganisms such as mycoplasma, chlamydia, and anaerobes from inflamed tonsils has been debated *(68–72)*. The pathogenic role of these bacteria is not known. Microbiologic studies of the core of tonsils removed from 150 children with recurrent tonsillitis due to group A β-hemolytic *Streptococcus* during three periods beginning in 1977 and ending in 1993 revealed mixed flora (8.1 microorganisms per tonsil) in all tonsils and an increased rate of recovery of β-lactamase–producing bacteria with time *(73)*.

Erysipelas, a soft tissue infection of the cheek due to direct extension of bacteria from the mouth, is often due to group A or C streptococci. This rare complication follows 2 to 3 days after oral surgery and represents bacterial entry into soft tissues injured by instrumentation.

Noma (gangrenous stomatitis) is an acute, fulminant, necrotizing infection of the cheek and facial tissue that destroys the oral and para-oral structures and is found predominantly in malnourished children, particularly in sub-Saharan Africa. Certain groups of patients in developed countries may develop noma-like lesions that are slowly progressive. These persons are malnourished or have underlying illnesses such as leukemia *(74)*. The antecedent lesions to noma are believed to be oral herpetic ulcers, necrotizing gingivitis, or a buccal abrasion due to the rubbing of a tooth or from surgery *(75,76)*. Infection of these precursor lesions with synergistic bacteria, such as *Fusobacterium necrophorum* and *Prevotella*, causes progressive full thickness necrosis of the cheek, leaving a large open defect through which the mandible and tongue can be seen *(76–78)*.

Cervicofacial actinomycosis is a rare disease most commonly caused by *Actinomyces israelii*. The portal of entry is through disrupted mucosal barriers after trauma, dental manipulations, or oral and maxillofacial surgery *(79,80)*. The infection often appears as a chronic, slowly progressive induration or soft tissue mass in the mandibular–preauricular area and is sometimes accompanied by fistulous tracts to the skin that release sulfur-like granules. Systemic signs usually are absent *(81)*.

Primary oral tuberculous lesions are seen rarely *(82–84)*. Primary lesions usually occur in younger patients, are painless, and are associated with cervical lymphadenopathy. Secondary oral tuberculous lesions are more common and are seen mainly in older persons. Although the lesions are variable in appearance, the ulcerative form is the most usual, occurring on the tongue base or gingiva. These lesions are often painful. Most of these patients have accompanying active pulmonary tuberculosis *(85,87)*.

There are many oral complications from cancer therapy, one of the most prominent of these being infection. As a result of treatment effects on the mouth and immunosuppression, the oral cavity has the potential to become a reservoir for opportunistic microorganisms. *Candida* microorganisms are the primary cause of opportunistic fungal disease in patients who are immunocompromised. As many as 60% of cases of fungal septicemia in cancer patients are associated with prior oral infections *(88)*. The most common oral manifestation of a candidal infection is pseudomembranous candidiasis, manifested by removable white curd-like plaques over an inflamed mucosa. Other forms include leukoplakia-like white plaques that are not removable, referred to as chronic hyperplastic candidiasis, and chronic erythematous candidiasis that appears as patchy or diffuse mucosal erythema. Oral infections can extend to involve the esophagus. Because of the widespread use of azole prophylaxis in leukemia patients, candidiasis has become less common in this population. However, *C. krusei*, a fluconazole-resistant *Candida* species, and *C. glabrata*, an azole dose-dependent *Candida* species, now make up the majority of cases in hematology units *(89)*.

Aspergillosis is the second most frequent fungal infection in cancer patients, particularly patients with hematologic malignancies *(90)*. The paranasal sinuses are the most common sites of *Aspergillus* infection in the facial region, but there have been a few reports of primary oral

aspergillosis *(90–95)*. The oral lesions initially manifest on the gingiva and then develop into necrotic ulcers covered by a pseudomembrane. Spread to the alveolar bone and facial muscles may occur rapidly.

HSV is the most common viral pathogen in patients receiving cytotoxic agents or bone marrow transplants. The vesicular lesions on an erythematous base may appear anywhere on the mucosa and in addition to the mouth can involve the respiratory and gastrointestinal tracts. In immunocompromised patients, the oral mucositis associated with HSV may be particularly painful, severe, and prolonged. The oral HSV ulcerations may act as portals of entry for bacterial and fungal microorganisms *(47)*.

The most frequent viral infection following solid organ transplants is CMV. This infection can develop in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis *(96)*. Oral manifestations, when they occur, are nonspecific and require biopsy to confirm the etiology. The infection often consists of a single, large, shallow ulceration *(97)*.

Infections by Direct Extension

An epidemiologic retrospective study of hospitalized patients with maxillofacial infections noted differences between pediatric and adult patients. Upper face infections predominate in children (81%), whereas in adults, lower face infections, mainly odontogenic or peritonsillar, are more common (66%) (98).

Osteomyelitis of the jaw (usually the mandible) most often results from chronic infection of a tooth, either from periapical abscess or from gingivitis. Other risk factors for osteomyelitis of the jaw include compound jaw fractures, diabetes mellitus, treatment with steroids, and surgery. Infection is particularly likely to occur when surgery is performed after irradiation of the mandible for tumor removal or after compound fracture of the mandible through the socket of a molar tooth. The causative agents reflect the broad range of microorganisms in the mouth, but most often seem to be due to streptococci and anaerobes (such as *Actinomyces, Prevotella, Bacteroides, Porphyromonas*, and *Fusobacterium*) in addition to *S. aureus* in persons with underlying illness *(81)*.

Peritonsillar abscesses arise by direct extension from infected tonsils and tonsillar remnants and are rarely healthcare associated in nature. It is critical to recognize and treat this infection to avoid respiratory compromise and other serious complications *(99–102)*.

Maxillary sinusitis caused by mixed aerobes and anaerobes is recognized as a complication of periapical dental abscesses in the upper teeth and following dental/oral procedures in this region of the mouth *(103,104)*. Sinusitis sometimes complicates extraction of the premolars and molars on the upper side, because the root tips of these teeth almost touch the lower border of the maxillary sinuses *(105)*.

Retropharyngeal abscesses arise by direct extension from uncontrolled tonsillar infection or after perforation of the posterior pharyngeal wall by a foreign body. The foreign body may be a bone or another sharp object carried in the mouth. A retropharyngeal abscess presents initially with pharyngeal discomfort, limited neck motion, and nonspecific constitutional symptoms, including fever and chills *(106)*. In its later stages, the abscess can be recognized by forward displacement of the posterior pharyngeal wall *(107)*. A lateral soft tissue film of the neck or computed tomography of the neck is required for diagnosis and will demonstrate air fluid levels or pockets of air in the retropharyngeal space. Clinical differentiation between a retropharyngeal abscess and cellulitis of the retropharyngeal space is difficult and may be accomplished by performing needle aspiration of the area. A return of pus signifies an abscess *(108)*. Prompt recognition and urgent surgical management by incision and drainage are the standard treatment, because the retropharyngeal space directly communicates with the posterior mediastinum and life-threatening complications such as necrotizing fasciitis and carotid artery rupture may occur rapidly *(109–112)*. There are reports of children being treated successfully without surgical intervention *(106)*.

Carotid artery mycotic aneurysm associated with dental surgery procedures have been noted in the literature on several occasions *(113)*. Patients develop fever and a rapidly enlarging neck mass shortly after the procedure. Prompt diagnosis and treatment are essential for an acceptable outcome.

Anaerobic pulmonary infection ("aspiration pneumonia") due to mixed anaerobes and facultatively anaerobic microorganisms occurs after aspiration/microaspiration of oropharyngeal secretions. Clinical evidence suggests that the presence of severe gingivitis and/or oral surgery on the gums is associated with subsequent development of aspiration pneumonia. Clearly, the very large numbers of microorganisms ($>10^{10}$ microorganisms per gram of tissue) found in gingival material provide a large inoculum if aspirated into the lungs. The interplay of local host defenses to clear the bacteria and the frequency of dental procedures on patients with gingivitis suggests that local host defenses usually overcome this inoculum.

Deep fascial space infections in the upper neck and underneath the jaw usually result from direct extension of odontogenic or oropharyngeal infection, and they have been associated with dental extraction *(114–119)*. Ludwig's angina is a diffuse fasciitis and cellulitis with edema of the soft tissues of the neck and floor of the mouth, originating in the submandibular and submental spaces. It is the result of a polymicrobial infection, often related to peritonsillar or parapharyngeal abscesses, mandibular fracture, or oral mucosal injuries. Airway compromise is the leading cause of death *(119)*. Progression of infection upward may involve the whole side of the face, including the eyelids and orbit, whereas downward movement of infection can lead to necrotizing cervical fasciitis or mediastinitis. The anatomic parameters influencing the spread of infection in these areas is beyond the scope of this chapter but is covered in other works *(19,50)*.

Distant Infection

Many distant abscesses have been reported as complications of dental and periodontal infection, including brain abscess, meningitis, paraspinal abscess, liver abscess, suppurative jugular thrombophlebitis (Lemierre's syndrome), septic cavernous sinus thrombosis, septic arthritis, cellulitis, and necrotizing cavernositis of the penis *(39–44,120–124)*. The route of migration is held to be bacteremia.

EPIDEMIOLOGY

The accuracy of published rates of infection for common dental procedures is limited generally by small numbers in the denominator and variable definitions of infection. Even with limited data, infection rates for some common procedures appear to be very low. For example, one 1992 review of the complications of oral surgical procedures commented that of approximately 50 million intraoral injections of local anesthetic each year, a literature search turned up only two case reports of injection-associated infection *(125)*. Even if this represents underreporting by 100 times, the rate is still 1 infection per 10,000 injections.

Risk factors for infection following oral procedures may variably include older age, female gender, oral contraceptive use, surgeon inexperience, site infection at time of procedure, and a mix of procedure dependent anatomic risks. Table 54-2 summarizes available data concerning the frequency of procedure-related infections (*126*,*127*,128,*129–140*).

TABLE 54-2

Healthcare-Associated Infection Rates for Oral and Dental Operations

Reference	*Procedure/Condition*	*Rate (%)*
126	After third molar extraction	5.8
	After partial bony impaction	4.4
	After complete bony impaction	10.1
	After cyst or tumor	17.0
127	After extraction of impacted third molar[a]	21
128	After extraction of impacted third molar	2.2
129	After third molar extraction	1.1
130, 131	After dental implant[b]	1.2
	Periapical infection in implant:	
	If edentulous	1–2
	If partial teeth	3–6
132, 133	With comminuted fracture of mandible	8
	If using fixed rigid internal device	2–9
134	Mandibular fracture involving teeth	25
135	After orthognathic surgery	10–25
	After compound maxillofacial fracture	50
	With antibiotic prophylaxis	10
136	After extraoral osteotomy	1–5
137	After transoral osteotomy	4–15
	After sagittal split osteotomy	1.3
138	After temporomandibular joint (TMJ) surgery	16
139	After TMJ arthroscopy:	
	Surgical site infection	2.5
	Ear infection	2.2
140	ENT surgery:	
	Clean	<1
	Clean—contaminated	18–87

[a]Alveolar osteitis.
[b]Surgical site dehiscence.

Dental caries and periapical abscess usually are not considered healthcare-associated infections because of their long incubation period and their association with poor oral hygiene and dental plaque formation. However, as noted above, the periodontal flora begins to change within 10 days of stopping active oral hygiene. Therefore, these complications could occur in head trauma, burns, and other patients with prolonged periods of unconsciousness or intubation. Insufficient salivary flow in critically ill patients facilitates the development of oral gingivitis, and the presence of endotracheal and feeding tubes promotes the formation of biofilms. Fourrier et al. (141) studied the relationship between dental status and colonization of dental plaque by aerobic pathogens and the occurrence of healthcare-associated infections in 57 intensive care unit (ICU) patients in France. The amount of dental plaque increased during the ICU stay. Colonization of dental plaque was present in 40% of patients, either acquired or present on admission. A positive dental plaque culture was associated with the occurrence of healthcare-associated pneumonia and bacteremia. In 6 of 15 cases of ICU-related healthcare-associated infection, the pathogen isolated from dental plaque was the first identified source of the healthcare-associated pneumonia or bacteremia. The results from this study, and others, suggest dental plaque colonization and oral flora may be a source of healthcare-associated infection (*142*,*143*,144,145).

Several prophylactic oral measures have been tried to decrease healthcare-associated pneumonia. In 1996, a prospective, randomized, double-blind, placebo-controlled trial in a cardiovascular ICU in a tertiary care center evaluating oropharyngeal decontamination with 0.12% chlorhexidine gluconate oral rinse demonstrated that the healthcare-associated respiratory infection rate and the use of nonprophylactic systemic antibiotics in patients undergoing heart surgery were reduced *(146)*. Since that time, numerous other studies have been done, with only some suggesting benefit in preventing healthcare-associated pneumonia. The variability in results may be explained in part by disparate methodologies, including the concentration of the topical chlorhexidine (0.2% vs. 0.12%) used, the number of applications/day employed, the manner in which the chlorhexidine is applied, and the approaches used for the control arms (Listerine vs. standard oral care). Two meta-analyses have examined this topic. The first included four randomized controlled trials that enrolled over 1,200 patients (147). The incidence of healthcare-associated pneumonia was lower in the chlorhexidine group, but it did not reach statistical significance (odds ratio 0.42, 95% confidence interval 0.16–1.06). Seven randomized controlled trials consisting of 1,650 enrolled patients were included in the second meta-analysis (148). This analysis showed that topical chlorhexidine decreased ventilator-associated pneumonia, but the benefit was most marked in cardiac surgery patients. There was no mortality advantage.

Acute suppurative parotitis was frequently reported in the past among patients undergoing general anesthesia for surgery. With better attention to adequate hydration and oral care and the widespread use of antibiotics in surgery,

it is now reported to occur <0.5% of the time after use of a general anesthetic *(125)*.

The prescribing of prophylactic antibiotics before implant surgery is common practice, but remains a controversial academic issue due to lack of supporting evidence in the literature. Dentoalveolar surgeries are Class II procedures (clean-contaminated) since they involve entry through the microbiologically contaminated oral cavity. Despite this classification, endosseous implant procedures generally lead to a lower infection rate (<5%) than what is seen with many Class II major surgical procedures, and serious adverse events are rare. Early studies suggested the risk of implant failure increased two to three times when preoperative antibiotics were not used, but most subsequent trials demonstrated minimal benefit (*149*,150,*151–153*). A 2003 Cochrane Review did not recommend or discourage antimicrobial prophylaxis for routine implant surgery due to lack of evidence (154). It concluded that antibiotics might be appropriate when implant surgery is extensive and prolonged and that antimicrobials should be used when systemic conditions warrant their use (i.e., such as for endocarditis prophylaxis). It is common for antibiotic prophylaxis to be given for periapical surgery, bone surgery, bone grafts, excision of tumors, and extractions of impacted teeth. For many procedures research support justifying the practice is limited.

Osteotomy for correction of maxillary or mandibular deformities is occasionally followed by surgical site infection. One retrospective analysis of 2,049 patients who underwent maxillofacial orthopedic surgery over a 21-year period reported only eight severe infections requiring incision and drainage, with no results compromised because of infection *(155)*. In a prospective evaluation over a 20-year period of 1,000 consecutive patients after LeFort I osteotomy, 1.1% developed significant infections such as abscesses and maxillary sinusitis, and no cases of osteomyelitis occurred (156).

The risk of bacteremia with dental manipulation has been quantified. One such study reported bacteremia in 72% of 183 patients undergoing one or more tooth extractions, and it occurred most frequently when teeth were extracted for inflammatory conditions *(157)*. Seventy-one percent of isolates were anaerobes. Other reports have identified predominantly the viridans *Streptococcus* group *(158)*. Even minor oral manipulation such as periodontal probing leads to bacteremia in as many as 43% of patients and is more frequent in patients with periodontitis than in patients with chronic gingivitis *(159,160)*. Forner et al. *(161)* discovered bacteremia in 15 of 20 patients with periodontitis after scaling. Some authors suggest employing antibacterial mouthwashes preprocedure to reduce gingival bacterial counts, and the incidence of procedure-related bacteremias though supportive evidence is minimal. The frequency of bacteremia during routine incision and drainage of dentoalveolar abscesses has also been examined. In one study, bacteremia occurred in 25% of such abscesses (3 of 12 patients) *(162)*. Blood cultures were positive only during the drainage procedure in two of three patients, and in the third instance, bacteremia was also demonstrated 5 minutes after the procedure ended. When abscesses were aspirated with a needle before incision and drainage, no blood cultures had growth, suggesting that the risk of bacteremia may be reduced by needle aspiration of the abscess contents before incision and drainage.

Oral infections may be an important cause of septicemia in patients with hematologic malignancies. Dens et al. *(163)* noted a marked reduction of the salivary flow rate in patients after bone marrow transplant that was more pronounced if total body irradiation had been included in the pretransplant therapy. A higher concentration of cariogenic microorganisms and a shift toward a lower buffering capacity in saliva were found. These changes may lead to an increased risk of caries and oral complications posttransplant. Some authors have suggested that radiation therapy in the head and neck region may cause long-term alterations in oral flora *(164,165)*.

Bergmann (166) prospectively followed 46 patients with hematologic malignancies through 78 febrile episodes. He estimated that a probable oral focus for septicemia was demonstrable in 10.5% of these individuals and that an oral origin was possible in an additional 21.1%. Other authors have sought a relationship between the mucositis that often follows chemotherapy for leukemia or bone marrow transplantation and the oral flora, as a way to explain the infections seen in these settings. Dreizen et al. *(167)* prospectively studied patients undergoing treatment for acute leukemia and found that 34.2% developed chemotherapy-related oral infection and 16.3% developed chemotherapy-related oral mucositis. Gradually, it has been recognized that cancer-treatment–induced mucosal injury is not limited to the mouth, but causes mucosal damage throughout the length of the gastrointestinal tract. This mucosal barrier injury is a source for bacteremia, particularly during neutropenia. In a European prospective oral mucositis audit of 197 patients with hematologic malignancies, it was found that patients with severe mucositis had a higher incidence of fever and a longer duration of fever than those without this complication *(168)*. Mortality risk has been reported to be increased among hematopoietic stem cell transplant recipients with severe oral mucositis *(169)*.

Ferretti et al. *(170)* demonstrated that antimicrobial mouthwashes such as 0.12% chlorhexidine gluconate protected against these oral complications. Barker et al. *(171)* showed a possible reduction in incidence of β-hemolytic streptococcal sepsis among children receiving myelosuppressive chemotherapy who received prophylactic oral vancomycin paste. Various oral protocols for preventing oral sequelae in immunocompromised patients have been suggested *(172–176)*.

Not all studies show a correlation between the oral cavity and sepsis in patients with hematologic malignancies. A 2002 retrospective study of 77 patients after hematopoietic stem cell and bone marrow transplant showed no relationship between advanced periodontal disease and septicemia within the initial 100 days after transplant *(177)*.

Fortunately, the frequency of fungal and viral oral infections in cancer and transplant patients has been reduced dramatically by the institution of prophylactic agents. However, one of the untoward consequences of this practice is the emergence of resistant microorganisms.

Oral candidiasis and hairy leukoplakia are conditions that should trigger an assessment of HIV infection risk factors. Many oral diseases in persons with HIV infection can be modified presentations of conventional disorders, such

as gingivitis, necrotizing periodontal diseases, and exacerbated periodontitis *(178,179)*. Lower frequencies of oral disease have been seen in those on antiretroviral therapy and in those who receive regular oral health care *(180–182)*. A retrospective review of 101 HIV-infected patients who underwent 314 procedures revealed an overall complication rate of 2.2% and 4.8% after invasive dental procedures. Those who had an invasive procedure had a 2.0% (3 of 147) infection rate, and there were no infections in those who had noninvasive procedures performed. There did not appear to be a correlation between complications and immunologic or virologic status. Preoperative antibiotics were taken by 33.3% of the patients with complications versus 5.9% of those without adverse events, suggesting that routine antibiotic prophylaxis may not be needed for these patients *(183)*. There are no large comparative trials describing the complication rates for HIV-positive patients undergoing invasive dental procedures (184).

Some literature on the risks of tongue piercing has emerged. Reported complications include pain, tongue swelling, tongue abscess, Ludwig's angina, airway obstruction, bleeding, mucosal or gingival trauma or recession, chipped or fractured teeth, granulomatous inflammation and scar tissue formation, nerve damage and paraesthesia, aspiration of jewelry, incorporation of foreign body into site of piercing, and interference with speech, mastication, and swallowing *(185–190)*. Lopez-Jornet et al. *(189)* described gingival inflammation/swelling in 26.8% and dental fractures or fissures/cracks in 20% of 30 intraoral piercings seen in a University Dental Clinic in Spain. There have been reports of endocarditis due to *Neisseria mucosa, Haemophilus aphrophilus*, and methicillin resistant *S. aureus* as well as polymicrobial cerebellar brain abscess subsequent to tongue piercing *(191–194)*. There may be fewer problems associated with lip piercing, though gingival recession of previously healthy tissue has been seen *(195)*.

Viral Agents

HSV is the latent herpesvirus in the oral cavity most commonly expressed during hospitalization. The virus is latent in the trigeminal ganglion and is secreted in saliva from the parotid gland. Reactivation of active labial lesions in a patient is triggered by oral surgical procedures, trauma, ultraviolet light, and major injuries such as burns. Because of the frequency of asymptomatic excretion of the virus in saliva (virus can be recovered at intervals from the saliva of over 50% of adults in the United States), the unprotected hands of dentists, dental hygienists, and oral surgeons, which are bathed in saliva, are exposed to HSV. The most common result of transmission has been herpetic whitlow, which is a painful infection localized to the periungual region of the fingernail. This is recognized as an occupational hazard for dental workers *(196)*. There are also reports of transmission of HSV from dental workers to patients, including an outbreak of gingivostomatitis in 20 patients treated by a dental hygienist with herpetic whitlow who did not use gloves *(197)*. Because acquisition of HSV infection depends on direct contact between saliva or active lesions and an opening in skin, the potential for transmission of HSV has been reduced by the use of gloves for blood-borne disease precautions (see also Chapter 44). Latex and vinyl gloves have also been shown to protect against HSV *(198)*.

Despite their recovery from saliva and associated oral tissues, EBV and CMV have not been recognized as important pathogens for healthcare-associated infections in the dental or oral surgery setting, either for spread to other patients or for transmission to staff. However, a seroprevalence study done in the United Kingdom suggests possible occupational risk of infection with EBV in dentists based on a higher seroprevalence to EBV among clinical dental students and qualified dentists than among preclinical dental students *(199)*. Another seroprevalence study done in England showed a greater prevalence of antibodies to influenza A and B viruses and respiratory syncytial virus in dental surgeons compared with control subjects, suggesting occupational risk for respiratory virus infections *(200)*. Based on questionnaire results, reported donning of masks did not reduce seroprevalence with these viruses.

Blood-Borne Pathogens

HBV may be transmitted both from patients to dentists and oral surgeons and from oral surgeons and dentists to patients *(201–204)*. HBV can cause a chronic latent infection of the liver and is associated with large numbers of virus particles circulating in the blood of chronically infected persons. Because all intraoral surgery and many dental procedures cause breaks in the mucosa of the oral cavity or gums that result in bleeding, the risk of spread of hepatitis B from the patient to the operator is substantial *(205)*. In prevaccine surveys, the annual incidence of HBV was 5 to 10 times higher among physicians and dentists than among blood donors *(204,206)*. Infections occur when blood from the patient enters the body of the dentist through small breaks in the skin. In recent years, gloves have been used routinely as part of Standard/Universal Precautions. However, exposures of breaks in the skin to blood still occur due to glove perforation. Glove puncture occurs in 2.1% to 16% of oral surgery procedures *(207,208)*. Aerosol transmission from high-speed drills used in dentistry with resulting aerosolization of saliva and blood has never been documented to result in occupationally related infections. Transmission of hepatitis B via human bite has been recognized *(209,210)*.

Several outbreaks of HBV infection have been reported among patients who underwent surgery by dentists and oral surgeons chronically infected with HBV *(22,202,205)*. The precise mechanism(s) resulting in transmission of infection has not been determined, but infection was likely transmitted from dental workers to patients rather than from one patient to another. Some outbreaks were terminated after the involved provider began to wear gloves when performing procedures. Prior to 1987, HBV transmission from 9 oral surgeons/dentists and 14 surgeons to patients were reported in the United States, including one outbreak involving 55 patients traced to a single oral surgeon (211,*212*). Since 1987, there have been no reports of transmission of HBV from dentists or oral surgeons to patients, although there has been one case of patient-to-patient transmission in the dental setting (211,213). The disappearance of transmission in the dental setting may be due to adherence to Standard/Universal Precautions, higher compliance with hepatitis B immunization, incomplete reporting, or isolated sporadic cases that are difficult to associate with a dental worker (213).

HCV was identified in 1989 and is the main agent of what was previously termed non-A, non-B viral hepatitis. The virus produces chronic infection of the liver in most infected persons, and HCV is the leading cause of chronic liver disease, cirrhosis, hepatocellular carcinoma, and liver transplants in the United States and Europe. It is estimated that 4.1 million people in the United States are infected with HCV, of whom 3.2 million have chronic infection *(214)*. Injection drug users account for approximately one-half of infected persons *(214,215)*. HCV RNA is variably detected in the saliva of infected persons *(216–218)*. Oral surgery appears to increase the occurrence of HCV in saliva *(219)*. Transmission of HCV through a human bite has been reported *(220,221)*.

Like HBV, HCV is a known occupational hazard for healthcare personnel by contact with contaminated blood, although HCV seems to be transmitted in the occupational setting less efficiently than HBV. To date, no dental worker is known to have acquired HCV occupationally, but the high frequency of sharp injuries occurring in the dental setting places the dental worker at risk of HCV acquisition *(222)*. Despite this risk, the prevalence of HCV infection among dental workers appears to be similar to that of the general population in most studies *(223–227)*. Anti-HCV may be more common in dental workers who are older, have more years of practice, and have serologic markers of HBV infection *(228)*. A review of self-reported and observational studies of occupational blood exposures among US dental workers between 1986 and 1995 suggested that percutaneous injuries steadily declined to an average of three injuries per year (229).

The data on the frequency of transmission of HCV to patients during dental care are very limited. Gingivectomy performed by a dental surgeon of unknown HCV status was identified as the only risk factor for the seroconversion of one patient *(230)*. Sporadic case–control studies demonstrate an association between the receipt of healthcare or dental care and HCV positivity *(231)*.

HIV infection causes a chronic infection of human lymphocytes and many other cell types and generally has a latency period of at least several years before onset of symptoms. The epidemiology of HIV in the medical setting likely is the same as that of HBV, except the risk of transmission of HBV is approximately 100 times the risk of transmission of HIV for comparable exposures (211,*232*). As of December 2006, the Centers for Disease Control and Prevention (CDC) received reports of 57 US healthcare workers with documented HIV conversion temporally associated with an occupational HIV exposure. An additional 140 cases are considered to have possibly been acquired occupationally, but the source of infection cannot be documented with certainty. No dental personnel are among any of the documented cases, but six dental workers are in the group of possible occupational transmissions *(233,234)*. Occupationally acquired HIV infection recognized among healthcare workers most commonly resulted from blood transmitted by hollow-bore needles *(233,234)*. Because hollow-bore needles are used less frequently in dental practice, the risk of occupationally acquired HIV infection for dental workers may be slightly lower than that for some other groups of healthcare workers. In a national survey, Canadian dentists reported an average of 3 percutaneous injuries and 1.5 mucous-membrane exposures per year *(235)*. Orthodontists reported the highest rate of percutaneous injuries (4.9 per year) and oral surgeons reported the greatest frequencies of blood splashes (1.8 per year). A serosurvey combined with a questionnaire administered to 321 oral and maxillofacial surgeons revealed no HIV-seropositive participants despite a mean number of recalled percutaneous injuries within the previous year of 2.4 (most commonly associated with wire) *(236)*. The results suggest a low occupational risk for HIV infection.

In the United States, the only documented transmission of HIV from an operating surgeon to a patient occurred with one cluster of six cases related to a single dentist in Florida *(237)*. The events that resulted in the infection of these patients remain unknown, although the evidence suggests that HIV was transmitted from dentist to patient rather than from patient to patient *(238)*.

PREVENTION AND CONTROL

Infections may be transmitted in the dental operatory through direct contact with blood, oral fluids, or other secretions; via indirect contact with contaminated instruments, equipment, or environmental surfaces; or by contact with airborne contaminants present in either droplet splatter or aerosols of oral and respiratory fluids (213,239). For more comprehensive recommendations on this topic, the author refers the reader to the CDC's "Guidelines for infection control in dental health-care settings—2003" (213).

Strategies to prevent patient dental infections focus on several areas. The first is sterilization of all instruments used in intraoral procedures and disinfection of related equipment. The second is use of good infection control practices in the dental operatory (213). These measures are aimed at preventing the spread of an infectious agent on instruments or dental apparatus from one patient to another. The third is rigid asepsis during intraoral procedures, including the use of preprocedure mouthwashes to reduce the burden of intraoral flora. Local antisepsis with topically applied antiseptic agents should be used particularly for root canal work, endodontic procedures, and gum surgery. The fourth is antibiotic prophylaxis or treatment of infected areas in which work is performed. These measures are directed at preventing the entry of the patient's own resident oral and gingival flora into the operative site in numbers great enough to cause infection.

Instruments used to penetrate soft tissue or bone (forceps, scalpels, bone chisels, etc.) are classified as critical and should be sterilized by heat after each use. Instruments that are not intended to penetrate oral soft tissues or bone such as mirrors and amalgam condensers but may come in contact with oral tissues are classified as semicritical and also should be sterilized after each use. If a semicritical item will be damaged by heat sterilization, the instrument should receive, at a minimum, high-level disinfection. Instruments or devices that come into contact only with intact skin such as external components of x-ray heads are classified as noncritical. These items may be reprocessed between patients with intermediate-level or low-level disinfection or detergent and water washing, depending on the intended use of the patient-care item (213).

All instruments should be processed in a designated area to control quality and safety. The processing area should be divided into separate sections for cleaning/decontamination, preparation/packaging, sterilization, and storage. Before sterilization or high-level disinfection, instruments should be cleaned thoroughly to remove contamination and debris. They should be placed into a presoak solution immediately after use to prevent the drying of saliva or blood on the instruments and to make cleaning easier. The soak contains an antimicrobial agent to reduce the levels of bacteria and viruses. Cleaning is accomplished by scrubbing in a detergent solution or, preferably, to minimize handling and the exposure of workers to sharps injuries, by placing the instruments into a mechanical device, an ultrasonic cleaner. After cleansing, the instruments should be thoroughly rinsed with water while they are still in the cleaning basket, inspected carefully to make sure all visible debris has been removed, and then allowed to dry. Critical and semicritical instruments should be then sterilized. The most common forms of sterilization used in a dental office include steam under pressure (autoclaving) and dry heat. Sterilization processes must be monitored routinely by using mechanical, chemical, and biological parameters (see Chapter 81).

The use of liquid chemical germicides, such as glutaraldehyde, for high-level disinfection of heat-sensitive semicritical instruments may require up to 10 hours of exposure. These agents are extremely toxic. Indications for wet sterilization are very limited. Manufacturers' directions regarding the correct concentration, exposure time, and safety precautions should be followed closely. The process should be followed by aseptic rinsing with sterile water, drying with sterile towels, and delivering in a sterile manner for storage if not used immediately (213) (see Chapter 80).

Because of the transmission of both HIV and HBV in the dental setting, much concern has been expressed over the dental handpieces used to transmit rotary energy to dental drills/bits *(240,241)*. These handpieces are composed of a number of moving parts and typically have many cracks and crevices, which make them difficult to clean. They cannot be adequately disinfected by wet disinfectants because the agent cannot penetrate into the crevices. Studies have shown that residual live bacteria are recoverable from handpieces even after cleaning and wet chemical disinfection. Because all currently manufactured high-speed handpieces and most low-speed handpieces are heat tolerant, these items should be cleaned and lubricated, followed by heat sterilization between successive patients. Handpieces that are not heat tolerant should be modified to make them tolerant to heat. Those that cannot be heat sterilized should not be used (213,*242*).

Another potential concern is with dental unit water systems supplying dental handpieces and air water syringes becoming contaminated with common heterotrophic microorganisms from the incoming water supply and, less often, with oral flora from entry of a small amount of oral fluid into the device during transient negative pressure immediately after the drill stops rotating (*243–246*,247). To minimize the risk of cross contamination, it is recommended to discharge water and air from the unit for minimum of 20 to 30 seconds after each patient, even when an anti-retraction valve is present (213). Although there is no epidemiologic evidence that high microbial counts in dental unit waterlines is a public health problem, in 1995 the American Dental Association requested manufacturers to supply equipment capable of delivering water with ≤200 CFU/mL due to concerns about potential adverse health effects *(248)*.

The physical construction of certain devices such as burs and endodontic files makes them difficult to clean adequately. In addition, the cutting surfaces tend to deteriorate with repeated processing. These factors, coupled with reports of poor sterilization success, lead to the suggestion that these devices be considered single-use devices (213,*249*).

Good infection control practices in the dental operatory are directed at the use of hand hygiene and personal protective equipment as well as attention to reducing the contamination of environmental surfaces by saliva and blood. These measures include the utilization of impervious paper or plastic covers to protect surfaces that may become contaminated during use and that are difficult to disinfect. Such surfaces include x-ray unit heads and light handles. Between patients, all surfaces potentially contaminated with blood or other potentially infectious material should be wiped off with an Environmental Protection Agency–registered hospital disinfectant, also labeled as "tuberculocidal" (213). These intermediate-level disinfectants are effective against most bacteria and viruses. Other methods to reduce salivary contamination of the operatory in the form of aerosols or spatter include patient use of an antimicrobial mouth rinse before the procedure, use of a rubber dam, and use of a high-speed air evacuator during high-speed drilling (213). Not surprisingly, methicillin-resistant *S. aureus* has been recovered from the surfaces of dental operatories, including the air–water syringe and dental chair *(250)*.

Creutzfeldt–Jakob disease (CJD), one of the transmissible spongiform encephalopathies (TSEs), is a rapidly progressive, invariably fatal neurodegenerative disorder believed to be caused by an abnormal isoform of a cellular glycoprotein known as the prion protein. Prions are resistant to conventional decontamination processes. Epidemiologic investigation has not revealed any evidence that dental procedures lead to increased risk of iatrogenic transmission of TSEs among humans. However, studies have shown that infected animals develop infectivity in gingival and dental pulp tissues, and transmission to healthy animals can occur by exposing root canals and gingival abrasions to infectious brain homogenate *(251)*. Somewhat reassuring is the report by Blanquet-Grossard et al. (252) in 2000 showing that there were no prions detected in the dental pulp of eight human patients with confirmed sporadic CJD.

There is lack of consensus regarding the optimal procedures for disinfection and sterilization of instruments potentially contaminated with the CJD prion. The World Health Organization suggests that usual infection control processes are sufficient when treating patients with TSEs during procedures not involving neurovascular tissue, but that extra precautions be considered for major dental procedures *(253)*. The CDC recommends that special precautions in addition to Standard Precautions may be indicated when treating patients with known disease until

more information emerges about the transmissibility of CJD (213). These additional precautions include utilizing single-use items and equipment if possible, and when reprocessing must be done, keeping the instruments moist until cleaning and disinfecting, and then steam-autoclaving at 134°C for 18 minutes. The Society for Healthcare Epidemiology of America categorizes the infectiousness of different body tissues based on animal studies *(254)*. Gingiva, saliva, sputum, whole blood, and peripheral nerves are all ranked as no-risk tissues. Therefore, the semicritical and critical medical devices that have been contaminated with no risk tissues are recommended to be cleaned and either disinfected or sterilized using conventional protocols.

Local antiseptics are intended to reduce bacterial contamination of the operative site. They are applied to the prepared sites of dental fillings for caries, crowns, and root canals before closing the defect. Presurgical rinsing with an antimicrobial mouthwash has not been shown convincingly to decrease the number of microorganisms introduced into the bloodstream *(255,256)*. Also there is little evidence that topical disinfection of the gingiva with antimicrobial mouth rinses before elective gingival surgery prevents clinical infection.

Marten and van Saene *(176)* discuss methods to prevent each of the seven major oral infectious complications of cancer therapy. Four of these complications (caries, osteomyelitis, periodontal disease, and mucositis) may be decreased by strict application of local measures in the mouth. These measures include good oral hygiene to prevent caries and periodontal disease and to reduce the likelihood of osteomyelitis, and topically applied antimicrobials to prevent osteomyelitis and mucositis.

Systemic antibiotics have a limited role in reducing the rate of infectious complications. Converse and McCarthy *(257)* list the following indications for the use of prophylactic antibiotics for surgery on the jaw (mandible): intraoral approach, previous irradiation of the operative field, use of a bone graft, use of an alloplastic implant, and surgery in a patient prone to infection (diabetes mellitus). As demonstrated in Table 54-2, the rate of surgical site infection is increased when a transmucosal or intraoral approach is used or when the socket of a tooth is involved in a fracture. In addition to the situations listed by Converse and McCarthy, systemic antibiotic administration is of demonstrated benefit for transoral procedures over 3 hours in length and for orthognathic or other major maxillofacial surgery. The Infectious Disease Society of America recommends antimicrobial prophylaxis for head and neck procedures that involve entry into the oropharynx *(258)*.

Patients may qualify additionally for antibiotics in an attempt to protect heart valves or other distant foci from bacteremia originating in the mouth. Routine antibiotic prophylaxis for patients undergoing dental procedures to prevent hematogenous prosthetic joint infections is not recommended, although premedication may be warranted in certain patients, including immunocompromised patients with a potential higher bacteremic risk and patients undergoing higher-risk dental procedures within 2 years postimplant surgery *(259)*.

SAFETY FOR DENTAL HEALTH-CARE PERSONNEL

Worker safety is provided by following measures (213):

1. An infection-control program for personnel that includes education and training; immunizations; exposure prevention and postexposure management; medical conditions, work-related illness, and work restrictions; contact dermatitis and latex hypersensitivity; and maintenance of records, data management, and confidentiality. The components should be contained in written policies, procedures, and guidelines.
2. Every dentist, oral surgeon, and assistant within the office with potential occupational exposure to blood or other potentially infectious material should be offered and encouraged to accept hepatitis B vaccination. U.S. Public Health Service/CDC recommendations for vaccination, serologic testing, follow-up, and booster dosing should be followed.
3. Exposures to blood and other potentially infectious material should be prevented by the use of Standard Precautions and engineering and work-practice controls, including regular evaluation and selection of devices with engineered safety features. Gloves should be worn for any work done in or around the mouth and for handling any instruments, surfaces, or substances contaminated with saliva or blood. A surgical mask and eye protection with solid side shields or a face shield should be worn during all procedures. Any visible wounds suffered from sharp instruments should be immediately cleansed and assessed. The assessment should include informed consent for testing the patient for HBV/HCV and HIV according to applicable state and federal laws. Additionally, a postexposure prophylaxis protocol should be followed (260,*261*).
4. Hand hygiene should be performed with soap (antimicrobial or nonantimicrobial) and water or an alcohol-based hand rub (if hands are not visibly soiled). Hand hygiene should be performed before and after caring for each patient, before donning gloves, immediately after removing gloves, after touching objects and surfaces likely to be contaminated, and when hands are visibly soiled.
5. Protective clothing that covers personal clothing and skin should be worn in the office/operatory setting, and the clothing should be changed if visibly soiled. These items should be removed before leaving work.
6. Because many studies have shown widespread salivary contamination of surfaces in the operatory, barrier protection of commonly touched surfaces such as radiographic handles and controls, bucket handles, and light switches should be provided. Clean and disinfect nonbarrier protected clinical contact surfaces with an EPA-registered low- to intermediate-level hospital disinfectant after each patient. An intermediate-level disinfectant should be used if visibly contaminated with blood.
7. The bacterial content of saliva can be reduced by rinsing the patient's mouth with water before any dental examination. Additional reductions can be accomplished by use of a preprocedural antimicrobial rinse.

8. A careful general medical history should be completed for all new patients and at periodic intervals to look for symptoms or signs of pulmonary tuberculosis. Patients with signs or symptoms suggestive of tuberculosis should not undergo elective dental or oral procedures until they have been evaluated by a physician. All dental office workers should receive a yearly test for tuberculosis *(262)*.

These measures are the minimum for providing reasonable protection to dental staff and patients against communicable diseases. Numerous studies demonstrate improved compliance by dental and oral surgery personnel with recommended infection control practices in recent years *(263–268)*. However, the results of these studies suggest that further education and encouragement are needed to attain a more desirable level of understanding and adherence to the recommended practices.

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CHAPTER 55

Healthcare-Associated Infections in Obstetric Patients

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The hospital obstetric unit is one of the first examples of a specialized hospital unit with a specialized patient population. "Lying-in" or obstetric hospitals were introduced in the 18th century, and some of the first significant studies on the epidemiology of healthcare-associated infections were made on obstetric services (1). Today's hospital is increasingly becoming a collection of specialized units; these units contain unique patient populations undergoing specialized treatments for specific diseases. Patients on these units may be more vulnerable to infection, or characteristics of the unit may facilitate transmission of infections. Obstetric care is unique in that both the primary patient and the newborn infant are at risk.

A survey of postpartum infections reported an overall infection rate of 6% (Table 55-1) (2). Ledger *(3)* pointed out that the frequent empiric use of antibiotics for febrile patients on the obstetric service probably leads to lower reported infection rates and obscures the true frequency of healthcare-associated infections. In recent decades, postpartum women have had shorter hospital stays. Shortened hospital stays may decrease exposure risk for healthcare-associated infections and may result in decreases in infection rates. Unfortunately, shortened hospital stays also make surveillance of infections more difficult; thus, changes in infection rates cannot be confirmed by current data.

TABLE 55-1

Infection Rates (Cases/100 Deliveries) on Obstetric Services by Site of Infection, 1993–1995

Type of Delivery	*Site of Infection*					
	UTI	*SSI*	*Epi*	*End*	*Mast*	*All Sites*
Cesarean	1.1	3.4	NA[a]	0.8	1.7	7.4
Vaginal	2.0	NA	0.3	0.2	3.0	5.5

[a]NA, not applicable.
End, endometritis; Epi, episiotomy; Mast, mastitis; SSI, surgical site infection (excluding endometritis); UTI, urinary tract infection.
(From Yokoe DS, Christiansen CL, Johnson R, et al. Epidemiology of and surveillance for postpartum infections. *Emerg Infect Dis* 2001;7:837–841.)

HISTORY OF HEALTHCARE-ASSOCIATED OBSTETRIC INFECTIONS

The establishment of obstetric hospitals in the mid-18th century created the setting for epidemics of puerperal infections (1). The epidemics in turn provided the opportunity both to demonstrate that puerperal fever was contagious and to develop prevention methods. Alexander Gordon was one of the first to document this *(4)* and, later, so did Oliver Wendell Holmes *(5)*, but the most famous was Ignaz Semmelweis in Vienna because of his extensive and carefully detailed observations *(6)*.

The "great free Vienna Lying-in Hospital" created a natural epidemiologic experiment that Semmelweis had the insight to appreciate. The hospital had two separate divisions: the first division for teaching medical students and the second division for teaching midwives. The mortality was so much greater in the first division (16% vs. 2% in the second division) that even the patients knew about it and tried to be admitted to the second division. Semmelweis took advantage of this natural experiment to carefully collect data to document and determine the cause of the epidemics. Not only did he evaluate the data on healthcare-associated infections but he also made anecdotal observations that supported his conclusions—the low infection rate in women who delivered in the street on the way to the hospital compared with those who delivered in the hospital.

The medical students in the first division performed autopsies, whereas the midwives did not. Semmelweis noted the similarity between the fatal illness in a pathologist who had been stuck in the finger by a medical student and the fatal infections in the obstetric patients. He concluded that material from the autopsies was being transmitted back to the patients and causing their illnesses. Hand washing with soap was done after autopsies, so Semmelweis concluded that this was inadequate to remove all "cadaveric particles." He added hand rinsing with chlorinated lime water after performing autopsies and after each patient contact *(7)*. The result was a dramatic decrease in mortality in the first division to rates similar to those of the second division.

It took decades for Semmelweis' ideas, stimulated by Lister's concept of antisepsis, to become standard practice.

Even then, obstetric infections and maternal mortality remained major problems into the 1930s. The appearance of the first antimicrobial agents and improvements in other aspects of obstetric care resulted in a major decrease in maternal mortality *(8)*. Presumably, the reason for the persistence of high obstetric infection rates into the 1900s was that even though epidemics of puerperal fever transmitted by cross-infections were prevented by hand washing and antiseptic techniques, infection from patients' endogenous flora remained a problem.

PATHOGENESIS OF OBSTETRIC INFECTIONS

Most obstetric infections are caused by maternal vaginal and cervical flora; thus, infections usually relate to risk factors that allow endogenous flora to cause disease. Hospital pathogens are seldom problems on obstetric services, because obstetric patients have short stays and obstetric units are separated from other hospital units.

As Bartlett and coworkers *(9,10)* pointed out, vaginal flora are a dynamic ecosystem, with some differences between vaginal and cervical flora. Anaerobic bacteria usually outnumber aerobes, with anaerobic and facultative lactobacilli predominating. Other anaerobes include *Peptostreptococcus* species, *Bacteroides* species, and *Prevotella* species. The aerobic gram-positive flora include coagulase-negative staphylococci, streptococci, enterococci, and *Staphylococcus aureus* [including methicillin-resistant *Staphylococcus aureus* (MRSA) *(11)*]; and the gram-negative flora include *Escherichia coli*, *Gardnerella vaginalis*, *Enterobacter* species, *Klebsiella pneumoniae*, and *Proteus mirabilis (12,13)*. Both *Mycoplasma* and *Ureaplasma* are also found in the vagina. Sexually transmitted diseases may add *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or herpes simplex virus (HSV) to this flora. Vaginal flora may change during pregnancy. Some studies suggest that lactobacilli increase in pregnancy and that other anaerobes decrease *(14)*. Antibiotics also change the flora, and the use of multiple doses of cephalosporins for prophylaxis has been reported to increase enterococci and perhaps *Enterobacter* species *(15)*.

As would be expected, most obstetric intrauterine infections are polymicrobial, representing contiguous spread from the vagina *(16)*. Ascending infection is demonstrated by both the presence of routine cervicovaginal flora in endometritis and surgical site infections (SSIs) and the ability to predict postcesarean infections by intraoperative lower uterine cultures *(17)*. Although a significant proportion of postcesarean SSIs are caused by staphylococci, as in other SSIs, most postcesarean infections are caused by endometrial contamination *(18)*.

Many risk factors have been proven or suggested to be associated with endometrial infection, including those that increase entry of vaginal flora such as prolonged rupture of the membranes, frequent vaginal and rectal examinations, or intrauterine monitoring; those that result in tissue injury such as soft tissue trauma, midforceps delivery, or inexperienced surgeons; and host factors that are associated with increased infections such as maternal age, lower socioeconomic status, diabetes mellitus, or obesity. Understanding these risk factors may become important in evaluating infection rates on specific obstetric units.

OBSTETRIC INFECTIONS (INFECTIONS RELATED TO PREGNANCY AND DELIVERY)

Postpartum Endometritis

The classic obstetric infection is postpartum endometritis. The postpartum patient develops fever that may be associated with abdominal pain, uterine tenderness, malaise, or foul-smelling discharge. In most cases the patient is started on antibiotics without obtaining cultures *(16)*. Endometritis can occur after either vaginal delivery or cesarean section but is more common after cesarean section. Infection has been reported to occur after fewer than 3% of vaginal deliveries and 5% to 95% of cesarean sections (2,*16*,*19*). The variation in infection rates results from the variation in risk factors in the population studied and patient's management. Endometritis after cesarean section occurs earlier than after vaginal delivery, as shown by hospital readmissions for postpartum endometritis. Most women who were readmitted for endometritis had delivered vaginally *(20)*.

Endometritis may be caused by either a single bacterial species or multiple microorganisms *(21)*. Common etiologic agents include the gram-positive cocci, such as streptococci and enterococci; gram-negative bacilli, such as *E. coli*, *K. pneumoniae*, and *P. mirabilis*; and anaerobes, such as *Bacteroides bivius* and peptostreptococci *(16,21,22)*. Some studies have distinguished between early and late postpartum endometritis *(23,24)*; late infection is a milder disease that occurs after vaginal delivery. It has been suggested that genital *Mycoplasma* and *Chlamydia* are important etiologic agents in late endometritis.

The most important risk factor for postpartum endometritis is cesarean section, and the risk of infection is greatest when it is a nonelective procedure after rupture of the membranes and the onset of labor *(16,19,25)*. General anesthesia, long duration of surgery, intraoperative problems, and poor surgical technique may all be risk factors. Currently patients undergoing both elective and nonelective cesarean sections are routinely given prophylactic antibiotics as they are shown to decrease postpartum endometritis and wound infections by 50% to 75% *(26)*. Administration of intravenous antibiotics is done before skin incision as it has been shown to be more effective than administration at cord clamping, the previous practice (27,*28*). In vaginal deliveries, prolonged rupture of the membranes, midforceps delivery, and soft tissue trauma increase the risk. With many other risk factors for postpartum endometritis, it is difficult to separate out relative risks, because the factors are interrelated. This applies to risk factors such as prolonged labor, frequent vaginal examinations, and internal monitoring. Host factors that increase risk include bacterial vaginosis, human immunodeficiency virus (HIV) infection, anemia, low socioeconomic status, maternal age, and obesity *(25,29,30)*.

Infection of the endometrium may extend into the myometrium and parametrial tissue, causing abscess formation

or sepsis. Septic pelvic thrombophlebitis (SPT) should be suspected in a patient who does not respond to antibiotic therapy *(31)*. If the workup fails to identify another infection, computed tomography should be performed to look for pelvic thrombophlebitis. Past treatment included the addition of heparin to broad spectrum antimicrobial therapy. However, a large randomized trial of SPT showed no benefit from adding heparin to antimicrobial therapy when compared to those receiving antimicrobial therapy alone *(32)*.

Evaluation of the febrile postpartum patient should include a relevant history and physical exam along with laboratory studies: complete blood count, chest X-ray, urine culture, and blood cultures. Leukocytosis is usually present but may also be seen in the noninfected postpartum patient. Uterine cultures are often not done because of the difficulty in interpreting the results. Because the microorganisms recovered are usually part of the normal maternal flora, these may either represent contamination during specimen collection or be the cause of endometritis. Unless a blood culture is positive, there is no way to confirm that the isolates are significant. However, good aerobic and anaerobic cultures do show the range of potential pathogens and detect infections caused by unusual pathogens such as the rare group A β-hemolytic streptococci (GABHS) infection. Uterine cultures can be collected with a cotton swab *(33)*.

Surgical Site Infections

Episiotomy infections are uncommon and usually not serious, but severe complications such as necrotizing fasciitis can develop *(34,35)*. Episiotomy sites should be examined carefully to detect infection early and infections should be treated to prevent complications.

A more serious problem is SSI of a cesarean section. SSIs are reported to occur in about 3% to 4% of cesarean section patients, including both incisional and organ and space infections (2,*36*). Recently, this rate has declined, perhaps as a result of administering perioperative antibiotics just prior to incision (37). SSIs are usually caused by maternal flora in the endometrium but, as with any other SSI, can be caused by microorganisms from exogenous sources *(18,38)*. In the latter cases, *S. aureus* is the most frequent cause of infection. Although the pathogenicity of genital mycoplasma in SSIs has not been proved, a study reported these to be the most common bacteria isolated in infected postcesarean surgical sites *(38)*. SSIs should be cultured before antibiotic therapy is begun (see also Chapter 21).

Urinary Tract Infection

Urinary tract infections are a common problem in pregnancy and during the postpartum period *(39)*. Risk factors for postpartum infections include urinary retention from anesthesia, trauma during delivery, and the need for catheterization. Urine cultures of the febrile patient with urinary tract symptoms should always be collected, although midstream samples may be contaminated by vaginal discharge. In those cases, the results are interpreted in the context of the clinical findings and the response to empiric antibiotic therapy. The major preventable risk factor in the postpartum period is catheterization. Catheterization is indicated for urinary retention but should be done only as needed *(40)*, with the catheter removed as soon as possible. Another risk factor for postpartum urinary tract infection is bacteriuria during pregnancy. Pregnancy is one of the few conditions for which treatment of asymptomatic bacteriuria is indicated (41). Detection and treatment of bacteriuria in pregnant women may decrease postpartum urinary tract infections.

Chorioamnionitis (Intraamniotic Infection)

Intrauterine infection during pregnancy, such as postpartum endometritis, is usually caused by ascending infection from vaginal flora and is caused by similar bacteria *(16,42,43)*. Most infections are also polymicrobial, and the major risk factor is prolonged rupture of the membranes. Infection is rare in women with intact membranes. Other risk factors are similar to those for postpartum endometritis: duration of labor, number of vaginal examinations, internal monitoring, and possibly bacterial vaginosis. A variety of other obstetric procedures may introduce infection, including amniocentesis, chorionic villus sampling, and percutaneous umbilical blood sampling.

Because fever can be the only presenting sign, initial diagnosis may be difficult. Specific diagnosis requires examination of amniotic fluid by gram stain, culture, and amniotic fluid glucose level *(44)*. Healthcare-associated chorioamnionitis can be suspected in patients who become febrile after vaginal examinations, internal fetal monitoring, or other such procedures, but there is no standardized definition for healthcare-associated infection. Once the diagnosis is suspected, the patient should be started on broad spectrum antibiotic therapy, including anaerobic coverage, and delivered as soon as possible.

Mastitis

In a study of obstetric patients who were contacted after discharge from the hospital, mastitis was the most common infection reported (45). Very few breast infections were seen during hospitalization, because mastitis and breast abscess usually occur several weeks into the postpartum period. A slight fever can develop early with breast engorgement, but it is transient. Later in the postpartum period, infectious mastitis must be distinguished from milk stasis and noninfectious inflammation *(46)*. Infection is associated with higher fevers, erythema, and unilaterality.

The most common cause of breast infection is *S. aureus (47)*. Epidemics of staphylococcal mastitis occurred in the past but have not been reported in recent years. Therefore, the traditional classification of infectious mastitis into sporadic and epidemic forms is seldom useful. Both types are usually caused by *S. aureus*. Increasing numbers of cases due to community-acquired MRSA are also being reported *(48)*. Predisposing factors for mastitis include the lack of nipple care, poor feeding technique, and inadequate emptying of the breasts. Infection can be confirmed by gram stain and culture and responds to antistaphylococcal antibiotics and, if needed, surgical drainage. Continued breast drainage is important and can be accomplished by continued nursing, if appropriate, or pumping and discarding milk.

NONOBSTETRIC INFECTIONS IN THE OBSTETRIC PATIENT

There are many nonobstetric infections that must be considered in the evaluation and management of obstetric patients, not only for the sake of the patient but also for the safety of the fetus or neonate and the protection of others on the obstetric service. Selected infections of particular importance in the obstetric patient are described.

Listeria

Approximately one third of *Listeria monocytogenes* infections occur in pregnant women. *Listeria* can cause a febrile illness in obstetric patients and may rarely result in severe diseases such as meningitis *(49)*, miscarriage, or premature delivery. It can be transmitted to the neonate and cause severe disease. Contaminated food, particularly soft cheeses, cold meats, and hot dogs, can infect the obstetric patient. Transmission of *Listeria* to neonates in the delivery room has been reported on several occasions *(50,51)*. Routine blood cultures should be obtained from febrile patients, providing a diagnosis and allowing directed antibiotic therapy.

Streptococcus pyogenes (GABHS Infections)

Historically, GABHS has been a significant cause of postpartum endometritis but now is uncommon *(3)*. These infections occur in previously colonized mothers or can be acquired by cross-infection from healthcare workers, other patients, or colonized infants. GABHS endometritis may differ from endometritis caused by the usual maternal vaginal flora, with an abrupt onset of high spiking fevers and diffuse tenderness. Diagnosis can be made by gram stain and cultures of uterine discharge. The streptococcal toxic shock syndrome caused by GABHS has been reported in postpartum patients *(52)*.

As illustrated by an outbreak reported from a hospital in Washington state in the 1960s *(53,54)*, despite good infection control practices, GABHS epidemics can still occur if a member of the obstetric team is a streptococcal carrier. Eleven patients (nine obstetric and two gynecologic) developed GABHS infections, and one died. Although nasopharyngeal cultures were negative from all staff who had contact with the patients, epidemiologic investigation identified the only staff member who had contact with all infected patients. When he stopped practicing, the infections disappeared, and when he returned to practice, the infections reappeared. This pattern was seen on three separate occasions, despite empiric antibiotic treatment with penicillin. Finally, the physician was hospitalized for clinical and microbiologic studies and was found to be an anal carrier of GABHS. It was demonstrated that he disseminated streptococci when he was moving about. Antibiotic treatment of the physician and his family cleared the carrier state and ended the epidemic.

Such outbreaks of GABHS infections continue to occur rarely but must be recognized quickly because of the potential for severe disease *(3,55)*. Even a single case of postpartum GABHS infection should be investigated immediately (see also Chapter 32).

Group B Streptococcal Infection

Group B β-hemolytic streptococci (GBS), normal flora in the gastrointestinal and genitourinary tracts, occasionally cause obstetric infections: chorioamnionitis, endometritis, urinary tract infections, or SSIs *(56)*. More often, the colonized mother may transmit GBS to the neonate, sometimes causing neonatal sepsis and/or meningitis. The Centers for Disease Control and Prevention (CDC) recommends universal prenatal screening of pregnant women for GBS colonization of vagina and rectum (57). Antibiotic prophylaxis is recommended for colonized women delivering vaginally, for those with GBS bacteriuria during current pregnancy, or for those who have delivered an infant previously with early-onset GBS disease (57). Prophylaxis is also given to those women whose culture status is unknown and who have preterm labor, premature rupture of membranes, >18 hours of ruptured membranes, or maternal fever during labor (57) (see also Chapter 32).

Staphylococcus aureus

An outbreak of MRSA at a large regional maternity unit in England identified 37 patients who had MRSA *(58)*. Perineal colonization was common in postpartum women, but not in staff members. The wards in this hospital differed from most American hospitals in that common toilet facilities with baths were provided for each ward rather than private bathrooms. Contamination of baths and bidets with MRSA was documented. Mattress covers were also contaminated and remained contaminated even after cleaning with detergent. Most mattress covers were found to be porous, and the core of some mattresses contained MRSA. The relative contribution of environmental transmission cannot be determined from this study because, as in most MRSA outbreaks, transient carriage by staff members was demonstrated. MRSA was eradicated from the maternity wards with multiple infection control measures, including replacement of all mattresses.

Clusters of *S. aureus* should be investigated thoroughly. Screening for carriers can be considered. Because a limited number of MRSA clones circulate, DNA fingerprinting has limited utility *(59,60)* (see also Chapters 28 and 29).

HIV Infection

One of the most important infections to identify in the pregnant patient is HIV. An estimated 21% of those individuals infected with HIV in the United States are unknown *(61)*. HIV antibody testing should be done as a part of the initial evaluation, and the CDC recommends an opt-out approach (62). High-risk patients should be tested again in the third trimester (62). For those pregnant women identified as HIV-positive, antiretroviral therapy is recommended regardless of their CD4 count or viral load *(63)*. The objective of treatment is to suppress the viral load so as to prevent transmission to the fetus *(63)*. Pregnant women with HIV should be seen by an HIV specialist along with their regular obstetric care. Cesarean section may be needed in those women whose viral load is not adequately suppressed *(63)*. HIV-infected mothers should be counseled not to breast-feed their infant as HIV can be transmitted through breast milk *(63)*.

Hepatitis B Virus Infections

All pregnant women should be tested for hepatitis B virus (HBV) surface antigen to prevent transmission of HBV infection to neonates. If HBV infection is identified in the obstetric patient, the neonate should be treated with HBV immunoglobulin and hepatitis B vaccine within 12 hours (64).

Healthcare workers with HBV also pose a risk to uninfected obstetric patients during high-risk procedures. Obstetricians with HBV have been reported to infect their patients during cesarean section and forceps deliveries *(65)*. Every obstetrician should know his or her HBV status, including tests for HBV surface antigen, e antigen and antibody, and core antibody. If susceptible to HBV, obstetricians should be immunized (see also Chapters 46, 73, and 75).

Hepatitis C Virus Infection

No prophylaxis is currently available to prevent transmission of hepatitis C virus (HCV) from an infected mother to her infant. The transmission rate of HCV from mother to child is approximately 7% to 8% but is higher in patients coinfected with HIV (64). The risk of transmission to the fetus is related to the HCV viral load titer at the time of delivery (66). No cases of HCV transmission through breast milk have been identified *(67)*, but it may be prudent not to breast-feed.

HSV Infection

Genital HSV, both primary and recurrent infection, occurs in obstetric patients and on rare occasion may result in disseminated disease *(68)*. HSV can be transmitted from mother to neonate intrapartum. Cesarean section is indicated for women with active HSV lesions or with a typical prodrome at the time of delivery (69). Internal fetal monitoring should not be done if HSV is suspected (69).

Postpartum, the mother with HSV lesions should be advised of potential risks of transmission to her newborn and be educated about appropriate measures to limit contact transmission (69). If healthcare workers with active lesions are allowed to continue working with patients, similar measures should be taken (70) (see also Chapter 44).

Chickenpox (Varicella Zoster Virus Infection)

Chickenpox in the obstetric patient may result in severe pneumonia, requiring hospitalization and antiviral therapy *(71)*. Because airborne transmission can occur, the obstetric patient with chickenpox who is not in labor should be admitted to a nonobstetric unit and placed in a negative pressure room (72,*73*). A patient admitted to an obstetric unit and placed in a regular hospital room with the door closed still infected a susceptible nurse who walked past the closed door *(73)*. After a pregnant woman with chickenpox delivers, the mother and infant should be separated until all of the mother's lesions have crusted over. Pregnant women should not receive the varicella vaccine (74) (see also Chapters 43 and 52).

Influenza

During the influenza season, pregnant women, especially those in the third trimester, are at higher risk for being hospitalized with an acute cardiopulmonary condition *(75)*. The 2009 pandemic H1N1 influenza A resulted in more severe complications in pregnant women. Although only 1% of the population, pregnant women accounted for 9% of the hospitalizations *(76)* and 6% of reported deaths (77). Pregnant women who are hospitalized with either confirmed or suspected influenza should have the same infection control policies utilized as for nonpregnant patients: placement in a single room, use of a surgical mask by hospital staff within 6 ft, and masking of the patient outside of her room (78). Empiric therapy with oseltamivir or zanamivir should be started; although these drugs are Food and Drug Administration Category C, benefit outweighs risk in this setting. Following delivery, the infant should be separated from the ill mother until she has been on treatment for 48 hours, she is afebrile for 24 hours, and she can control cough and respiratory secretions (78). Women who are considering pregnancy during the flu season should be immunized (74). Inactivated influenza vaccine is safe and recommended for pregnant women; the live-attenuated (intranasal) form of the vaccine is not approved in pregnancy (74) (see also Chapter 42).

INFECTION CONTROL PROGRAM FOR OBSTETRICS

Surveillance

Surveillance data are available on healthcare-associated infections on obstetric units. The National Healthcare Safety Network (NHSN) (formerly the National Nosocomial Infections Surveillance (NNIS) system) and other organizations do provide some benchmarking data (37). As would be expected, these reports show that SSIs are the major healthcare-associated infection in obstetrics. However, the reported infection rates on obstetric services are lower than those on medical and surgical services. The infection rates vary by the size and type of hospital, and the SSIs vary by the number of risk factors. More recent NHSN reports are limited to data on SSIs from in-hospital surveillance of patients who have had cesarean sections (37). Hospitals can either benchmark against these published rates or their own historical rates *(79)*. The CDC provides standardized definitions for surveillance (Table 55-2) and risk stratification (80,81). As discussed previously, many risk factors have been identified for obstetric infections. A simplified approach is to relate infections to the type of delivery—vaginal or cesarean—and to distinguish between elective and nonelective cesarean sections.

The general value of surveillance and infection control programs in hospitals has been documented by the CDC Study on the Efficacy of Nosocomial Infection Control (82), and the effective use of surveillance data on an obstetrics and gynecology service has been demonstrated by a study at a Swedish hospital *(83)*. In the Swedish report, data collected on patients having cesarean sections showed that 15% of them were infected (urinary tract infections excluded). The infection rates decreased to 9% after the introduction of quarterly surveillance reports to obstetric personnel. These reports included surgeon-specific infection rates.

A traditional method of surveillance on obstetric services is to monitor fevers in all patients. Most infected patients will be detected by this approach, and a routine fever workup in the postpartum patient will identify many

TABLE 55-2

Definitions for Surveillance of Healthcare-Associated Infections on Obstetric Units: Centers for Disease Control and Prevention

Endometritis must meet either of the following criteria:
Microorganism isolated from culture of fluid or tissue from endometrium obtained during surgery, by needle aspiration, or by brush biopsy
Two of the following are present: purulent drainage from uterus, fever (>38°C), abdominal pain, or uterine tenderness
Episiotomy site infection must meet either of the following criteria:
Purulent drainage from episiotomy
Episiotomy abscess
Other infections (excluding surgical site infections) must meet either of the following criteria:
Microorganism isolated from culture of tissue or fluid from affected site
Abscess or other evidence of infection seen during surgery or by histopathologic examination
Two of the following: fever (>38°C), nausea, vomiting, pain, tenderness, dysuria, and either of the following:
Microorganism isolated from blood culture
Physician's diagnosis
Postcesarean surgical site infections must meet the definitions used for all surgical site infections and are classified into the following categories:
Superficial incisional involves only skin or subcutaneous tissue and excludes stitch abscess or an episiotomy infection
Deep incisional involves deep tissues, e.g., fascial or muscle layers
Organ/space involves any part of the anatomy, other than an incision, opened or manipulated during surgery and includes postoperative endometritis

(Data from Horan TC, Andrus M, Dudeck, MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332; and Horan TC, Gaynes RP, Martone WJ, et al. CDC definitions of nosocomial surgical site infection, 1992: a modification of CDC definitions of surgical wound infections. *Am J Infect Control* 1992;20:271–274.)

infectious causes. The limitation of fever surveillance is lack of specificity: half of the fevers are either noninfectious or of unknown cause *(84)*. Despite this limitation, fever surveillance on an obstetric unit is a good screening technique and can indicate the development of potential problems.

Mead et al. *(83)* reported the use of a "sentinel list" technique on an obstetric unit, where the bedside nurse is involved in collecting information including fever and antimicrobial therapy and the collected information is reviewed for continuous surveillance. This method may be implemented and maintained by the obstetric staff, who would report to infection control when problems develop.

Short hospital stays and outpatient management of most postdischarge infections limit hospital-based surveillance of obstetric patients. Supplemental postdischarge surveillance systems are needed to provide an accurate picture of obstetric infections.

Several different approaches to postdischarge surveillance have been tried, involving either the patients directly or their physicians. The gold standard of postdischarge surveillance is direct observation of patients after hospital discharge. Couto et al. *(86)* did this at a Brazilian hospital by having postcesarean patients return on the 10th to the 15th postoperative day *(86)*. While in the hospital, 1.6% of the patients had SSIs, and this increased to 9.6% with inclusion of postdischarge examination.

A more practical approach was used by Holbrook et al. (45) who mailed one-page questionnaires to 19,650 women who delivered at their hospital. They received responses from only 36% of them (45). Ten percent of the patients who responded reported infections after discharge, including mastitis (6%), urinary tract infections (3%), and endometritis (1%). Postdischarge surveillance detected twice as many infections as in-hospital surveillance. The additional infections that were identified were mostly mastitis and urinary tract infections. Most cases of endometritis were reported by in-hospital surveillance, but an additional 1% of women reported endometritis after discharge. A major limitation of this approach is the poor response rate by the patients.

Postdischarge surveillance using physician questionnaires to identify infections after cesarean section has been reported to be more successful *(87)*. In a study by Hulton et al. *(87)*, 90% of physicians completed questionnaires about their patients. These questionnaires indicated an infection rate of 6.3% compared with 1.6% observed by in-hospital surveillance. The increase occurred in incisional SSIs (0.3–3.9%) and endometritis (1.3–2.5%). A limitation of this method is variability among physicians in self-identifying infections *(88)*.

Data mining of computerized records can augment traditional surveillance. Yokoe et al. (2) have used this method to determine postpartum infection rates among women in a large managed care organization. Computers can link patients with cesarean section procedure codes to later infection codes *(89)*. Various computer algorithms have been developed and commercialized to aid in identification of infections. These aim to reduce both labor and subjectivity.

Facilities on an Obstetric Unit

Obstetric units vary greatly in design, ranging from birthing centers designed for low-risk deliveries to standard labor and delivery units including operating rooms for cesarean

sections. The design needs are similar to other patient care areas in the hospital, including conveniently placed alcohol hand rubs and sinks for hand disinfection by staff, easily cleaned surfaces, and, in the case of complicated deliveries, a fully equipped operating room. The American College of Obstetricians and Gynecologists outlined basic standards for obstetric facilities *(90)*. An isolation facility should be available for the rare delivery of an obstetric patient with airborne infectious diseases such as chickenpox or tuberculosis. A pregnant patient with such an infection who is not in labor can be isolated on other hospital units in a room with negative air pressure.

The use of hydrotherapy to assist in labor raises additional environmental infection control concerns *(91)*. Some obstetric units use baths, whirlpools, or Jacuzzi showers as an aid in delivery. This practice raises the same concerns about bacterial contamination as hydrotherapy in physical therapy. Very few studies have been reported that evaluate the potential infectious risks of obstetric hydrotherapy. In one nonrandomized study of 1,385 women with prelabor rupture of the membranes *(92)*, 538 chose to use a warm tub bath during labor and 847 did not. Of those who used the bath, 1.1% developed chorioamnionitis and 0.6% developed endometritis. Of those who did not, 0.2% developed chorioamnionitis and 0.4% developed endometritis, suggesting no infectious risk. However, in a small study of 32 women *(93)*, one infant developed a *Pseudomonas* infection; *Pseudomonas* was isolated from the prelabor bath water. Presumably, this resulted from a lapse in cleaning technique and indicates a potential infectious risk. Whirlpool baths present even more complex maintenance problems. In a randomized controlled trial of whirlpool baths, 785 patients were studied *(94)*. Benefits in regard to analgesics, instrumentation, and perineal conditions were reported, and no difference was observed in maternal and neonatal infections.

These studies provide limited guidance in making an infection control decision regarding maternal hydrotherapy. If a facility decides to use hydrotherapy, detailed policy and procedure must be followed for cleaning and maintenance. Women with complicated pregnancies should be excluded, and many facilities require that the patient sign a consent form. Cleaning and maintenance depends on the type of equipment used. To avoid these problems, some facilities use inflatable single-use tubs.

Prevention

Antepartum The goal of good medical care during pregnancy is to ensure that a healthy patient presents for delivery. Conditions that place the pregnant patient at risk for postpartum infection, including urinary tract infection and perhaps bacterial vaginosis, should be identified and treated during routine prenatal care *(39,95)*. Routine screening for infections, including sexually transmitted and blood-borne diseases such as HIV, HBV, syphilis, *Chlamydia*, and gonorrhea should identify other infections in the pregnant patient. Dietary restrictions, such as no unpasteurized soft cheese, cold deli meats, or undercooked hot dogs, are appropriate to avoid infection with *Listeria (96)*. All pregnant women should receive inactivated influenza vaccine.

Intrapartum Semmelweis' *(6,7)* original observations on the value of good hand washing with an antibacterial agent remain the cornerstone of good obstetric infection control. The number of vaginal examinations should be limited, and internal monitoring with pressure catheters and scalp electrodes should be used only when necessary and should be introduced with aseptic technique. Fetal electrodes should be avoided in women with HSV, HIV, or HBV.

Studies during obstetric procedures *(97–100)* have clearly shown the high risk of exposure during deliveries of the obstetric team to blood and body fluids. In one study, observers were placed in delivery rooms and directly recorded the frequency of blood or amniotic fluid exposures *(97)*. In 230 deliveries observed, blood or amniotic fluid exposure occurred in 39% of 202 vaginal deliveries and 50% of 28 cesarean sections. The highest rates of exposure occurred in obstetricians and midwives. Another study *(98)* comparing different surgical procedures showed that the frequency of blood exposures during cesarean sections was exceeded only by cardiothoracic and trauma surgery. Tichenor et al. *(99)* demonstrated the need for good eye protection. They collected eye shields attached to surgical masks worn during deliveries and counted the visible splashes. This study found that 54% of the eye shields from the primary obstetricians had been splashed, including 30 of 68 shields from vaginal deliveries and 30 of 44 from cesarean sections. Perforation of surgical gloves is also common during deliveries and often goes unrecognized. Serrano et al. *(100)* collected 754 surgical gloves used by obstetricians during vaginal and cesarean deliveries and postpartum ligations. The gloves were examined for perforations by an air inflation—water submersion technique, and 13% of the gloves had been perforated. They noted that 62% of the perforations were not recognized during the surgical procedure; thus, the obstetricians were unaware of the potential exposure to blood or body fluids.

Because all deliveries are associated with the splatter of blood and body fluids and exposures are common, the delivery team cannot predict exposures. Further, any patient may have a blood-borne disease. Therefore, personal protective equipment should always be worn: gloves, long-sleeved impervious gowns, shoe covers, masks, and eye protection. The obstetrician should always be aware of the possibility of glove perforation.

Prophylactic antibiotics are given for all cesarean sections and will prevent 50% or more of postpartum endometritis (*25*,27,*28*,*29*). Good surgical technique is critical as well to the prevention of surgical infections *(101)*.

Postpartum Good perineal, surgical site, and breast care is important in the postpartum period. Mother and newborn should be separated in the case of infections such as tuberculosis, chickenpox, or influenza. Masks should be worn during minor respiratory infections. The patient should be monitored for urinary retention, with urinary catheterization used only as needed.

CONCLUSIONS

Healthcare-associated infections in obstetric patients have a long and dramatic history, but modern obstetric practices have produced low infection rates and extremely

low maternal mortality. Nonetheless, it is important to appreciate that these infections still occur, produce significant maternal and neonatal morbidities, and require careful monitoring. Recent drops in infection rates (37) and improvements in perioperative antibiotics for cesarean section both demonstrate that further advances in infection prevention are possible.

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CHAPTER 56

Healthcare-Associated Infections in Patients with Spinal Cord Injury

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About 262,000 Americans suffer from spinal cord injury and its complications, with 12,000 new cases accruing each year (1). Although it remains unknown if the incidence of spinal cord injury has changed over the years, it is estimated that about 40 cases occur in the United States per million persons (1). However, the number of patients living with spinal cord injury is expected to continue to rise owing to the increase in their life expectancy that is almost similar to that in the able-bodied population. Most cases of spinal cord injury are traumatic, most notably due to motor vehicle accidents, gunshot wounds, falls, contact sports, diving injuries, earthquakes, and acupuncture *(2–4)*. Nontraumatic causes include spinal tumors, infection, transverse myelitis, and iatrogenic events, especially perioperative hypotension *(5)*. Although the vast majority of cases of spinal epidural abscess are bacterial and are caused mostly by *Staphylococcus aureus* (6), a variety of other microorganisms, including agents of tuberculosis *(7)*, brucellosis *(8)*, actinomycosis *(9)*, neurocisticercosis *(10)* and shistosomiasis *(11)* as well as fungi-like Candida *(12)* and Aspergillus *(13)* species, and HIV, may also be causes of spinal epidural abscess *(14)*.

Healthcare-associated infections in patients with spinal cord injury have unique attributes and commonly require multidisciplinary management. Healthcare-associated infections in spinal cord–injured persons are also a major cause of morbidity and often are lethal. Compared to those who do not become infected, patients with spinal cord injury who develop healthcare-associated infections have lower functional improvements, shorter survival, and a higher likelihood for prolonged future hospitalization *(15,16)*.

The three most prevalent infections in patients with spinal cord injury affect the urinary tract, respiratory tract, and the skin and soft tissues, in the form of decubiti, with or without involvement of the underlying bone. The main objectives of this chapter are to: (a) address the factors that predispose to healthcare-associated infections in relation to the time of injury; (b) delineate the interrelated pathogenesis and microbiology, unusual clinical manifestations, problematic diagnosis, and difficult prevention of infections involving the urinary tract, the respiratory tract, and the skin and soft tissues with or without involvement of the underlying bone; and (c) assess the spread, colonization, and infection by multiresistant microorganisms.

FACTORS THAT PREDISPOSE TO HEALTHCARE-ASSOCIATED INFECTIONS

Patients with spinal cord injury are predisposed to healthcare-associated infections both in the acute and the chronic settings after injury (Table 56-1). The administration of high doses of glucocorticosteroids immediately after traumatic injury is associated with a significant increase in respiratory and total infections *(17)*. Immediately after the spinal cord injury, patients are admitted to the hospital for management of injuries to the spinal cord and possibly other bodily organs. Not only do some injured patients initially require acute intensive care that poses its own risks for acquiring infection, but all subsequently undergo in-patient rehabilitation for up to few months (5). Critically ill patients and those residing in specialized spinal cord injury units have a particularly high risk of developing infections with resistant microorganisms, including extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacilli, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE).

TABLE 56-1

Factors that Predispose to Healthcare-Associated Infections

Soon after the spinal cord injury
Administration of glucocorticosteroids after the injury
Surgical management of injuries to the spinal cord and other bodily organs
Admission to the intensive care unit
Prolonged initial hospitalization
Bladder catheterization
Mechanical ventilation
Insertion of vascular catheters
Long after the injury
Bladder catheterization
Decubiti
Tracheostomy in patients with high cervical lesions
Surgical intervention for chronic complications emanating from the spinal cord injury
Immunologic changes

Furthermore, patients with spinal cord injury frequently have sustained concurrent wounds of the neck, chest, and abdomen that may require surgical intervention, thereby imposing additional risks for postoperative infections. The majority of patients during the period of spinal cord shock suffer from neurogenic bladder that necessitates catheter drainage, often leading to development of urinary tract infection. Likewise, the insertion of central vascular access for administration of fluids, blood and blood products, and medications or for hemodynamic monitoring may cause bloodstream infection. Patients with high cervical injury usually require mechanical ventilation and can develop ventilator-associated pneumonia.

Although the likelihood of developing infection appears to be the highest in the acute postinjury period, the vast majority of infections occur long after the spinal cord injury. This finding is attributed to the fact that many patients sustain spinal cord injury when still young and have an almost normal life expectancy. Since most patients with spinal cord injury chronically rely on bladder catheters for urinary drainage, urinary tract infection is the most common infection long after the injury. Second in frequency are infections associated with decubiti. Patients with high cervical lesions are especially predisposed to both tracheostomy- and endotracheal tube-related respiratory tract infections. Surgical management of the chronic sequelae of spinal cord injury can be complicated by surgical site infections. Injury to the spinal cord can result in immunosuppressive effects, particularly in patients with high-level injury that causes alteration to the sympathetic nervous system or the hypothalamic-pituitary-adrenal axis *(18)*. Possible immunologic deficits include impaired antibody synthesis *(18)*, reduced phagocytic activity (19), and aberrant accumulation of glucocorticoids and norepinephrine in the blood and spleen *(20)*.

URINARY TRACT INFECTIONS

Pathogenesis and Epidemiology

Accounting for 25% to 50% of all infections, urinary tract infections are the most common healthcare-associated infection in patients with spinal cord injury *(21)*. The two unique factors that predispose this population to urinary tract infection include bladder catheterization and urinary stasis. The incidence of urinary tract infection appears to be the same in patients with spinal cord injury who have either an indwelling transurethral or a suprapubic bladder catheter *(22)*. Since intermittent bladder catheterization predisposes to urinary tract infection less than indwelling bladder catheterization, the former approach is advised whenever feasible. Unfortunately, only one-fifth of patients continue to practice this method of bladder drainage *(23)*. Although the sterile technique of bladder catheterization can theoretically be safer, at least in hospitalized patients, than the clean technique, both catheterization techniques can introduce pathogens into the urinary tract. Urinary stasis impairs the naturally occurring mechanisms that protect the urinary tract from infection, including the washout effect of voiding and the phagocytic capacity of bladder epithelial cells. Multiplication of bacteria in the urine and invasion of host tissues are promoted in the presence of reduced bladder emptying, increased residual urine, and high bladder pressure.

Although more than 90% of episodes of urinary tract infection in this population seem to involve only the lower urinary tract, serious complications can still arise secondary to such infections. Ascending infection of the urinary tract may evolve in the presence of vesicoureteral reflux or as a consequence of manipulations aimed at emptying the bladder. Taking into consideration that renal failure was once the leading cause of death in this population, kidney infection with loss of renal function is particularly worrisome. Additionally, urinary tract infection can be associated with a number of anatomic changes, such as renal calculi (occupying the bladder, ureters, or kidneys), bladder diverticulae and fibrosis, penile and scrotal fistulas, epididymoorchitis, and abscesses. The frequency of these anatomic changes depends on the type and the duration of bladder drainage; for instance, these changes are most commonly detected in patients with indwelling bladder catheters.

The vast majority of episodes of urinary tract infection in patients with spinal cord injury are caused by commensal bowel flora, primarily gram-negative bacilli and enterococci. The microbiology of microorganisms residing in the bladder can be affected by patients' gender, the source of pathogens (i.e., healthcare-associated vs. community-associated), and the method of urinary drainage. For instance, *Klebsiella pneumoniae* is a very common cause of urinary tract infection in hospitalized patients, whereas *Escherichia coli* and the enterococci cause more than two-thirds of cases of urinary tract infection in female patients undergoing intermittent bladder catheterization. The presence of condom catheters increases the likelihood of colonizing the urethra and the perineal skin with *Pseudomonas*, *Klebsiella*, and other gram-negative bacilli. As in able-bodied subjects, the presence of renal calculi in patients with spinal cord injury suggests etiology by urease-producing bacteria. Spinal cord injury units are no different from other types of specialized care units as to the occurrence of outbreaks of urinary tract infection due to multiresistant gram-negative bacilli. Increasing antibacterial usage has been associated with occurrence of candiduria *(24)*. Polymicrobial growth is detected in almost half of positive urine cultures obtained from patients with spinal cord injury, particularly those with chronic indwelling urethral catheters *(25)*.

Clinical Manifestations

Urinary tract infection may manifest differently in patients with spinal cord injury than in the general population. For instance, infected patients with spinal cord injury may not complain of dysuria, frequency, and urgency—symptoms that usually exist in able-bodied patients with urinary tract infection. Furthermore, suprapubic and flank pain or tenderness are not felt in insensate patients. More common manifestations of urinary tract infection in patients with spinal cord injury include worsening spasm, increasing dysreflexia, and change in voiding habits. Fever is usually, but not always, present.

Diagnosis

Diagnosing urinary tract infection in patients with spinal cord injury can be problematic for several reasons. First, by masking urinary-specific symptoms, absent sensations

constitute the single most important obstacle in diagnosing this infection in this population. Second, the unusual manifestations of urinary tract infection in these patients are nonspecific and may be caused by a variety of other infectious or noninfectious conditions, including osteomyelitis beneath decubiti, ingrown toe nails, and heterotopic bone ossification. Third, bacteriuria, the cornerstone for diagnosing urinary tract infection, is nonspecifically prevalent in this population. Bacteriuria is most frequent in patients who have chronic indwelling bladder catheters, as cultures of randomly obtained urine samples yield bacterial growth in more than 90% of instances. Even patients who undergo intermittent bladder catheterization have a 70% likelihood of being bacteriuric. Most cases of bacteriuria in patients with spinal cord injury represent asymptomatic bladder colonization. Although asymptomatic bladder colonization can progress to symptomatic infection, often it does not. Fourth, the finding of pyuria, which can reflect inflammation of the uromucosal lining and signal the transition from bladder colonization to symptomatic urinary tract infection, is not specific for infection. Pyuria can be caused by a variety of noninfectious conditions, including catheter-induced trauma, renal stone, recent urologic procedure, and interstitial nephritis.

Because of these potential problems in establishing a diagnosis, particularly when based on patients' prediction *(26)*, there exists no universally accepted definition of symptomatic urinary tract infection in patients with spinal cord injury. A commonly used definition of symptomatic urinary tract infection in these patients requires the presence of significant bacteriuria ($\geq 10^5$ colony-forming units [CFU]/mL), pyuria (>10 WBC/high power field [hpf] for spun urine), and fever (>100°F) plus more than one of the following signs and symptoms—(a) suprapubic or flank discomfort, (b) bladder spasm, (c) change in voiding habits, (d) increased spasticity, and (e) worsening dysreflexia—provided that no other potential etiologies for these clinical manifestations can be identified (27,*28*). Most healthcare providers tend to distinguish upper from lower urinary tract infection based on clinical manifestations and laboratory rather than imaging findings. For example, the presence of high fever (>102°F), chills, systemic toxicity, high-grade leukocytosis (>20,000 per mm^3), and/or leukocyte casts in urinary sediment supports the presence of pyelonephritis.

Prevention

Mechanical Approaches Since the indwelling transurethral and suprapubic catheters pose a higher risk of infection than intermittent bladder catheterization, the latter method of bladder drainage should always be considered, barring any anatomic or functional constraints. Increasing the frequency of intermittent bladder catheterization can decrease the risk of urinary tract infection. Although the technique of clean nonsterile intermittent self-catheterization is considered rather safe for use by outpatients, sterile intermittent catheterization is implemented by most hospitals owing to the fear of healthcare-associated introduction of multiresistant and virulent microorganisms into the urinary tract. In patients with persistent or recurrent urinary tract infections, the urinary tract should be investigated for anatomic abnormalities (including abscess, stone, obstruction, and stricture) and functional alterations (such as vesicoureteral reflux, high residual volume of urine in bladder, and elevated bladder pressure). The use of drugs and surgical procedures to reduce bladder pressure and aid bladder emptying can help alleviate the risk of urinary tract infection. Recent evidence suggested that the use of a catheter-securing device has the potential for preventing symptomatic urinary tract infection in patients with spinal cord injury *(29)*.

Antimicrobial Approaches Treatment of asymptomatic bacteriuria with bladder instillation of antibiotic solutions may alleviate bacteriuria temporarily. However, this may result in the emergence of antibiotic resistance and there is no evidence that this practice prevents clinical urinary tract infection. Studies that examined the administration of systemic antimicrobial agents in patients with spinal cord injury *(30–32)* have yielded either conflicting or disappointing results in terms of efficacy and emergence of antibiotic resistance. In general, systemic antimicrobial use is discouraged for treatment of asymptomatic bacteriuria in patients with spinal cord injury (33,*34*,35). Exceptions may include patients with (a) enlarging struvite stones associated with urea-splitting microorganisms, such as *Proteus mirabilis* and *Providentia stuartii (36)*; (b) conditions that enhance the likelihood of developing significant complications from having asymptomatic bacteriuria, such as premature birth in pregnant women; and (c) recurrent episodes of upper urinary tract infection that are complicated by sepsis or other clinical complications, particularly if the recurrent infections are caused by the same microorganism. It is important to note that, in general, antimicrobial treatment of asymptomatic bacteriuria in women with diabetes mellitus is probably not warranted (37). Although Cochrane reviews suggested that the use of cranberry supplements (38) or methenamine hippurate (39) could be beneficial in some clinical scenarios, the applicability of these approaches in the population of patients with spinal cord injury is of unclear value *(40–42)*. The clinical efficacy of antimicrobial-impregnated bladder catheters has not been tested in the population of patients with spinal cord injury, or for that matter, in patients with chronic indwelling bladder catheters. Preprocedure systemic antibiotic prophylaxis is generally indicated before urologic procedures, including urodynamics, and the administered antibiotic regimen is best chosen based on results of urine cultures and antimicrobial susceptibility tests obtained before the procedure.

Bacterial Interference Approach The limited success of traditional antimicrobial prophylaxis prompted interest in exploring the novel approach of active bacterial interference *(43)*. This approach is based on the principle that nonpathogenic microorganisms may prevent colonization of the urinary tract by pathogenic microorganisms. A number of relatively small open-label or randomized, placebo-controlled double-blind clinical trials in patients with spinal cord injury who had suffered from frequent episodes of infection indicated that intentional colonization of the neurogenic bladder by a nonpathogenic strain of *E. coli* 83972 reduced the rate of symptomatic urinary tract infection and posed no safety issues (27,*28*,*44–46*).

The potential clinical benefit of artificially boosting the lactobacillus numbers through probiotic instillation into the genital tract to limit the inflammation due to urinary tract infection is too early to judge *(47)*.

RESPIRATORY TRACT INFECTIONS

Pathogenesis and Epidemiology

Respiratory complications are the most common cause of morbidity and mortality in patients with acute spinal cord injury *(48,49)*. Pneumonia, the most serious respiratory tract infection and the leading cause of death due to infection in this population, is the most common pulmonary complication in the immediate period after injury as almost one-third of patients developed pneumonia while undergoing initial rehabilitation in the hospital *(50)*. Pulmonary function at the time of completing the initial hospital course after sustaining spinal cord injury can predict subsequent respiratory infections *(51)*. Pneumonia is particularly likely to occur in the first few months after cervical or high thoracic injury and among quadriplegics and persons older than 55 years. Upper respiratory tract infections and acute bronchitis may be precipitating factors in the development of pneumonia or ventilatory failure *(52)*.

Factors that predispose patients with spinal cord injury to develop pneumonia or tracheitis include: (a) weakness of the diaphragmatic and intercostal muscles in patients with cervical or high thoracic spinal cord injury, which would impair the capacity to clear respiratory secretions; (b) aspiration that is promoted either by an abnormal state of consciousness due to illicit drug ingestion or associated head injury or by paralytic ileus that often occurs soon after spinal cord injury; and (c) indwelling respiratory devices, such as endotracheal or tracheostomy tubes.

The microbiology of healthcare-associated respiratory tract infections in this population is affected by the type of predisposing factor(s). For example, *S. aureus* (particularly MRSA) and *Pseudomonas aeruginosa* are the two most common causes of pneumonia and tracheitis in patients with respiratory devices, whereas aspiration pneumonia is mostly caused by gram-negative and anaerobic bacteria. Unfortunately, prescriptions for broad-spectrum antibiotics that are not indicated for specific clinical scenarios have recently increased *(53)*.

Clinical Manifestations

Patients with cervical or thoracic spinal cord injury can have absent or altered sensations of chest pain and dyspnea. Infected patients with weakness of the diaphragmatic and intercostal muscles may also have no or minimal cough, and are unlikely to spontaneously produce sputum. In such patients, the only clinical manifestations of pneumonia may consist of physical findings (distressed appearance, fever, tachypnea, and tachycardia) and abnormal test results (leukocytosis, hypoxemia, and infiltrates on chest radiographs).

Diagnosis

Because of ineffective cough, patients with cervical or high thoracic lesions may not be able to provide adequate sputum samples for Gram stain and cultures. If tracheal secretions cannot be adequately suctioned, bronchoscopy may be required for both diagnostic and therapeutic purposes. The most prominent impediment to diagnosing pneumonia in patients with spinal cord injury arises from the limited ability to clinically distinguish pneumonia from a number of noninfectious pulmonary complications, including atelectasis, chemical pneumonitis, pulmonary embolism, and fat embolism. For instance, atelectasis, like pneumonia, commonly occurs in patients with cervical or high thoracic spinal cord injury who retain pulmonary secretions and can also manifest with fever. Furthermore, the site of pulmonary involvement may not help differentiate atelectasis from pneumonia since both conditions predominantly affect the left lung. Chemical pneumonitis due to aspiration can also mimic bacterial pneumonia. When adequate samples of respiratory secretions are available, microbiologic examination may help distinguish between these two clinical entities by showing a plethora of microorganisms (along with WBCs) in samples obtained from patients with bacterial pneumonia. Pulmonary embolism can also be clinically confused with pneumonia. This is partially attributed to the fact that the majority of patients with spinal cord injury disclose no thrombotic source for pulmonary embolism *(54)*. Furthermore, since patients with spinal cord injury commonly display baseline roentgenographic changes in the lungs due to atelectasis or other causes that make it difficult to interpret ventilation-perfusion lung scans, a definitive diagnosis of pulmonary embolism often requires pulmonary angiography. Fat embolism, which can occur acutely after spinal cord injury in association with fracture of long bones, may be suspected if petechiae and cerebral dysfunction are present.

Prevention

Potential approaches for preventing pneumonia in patients with spinal cord injury include some that center around control of predisposing conditions and others that provide antimicrobial activity. The first group of approaches is intended to augment cough and lessen retention of secretions. Cough can be assisted by using abdominal binders or corsets. Adequate hydration, chest physical therapy, and postural drainage can enhance drainage of secretions, although it may be difficult to achieve certain optimal positions during the acute period following spinal cord injury.

Antimicrobial approaches include antibiotics and immunization. In general, the use of systemic antibiotics for prevention of pneumonia in high-risk patients with spinal cord injury is not advocated. Because pneumonia can either occur more frequently or result in more serious complications in patients with spinal cord injury than in the general population, eligible patients should be immunized against potentially preventable causes of pneumonia. Almost two-thirds of patients with spinal cord injury are eligible for vaccination against *Streptococcus pneumoniae* and influenza virus by virtue of old age, chronic respiratory disease, and/or residence in long-term care facilities (55). The antibody response to pneumococcal *(56)* and influenza vaccination *(57)* of patients with spinal cord injury appears adequate. Although there have been no prospective studies of the clinical efficacy of these vaccinations in patients with spinal cord injury, it is generally recommended that patients at risk receive influenza vaccine every year and

pneumococcal vaccine every 5 years. Mailing of reminders and educational materials to patients has been reported to increase rates of vaccination (58,*59*). Strategies to increase vaccination rates among healthcare workers should be effectively implemented by addressing the concerns about side effects, effectiveness, and protective value of the available vaccines *(60)*.

INFECTIONS OF DECUBITI AND UNDERLYING BONE

Pathogenesis and Epidemiology

Due to changes in the composition of the skin, alterations in local tissue pressure, infection by tinea pedis, and occurrence of onychomycosis, patients with spinal cord injury suffer from defects and infections of the skin and soft tissue more so than able-bodied persons *(61)*. In general, about one-third of patients develop clinically relevant decubiti at one time or another after the injury. However, the prevalence of decubiti varies among medical centers and is affected by the level and completeness of spinal cord injury. Decubiti delay rehabilitation, prolong hospital stay, and incur excessive costs, particularly when infected. Although decubiti may develop either at home or while residing at a medical institution, most patients get admitted for management of the infectious complications of the ulcers. Factors that contribute to skin and soft tissue infection in the vicinity of decubiti include break in skin integrity and bacterial contamination due to soiling of the ulcer by stools or urine. The former factor predisposes to infection by skin flora including staphylococci and streptococci, whereas the latter factor promotes infection by gram-negative bacilli and anaerobic bacteria. Infected decubiti involve mostly the ischial tuberosities, trochanters, and sacrum—areas that are anatomically exposed to high pressure and likely to be exposed to fecal or urinary microorganisms.

Decubiti often harbor multiple aerobes and anaerobes. The concentration and type of microbes colonizing the decubiti can be affected by the presence of devitalized tissue. For instance, deep necrotic tissues yield high concentrations of bacteria, both aerobes and anaerobes, but the bacterial density and the presence of anaerobes decrease after excising the necrotic tissue. *Bacteroides* species, *Peptostreptococcus* species, *E. coli*, *Proteus* species, and enterococci are more likely to be isolated from necrotic than relatively healthy tissues. Resilient microorganisms like *S. aureus* and *P. aeruginosa* are frequently cultured from necrotic and healing decubiti. There exists some variability in the culture results of deep tissue obtained from different parts of the decubitus, and the value of obtaining repeated cultures of decubiti remains in question. The polymicrobial spectrum of flora in decubiti in children is rather similar to that in adults, but, additionally, includes *Haemophilus influenzae (62). Candida* infection of decubiti in patients with spinal cord injury is quite unusual.

In patients with spinal cord injury, most cases of osteomyelitis occur beneath decubiti. Most such cases are caused by two or more bacterial species, including gram-positive cocci (particularly *S. aureus* and *Streptococcus* species), gram-negative bacilli (including the Enterobacteriaceae group and *P. aeruginosa*), and anaerobic bacteria (mainly *Bacteroides* species). Vertebral and cranial osteomyelitis may also occur in association with implanted spinal hardware and cervical halos, respectively.

Clinical Manifestations

Infection of decubiti can be associated with cellulitis, abscess formation, osteomyelitis of underlying bone, septic arthritis, infected bursa, and septicemia. Local signs of infection include erythema, drainage, and foul-smelling or purulent drainage. Systemic manifestations of fever and leukocytosis commonly, but not invariably, occur. Septicemia is much less frequent in the context of osteomyelitis beneath decubiti in patients with spinal cord injury than in able-bodied adult patients with spinal osteomyelitis or children with long bone osteomyelitis. Clinically relevant blood cultures in patients with infected decubiti suggest the presence of soft tissue abscess or, less commonly, an infected hematoma.

Diagnosis

A number of factors can impede making a proper diagnosis of infection of decubiti with or without underlying osteomyelitis in patients with spinal cord injury.

Inadequate History Patients with spinal cord injury usually have no or altered sensations in the area of the decubitus. Since most decubiti occur in the trochanteric, ischial, and sacral regions, immobile patients cannot directly visualize the ulcers. Furthermore, such patients often complain of neurogenic or referred pain that may have no relation to the infection. These factors frequently result in obtaining an incomplete or inaccurate history from patients and underscore the diagnostic importance of performing comprehensive physical examination by healthcare providers.

Microbiologic Uncertainties Since decubiti are universally colonized by bacteria, swab cultures of open ulcers should not be obtained unless infection is clinically evident. Sinus tract cultures are also usually unreliable. Cultures of material obtained by needle aspiration tend to overestimate the number of bacterial isolates *(63)*. Although cellulitis adjacent to a decubitus can theoretically be caused by a microorganism(s) present in the decubitus, there is no evidence that skin biopsy in patients with spinal cord injury yields clinically relevant results. Cultures of biopsied deep soft tissue remain the most accurate means for determining the microbiologic cause of soft tissue infection.

In patients with underlying osteomyelitis, swab cultures of decubiti do not accurately predict the microorganisms causing bone infection. Moreover, since fibrotic tissue adherent to bone is usually colonized with bacteria, bone cultures are positive in at least two-thirds of patients in whom histopathologic examination of bone tissue is incompatible with osteomyelitis. Therefore, osteomyelitis should not be diagnosed solely by positive cultures of biopsied bone.

Radiologic Limitations Another diagnostic problem in patients with spinal cord injury arises from the limited ability to delineate the extent and the depth of infection in association with decubiti. Deep soft tissue abscesses can

exist beneath apparently healed decubiti. Although highly sensitive for detecting soft tissue abscesses, radionuclide scans can yield false-positive results in patients with spinal cord injury who have an infected decubitus without an associated abscess. Computed tomography (CT) and magnetic resonance imaging (MRI) can detect abscesses in both soft tissue and muscle, as is the case with the infrequently diagnosed iliopsoas abscess *(64)*. Since the incomplete complaints by the insensate patient with spinal cord injury can limit the clinical ability to assess the depth and extension of the infection, it is important to radiologically assess these parameters, particularly in rapidly progressive infections such as Fournier's gangrene *(65)*.

Because pressure necrosis affects subcutaneous and muscular tissues more than skin, the visualized skin opening of a sinus tract may seem deceptively small. Although generally helpful, probing of the sinus tract may still not reveal the full depth of the sinus tract. Sinography can better delineate the full depth of the sinus tract and reveal potential communications with bone, joint, visceral organs, or deep-seated abscesses. In patients with nonhealing decubiti who have persistent or recurrent infection, injection of dye into the bladder or intestines may help establish the presence of fistulous communications.

Misinterpretation of the findings of imaging studies is particularly prominent when attempting to diagnose bone infection beneath decubiti. Bone scan is very sensitive (almost 100%) but poorly specific (<33%) for diagnosing osteomyelitis beneath decubiti (66). The low specificity of bone scan is attributed to the aggregation of technetium in areas of bone that are affected by pressure induced changes and in foci of heterotopic bone ossification. Therefore, bone scan should be used primarily for its high negative predictive value (i.e., in an attempt to rule out osteomyelitis and, therefore, obviate the need for bone biopsy) rather than its low positive predictive value (i.e., to diagnose osteomyelitis). Neither clinical evaluation (duration of ulcer, bone exposure, purulent drainage, fever, peripheral WBC count, and erythrocyte sedimentation rate) nor radiologic examination (plain roentgenogram and bone scan) correlates well with the likelihood of finding histopathologic evidence for bone infection (66). Although the finding of bone changes by CT scan or MRI can be very helpful in supporting the diagnosis of osteomyelitis, there are no studies in patients with spinal cord injury that correlate the abnormal findings of these imaging studies with bone biopsy results.

Multiple Decubiti Patients with spinal cord injury often have multiple decubiti. In such patients, infection of soft tissue and/or bone may exist at some sites but not others. Furthermore, different sites may be infected by different microorganisms.

Because of the above-described diagnostic limitations, definitive diagnosis of osteomyelitis beneath decubiti requires histopathologic examination of bone tissue (66). Percutaneous needle bone biopsy yields histopathologic evidence for infection of bone beneath nonhealing decubiti in only one-fifth to one-third of cases (66). These findings support the clinical observation that nonhealing of decubiti is much less likely to result from underlying osteomyelitis than from noninfectious conditions, such as pressure-related changes, malnutrition, anemia, heterotopic bone ossification, and spasticity.

Prevention

The process of preventing infection of decubiti and underlying bone starts with preventing the development of decubiti. This consists of quality nursing care, frequent turning of the patient for pressure relief, careful attention to bony prominences, avoidance of friction and shear forces, correction of anemia, adequate nutrition, and training patients and their attendants in skin care. The relationship between bacterial counts in wounds and delayed healing remains controversial, and there exists no evidence from prospective randomized studies that local or systemic antimicrobial agents enhance wound healing or prevent infection in patients with spinal cord injury. Systemic antibiotics, however, ought to be given perioperatively in patients undergoing myocutaneous flap surgery. Although perioperatively administered antibiotics are typically active against the gram-positive skin flora, a broader-spectrum regimen that provides additional coverage against gram-negative bacilli and anaerobes may be warranted if supported by the results of clinically relevant preoperative or intraoperative wound cultures. There exists no convincing evidence to support the prevailing practice of continuing perioperative antibiotics until wound drains are removed, usually 10 to 14 days after myocutaneous flap surgery.

SPREAD, COLONIZATION, AND INFECTION BY MULTIRESISTANT MICROORGANISMS

Like other closed hospital units, the spinal Cord Injury Unit is not immune from healthcare-associated transmission of highly resistant microorganisms. Patients in spinal cord injury units may acquire multiresistant microorganisms while residing at a referring institution (hospital or nursing home) or another unit (particularly the intensive care unit) within the same hospital. Alternatively, patients may acquire multiresistant microorganisms while hospitalized at the spinal cord injury unit either directly from already-colonized patients or indirectly via the hands of healthcare providers (who care for colonized persons) or contaminated inanimate surfaces (in patients' rooms, rehabilitation areas, and whirlpools). Fortunately, most cases of growth of multiresistant microorganisms in clinical specimens represent colonization rather than clinical infection.

MRSA

The most commonly studied multiresistant microorganism in spinal cord injury units is MRSA *(67)*, which accounts for almost two-thirds of all clinical isolates of *S. aureus*. The generally problematic diagnosis of infection in these insensate patients makes it sometimes difficult to distinguish between clinical infection and colonization. This microorganism most frequently infects the urinary tract, wounds, lungs, and blood. The sites that are most commonly colonized by MRSA include the anterior nares, wounds, urine, perineum, and stools. Patients may remain colonized with MRSA for months or years. Although topical mupirocin and some systemic

antibiotics may eradicate MRSA colonization, it is unwise to routinely attempt to eradicate MRSA colonization in this population of patients *(68)*. However, control of MRSA is feasible if infection control policies are vigorously applied (69). Unfortunately, transfer of hospitalized patients to nursing homes may be delayed until MRSA colonization is eradicated.

VRE

The prevalence of VRE in spinal cord injury units appears to have increased in recent years. For instance, unreported findings from our center indicated that the gastrointestinal tract of one-third to one-half of patients residing in the spinal cord injury unit is colonized with VRE. In the vast majority of instances, isolation of VRE from stools was not associated with clinical infection. Molecular typing demonstrated that the majority of VRE isolates had distinctly different patterns, even in the case of patients sharing bedrooms. These findings suggested that healthcare-associated transmission of VRE within the spinal cord injury unit was rather unusual.

Gram-negative Bacilli

Patients with spinal cord injury often harbor multiresistant gram-negative bacilli that produce ESBL. Such microorganisms are isolated mostly from the urine, wounds, and respiratory secretions *(70–71)*. Most urinary ESBL-producing isolates belong to the *Klebsiella–Enterobacter* group of microorganisms that are fully susceptible only to carbapenems, but some isolates are also susceptible to aminoglycosides.

Clostridium difficile

This toxin-producing microorganism is very likely to cause environmental contamination in nonisolation rooms, work areas for physicians and nurses, and portable equipment *(72)*. Equally important, patients with spinal cord injury who are admitted to rehabilitation units may have an elevated rate of intestinal colonization by *C. difficile* without having clinical symptoms *(73)*.

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CHAPTER 57

Healthcare-Associated Infections in Patients with Neoplastic Diseases

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A patient with a diagnosis of underlying cancer is at particular risk of infection related to a multitude of factors including immune suppression from the underlying disease and its treatment (e.g., chemotherapy, radiation, or stem cell transplantation) as well as breach in continuity of skin and mucosal barriers related to permanent central venous catheters (CVCs) and therapy-associated mucositis. The source of such infections can be endogenous (e.g., gastrointestinal tract flora) or exogenous (e.g., air, water, or fomites), and the setting of acquiring such infections can be at home, in the community, or a healthcare facility. Overall, advances in the field of oncology often test the fine balance between more aggressive therapy, leading to improved survival, and complications, predominantly infections. In this chapter, we review healthcare-associated infections (HAIs), that is, infections that patients acquire in a healthcare setting, in patients with an underlying malignancy. The more general term, "healthcare-associated," is now increasingly used in place of "nosocomial" (1,*2*). Especially for the oncology patient population that has repeated "encounters" with the healthcare system in the form of frequent hospitalizations, treatment in day-care facilities, and visits to outpatient clinics, the line that differentiates HAIs from community-acquired infections can become particularly blurry, with the actual source of infection often hard to discern. Early diagnosis, treatment, containment, and prevention of HAIs are of great importance to the management of neoplastic diseases.

PATHOGENESIS OF HEALTHCARE-ASSOCIATED INFECTIONS IN PATIENTS WITH NEOPLASTIC DISEASE

The Host

Influencing the pathogenesis of infections, including HAIs, in the cancer patient are a multitude of vulnerabilities in host defenses. First, in most patients, the defect is an iatrogenic impairment of the immune system such as suppression of B lymphocytes and antibody production, impairment of T lymphocytes impeding cell-mediated responses, or neutropenia due to intensive chemotherapy or irradiation. While the risk of bacterial infections in patients with neutropenia has long been recognized and drives the empiric management of febrile patients with low neutrophil counts, there is increasing recognition of the risk for viral infections and related morbidity in patients who are lymphopenic *(3)*.

Second is the role of compromised natural barriers to infection. A breach in the integrity of the skin and mucous membranes is a frequent portal of entry for microbes composing the resident flora of these sites. This is especially true in the neutropenic host. Factors that affect skin and mucosal integrity include chemotherapy-related gastrointestinal tract mucositis, skin graft-versus-host disease, urinary catheters, and insertion of temporary or permanent indwelling CVCs. In addition, a tumor mass may obstruct a vital organ, impair circulation, or invade adjacent tissue, resulting in an altered regional anatomy that provides a nidus for infection.

Third are differing levels of infection risk based on the nature of cancer treatment. Prednisone, although not a cause of neutropenia, is a potent inhibitor of both humoral and cell-mediated immune responses, especially T-lymphocyte activity. Cyclosporin adversely affects T lymphocytes by decreasing $CD4^+$ lymphocytes and interleukin-2 synthesis. Irradiation and malnutrition cause decreases in T-lymphocyte function. Mucositis in recipients of high-dose cytosine arabinoside is well recognized and is associated with increased infection risk from oral/gastrointestinal pathogens such as viridans streptococcal species. While most chemotherapeutic agents are associated with some degree of neutropenia, some chemotherapeutic agents may also influence infection risk via other mechanisms, including lung fibrosis related to busulfan, lymphopenia with rituximab, and cyclophosphamide-induced hemorrhagic cystitis.

The Pathogens Because of the extensive use of antibiotics and antifungal agents, the normal microbial flora is deranged, and selective antimicrobial pressure creates a microbial milieu that poses an infection risk to the compromised host. While methicillin-resistant *Staphylococcus aureus* (MRSA) infection was always considered a classic example of an HAI, the past decade has shown a marked increase in community-acquired MRSA *(4)*, making an assessment of every MRSA infection as a suspected HAI no longer accurate. Bacteria such as coagulase-negative staphylococci (CoNS), *Corynebacterium* species, and

Bacillus cereus (5), often regarded as contaminants in sterile site cultures collected from the immunocompetent host, pose a real infectious threat to the immunocompromised host. These infections are often associated with CVCs or prosthetic joint infections. Finally, with advances in the field of molecular microbiology, the ability to diagnose long-recognized viral pathogens such as respiratory syncytial virus (RSV) and influenza and the more recently identified viruses, such as human metapneumovirus *(6)*, has increased tremendously *(7)*.

DEFINING HEALTHCARE-ASSOCIATED INFECTIONS IN PATIENTS WITH NEOPLASTIC DISEASE

When reviewing the literature pertaining to surveillance of HAIs in patients with cancer, one should be cognizant of the criteria used to define such infections and the denominator used to quantify them, characteristics of patient populations primarily in terms of risk factors such as duration of neutropenia, existing infection control policies including antimicrobial prophylaxis, and types of resources available to diagnose infections. All of these influence the reported HAI rate. In two prospective surveillance studies in adult and pediatric hematology-oncology patients from Bonn, Germany, the researchers noted an overall HAI rate of 11 and 10.8 per 1,000 patient days, respectively, with roughly 75% of the infections occurring in patients who were neutropenic (11,61). To ensure comparability of surveillance data, these researchers recommend that all surveillance studies in the cancer population should include infection rates based on number of patient days at risk, where "at risk" may be defined as the period of neutropenia.

The National Healthcare Safety Network (NHSN) definitions for HAIs are widely used in the United States (1). While these Centers for Disease Control and Prevention (CDC) definitions are designed for surveillance purposes for use in all acute-care settings, including subpopulations such as patients with cancer, their interpretation in an oncology setting can sometimes be challenging. Consider adjudicating a bloodstream infection (BSI) in a patient with a CVC as a primary CVC-associated BSI versus a secondary BSI with oral or lower gastrointestinal tract mucositis as the source of infection. In a patient population with high baseline chemotherapy-related morbidity such as gastrointestinal tract mucositis, the adjudication of BSIs as secondary BSI by applying NHSN definitions of oral or intestinal tract infection can become particularly contentious.

The NHSN definitions recommend two or more blood cultures drawn on separate occasions to be positive to meet the criteria for a laboratory-confirmed BSI for common skin contaminants such as CoNS. With peripheral cultures becoming increasingly uncommon in cancer patients who have CVCs, most clinicians would consider two cultures drawn from two lumens of a double-lumen CVC as two separate cultures, which, if positive for CoNS, warrant considering that episode as a BSI. The latter is not clarified in the NHSN definitions, which leave room for variable interpretation.

The CDC NHSN criteria state that, for an infection to be called an HAI, "there must be no evidence that the infection was present or incubating at the time of admission to the acute-care setting" (1). Because infections have variable incubation periods, determining whether an infection was incubating at the time of admission may be difficult. For this reason, many define an HAI as occurring within 24 hours (8), 48 hours (9), or 72 hours after admission.

In conclusion, the above examples highlight the importance of having a standardized definition for HAIs for oncology patients that takes into account the nuances of this patient population. A consistent way of collecting and reporting the numerator and denominator information when it comes to describing HAI rates in this patient population is key to assessing the effectiveness of interventions to reduce HAIs and facilitate crosscenter comparisons. Of note, even with standardized definitions, there is variable interpretation, as shown by a survey of Australian infection-control professionals, who showed concordance of opinion only 62.5% of the time when adjudicating case scenarios as primary versus secondary BSI based on the NHSN definitions *(10)*.

EPIDEMIOLOGY

Cancer patients present the healthcare epidemiologist with several unique challenges. Foremost is the distinction between an HAI and a community-acquired infection. Cancer patients have a high frequency of interaction with the healthcare setting, with frequent outpatient visits and admissions related to chemotherapy and other noninfectious reasons. Under these circumstances, an HAI may be diagnosed when the patient is not in the hospital and vice versa. In addition, the endogenous microbial flora may change after hospitalization. Especially during prolonged hospital courses, microorganisms of the hospital environment may be acquired that will increase the patient's risk for an infectious episode. Furthermore, because of the multidisciplinary management, some cancer patients may move through many sites during one hospitalization, such as the operating room, intensive care unit, medical service, physical rehabilitation units, and diagnostic imaging and irradiation departments. Under such circumstances, tracking the source of infection sometimes requires exhaustive epidemiologic investigation.

The ability to diagnose viral infections with increased sensitivity using polymerase chain reaction (PCR)-based techniques may complicate distinguishing between reactivation of latent viral infections and new infections. Latent infections acquired early in life may become activated during immunosuppression and hospitalization. These must be differentiated from acute primary infections caused by the same microorganism that could have been acquired during hospitalization. Notable among these are the herpes virus infections, including herpes simplex and cytomegalovirus (CMV) disease. Also, recurrent *Varicella zoster* virus (VZV) infection in the form of disseminated zoster is sometimes difficult to differentiate from primary varicella. Evidence suggests that some cases of *Pneumocystis jiroveci* pneumonitis may be acutely acquired infections in the hospital rather than the more usual reactivation of a latent infection.

There are also challenges in establishing the etiology of an infectious episode in the immunocompromised cancer patient. Since most infections are due to commensal or opportunistic microorganisms of the normal microbial flora, the isolation of a microorganism by culture may not necessarily prove it to be the cause of the illness. For example, in the febrile neutropenic patient, a microorganism such as *Corynebacterium* species isolated from a blood culture may be the causative agent or may merely be a skin commensal or contaminant of the culture. Additionally, the recognition of an infected site can be challenging. In the severely neutropenic and anemic patient with cancer, the key signs of infection may be absent because of a lack of inflammatory response. *S. aureus* may be introduced in a healthcare setting at the time of a finger stick for a blood count. Without neutrophils, no infiltration occurs, so swelling of the affected finger may be absent; furthermore, the anemia does not allow the appearance of erythema, so the sole manifestation of the infected finger stick site may be local pain or fever. Meningeal infection in the neutropenic patient may lack the typical signs of meningeal inflammation such as a stiff neck and a paucity of neutrophils in the spinal fluid. Even with fairly extensive bacterial infection in the lung parenchyma, the neutropenic patient may not be able to mount a sufficient inflammatory response to create an infiltrate recognizable on a chest radiograph. Finally, as previously discussed, consideration should be given to creating oncology population–specific definitions of HAIs that allow for comparisons within and between institutions.

Thus, the healthcare epidemiologist must consider these and other nuances of the compromised host with cancer when tracking HAIs. Molecular techniques to characterize microbes by subcellular and genetic components are evolving as powerful tools for healthcare epidemiology. Analysis of chromosomal DNA by pulsed field gel electrophoresis, ribotyping, and random primer PCR methods permits more precise characterization than more conventional phenotyping techniques.

ETIOLOGIES OF INFECTION

HAIs in cancer patients can be caused by a variety of infectious microorganisms, but the most common pathogens that have been reported are bacterial, followed by fungal and then viral. This may change, as viral diagnostics have greatly improved and the routine use of molecular amplification techniques for diagnosis of respiratory infections is increasingly mainstream. These improved viral diagnostics are likely to influence diagnosis of polymicrobial infections (viral and bacterial coinfections) and lead to some reduction in the number of episodes categorized as healthcare-associated fever of unknown origin (FUO) (11). In previous reports from oncology centers, bacterial microorganisms were isolated in more than 75% of HAIs, fungal pathogens in approximately 3% to 10%, and viruses in only 2% (12,13). The distribution of 263 HAIs, prospectively assessed across 7 pediatric oncology centers in Switzerland and Germany between 2001 and 2005, is shown in Table 57-1 (8). Of all HAIs in this study, 58% were BSIs. The rate of fungal infections varies between institutions and even among units within an institution. In one oncology intensive care unit, fungal infections accounted for 22% of all their HAIs *(14)*. Another study of HAIs in neutropenic patients reported a rate of 19% (15). Polymicrobial infections are not uncommon in this patient population. Robinson et al. (12) noted multiple isolates

TABLE 57-1

Distribution and Incidence Densities of 263 Healthcare-Associated Infections

HAI	*N (Proportion)*	*ID*
All HAIs	263 (100%)	4.80
Bloodstream infections (BSI)	153 (58%)	2.79
Laboratory-confirmed (blood-culture–positive) BSI	138 (52%)	2.52
Blood-culture–negative BSI	15 (6%)	0.27
Radiologically confirmedpneumonia	20 (8%)	0.36
Invasive aspergillosis	26 (10%)	0.47
Respiratory syncytial virus infection	2 (1%)	0.04
Surgical site infection	15 (6%)	0.27
C. difficile–associated enterocolitis	24 (9%)	0.44
Rotavirus-associated enterocolitis	6 (2%)	0.11
Urinary tract infection	8 (3%)	0.15
Ventriculitis related to external CSF drainage	1 (0%)	0.02
Local infections at the central venous access device exit site	8 (3%)	0.15

HAI indicates healthcare-associated infection; N indicates the absolute number; ID indicates incidence density per 1,000 inpatient days.
(Adapted from Simon A, Ammann RA, Bode U, et al. Healthcare-associated infections in pediatric cancer patients: results of a prospective surveillance study from university hospitals in Germany and Switzerland. *BMC Infect Dis* 2008;8:70.)

in one-third of their infections. Both multiple bacterial isolates and mixed infections can occur. As mentioned earlier, when making comparisons between studies and centers, one has to keep in mind the differences in definitions, patient populations, and institute characteristics.

Bacterial Infections

The most important bacterial healthcare-associated pathogens are CoNS, *S. aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (12,13) (see Chapters 28, 30, 34, and 35). Together, these four microorganisms account for more than half of healthcare-associated bacterial infections in cancer patients.

Gram-Positive Microorganisms *S. aureus* was the most frequent bacterial isolate in two surveys of healthcare-associated pathogens in cancer patients, accounting for 14% to 18% of isolates (12,13). Surgical sites were most often involved. CoNS infections have increased dramatically over the past decade; these microorganisms are the most common microorganisms isolated from BSIs in some centers *(16,17)*. The rise of these fairly nonpathogenic bacteria has been linked to the use of tunneled CVCs, such as the Hickman catheter.

Viridans streptococci are normal inhabitants of the oropharynx that invade through damaged mucous membranes and cause bacteremia and pneumonia in cancer patients. A syndrome of severe shock and adult respiratory distress syndrome can result. There is a potential causal relationship with cytosine arabinoside administration *(18,19)*.

Clusters of *Corynebacterium jeikeium* bacteremia have been reported from several cancer centers *(20–22)*. Risk factors include immunosuppression and use of plastic devices such as intravenous catheters. Some evidence suggests that patient-to-patient transmission does not occur *(22)*. The microorganism is resistant to multiple antibiotics, and vancomycin is the suggested therapy.

Gram-Negative Microorganisms As a family, Enterobacteriaceae are common pathogens for HAIs in cancer patients. *E. coli* and *Klebsiella pneumoniae* predominate (12,*23*). These microorganisms, along with *Serratia* species *(24)*, *Enterobacter* species *(25)*, and *Citrobacter* species *(26)*, have been isolated in sporadic infections and in epidemics. They are common causes of bacteremia, pneumonia, and urinary tract infections (UTIs). Frequently, patients are already receiving antibiotic therapy when these infections develop *(23–26)*. *P. aeruginosa* is the most notorious pathogen in patients with malignancies. It is associated with healthcare-associated bacteremia, pneumonia, UTIs, and wound infections. Although a frequent healthcare-associated pathogen, it has a special predilection for granulocytopenic hosts. In a review of *P. aeruginosa* infections in cancer patients in the 1990s, Maschmeyer et al. *(27)* noted that the proportion of these infections among cases of gram-negative bacteremia over the past two decades has not generally declined, but there were marked local and regional differences in the incidence of infections. Infections with *P. aeruginosa* account for approximately 10% of all HAIs in cancer patients (12,13,*28*). In the hospital environment, *P. aeruginosa* is associated with respiratory equipment, sinks, and fresh fruit and vegetables. Colonization often precedes infection *(28,29)*. Historically, the case fatality rate for *P. aeruginosa* infections was reported to be as high as 65% to 70%, which was significantly higher than the rate for other gram-negative bacterial infections *(29,30)*. Newer antimicrobial agents with improved anti-*Pseudomonas* activity have lowered fatality rates *(31)*.

A variety of other gram-negative microorganisms have also been linked with HAIs in cancer patients. The *Legionella* species are fastidious gram-negative bacilli. Approximately 42% of cancer patients with Legionnaire's disease are infected in a hospital setting. The use of steroids and neutropenia appears to have causal roles *(32)*. *Stenotrophomonas maltophilia* (previously *Xanthomonas maltophilia*) has been reported as a cause of bacteremia, UTI, pneumonia, and wound infections in cancer patients. It is most often detected in patients who have received antibiotics and respiratory therapy. The microorganism has been isolated from hospital sinks and respirators. The association between the use of respiratory equipment and isolation of *S. maltophilia* from sputum suggests that the equipment may be a significant reservoir for the microorganism *(33)*.

Anaerobes Anaerobes are infrequent healthcare-associated pathogens in the oncology patient and are isolated in <5% of infections. Usually, obvious disruption of normal gastrointestinal barriers is apparent when infections do occur *(34)*.

Antibiotic-Resistant Bacteria Widespread use of antibiotics, both prophylactic and empiric, has resulted in HAIs caused by multiply resistant microorganisms. MRSA, vancomycin-resistant enterococci *(35)*, and fluoroquinolone-resistant enteric microorganisms have been reported to cause significant problems in an oncology population *(36–38)*. A single-center retrospective study in cancer patients shows recent receipt of carbapenem therapy as an independent risk factor for vancomycin-resistant *Enterococcus faecium* bacteremia, and recent receipt of aminoglycoside therapy as an independent risk factor for vancomycin-resistant *Enterococcus faecalis* bacteremia *(39)*. Prudent use of antibiotics and careful surveillance of this population are necessary to detect and control the spread of these pathogens.

Fungal Infections

Perhaps the most serious infectious threat to the cancer patient is that caused by the opportunistic fungi, especially candidiasis and aspergillosis. The secular trends in the epidemiology of healthcare-associated fungal infections in the United States from 1980 to 1990 have been described *(40)*. During this decade, the National Healthcare-associated Infections Surveillance system hospitals reported 30,477 healthcare-associated fungal infections. During this time, the fungal infection rate increased from 2.0 to 3.8 infections per 1,000 patients discharged. The medical specialty with a high infection rate was oncology, with rates that varied from 8.9 to 10.6 infections per 1,000 discharges. *Candida albicans* was the most frequently isolated fungal pathogen (59.7%), followed by other *Candida* species (18.6%).

While *C. albicans* is the most common fungal pathogen in cancer patients (see Chapter 40), studies have noted

increases in the frequency of other *Candida* species, including *Candida tropicalis*, *Candida parapsilosis*, and *Candida krusei (41)*. Within individual cancer centers, a significant species shift has been noted even within the non-*C. albicans* group, such as an increase in *C. parapsilosis* and a decrease in *C. tropicalis (42)*. Overall, these differences between institutions to some extent are influenced by institutional antifungal prophylaxis guidelines, the use of indwelling catheters, and the types of malignancies treated. A study of candidemia in cancer patients from November 1992 to October 1994 found that, of 249 episodes of candidemia, non-albicans candidemia accounted for 64% (101/159) of episodes in patients with hematologic malignancies and 30% (27/90) of the episodes in patients with solid tumors *(43)*.

Fungemia, pneumonia, UTI, or disseminated disease with involvement of the abdominal viscera may occur. Infections are usually preceded by colonization of the gastrointestinal tract with the offending microorganism, but common source outbreaks have also been reported. Risk factors include the use of antibiotics, colonization with the microorganism, neutropenia, and the presence of tunneled CVCs.

While it is clear that the incidence of invasive aspergillosis has been increasing in patients with cancer, especially those with hematologic malignancies and bone marrow transplant recipients *(44)*, controversy exists regarding the definition of healthcare-associated versus community-acquired infection. This is in part due to factors such as an unknown incubation period and size of "infectious" inoculum as well as lack of uniform, reliable methods for environmental sampling in studies that attempt to trace the source of infection *(45)*. The overall case fatality rate of this disease is very high, with the highest being in bone marrow transplant recipients *(46)*. Sites most often involved include the lungs and the paranasal sinuses. Inhalation of conidia (spores) is requisite to the development of this infection. Direct inoculation of *Aspergillus* species spores from occlusive materials, such as tape, has also been reported.

Although *Aspergillus* causes a much lower rate of infection than candidiasis, it is the mycosis that has been most convincingly associated with the hospital environment. Outbreaks of healthcare-associated aspergillosis have been reported to be due to hospital construction and renovation activities *(47–50)*. Bone marrow transplant patients are especially susceptible. The source of infection is airborne conidia of *Aspergillus* species often associated with contaminated air–handling systems. Evidence suggesting the hospital water distribution system as an additional indoor source for pathogenic airborne fungi has also been reported *(51)*.

Historically, while *C. albicans* accounts for the majority of infections in compromised patients, recent epidemiologic trends indicate a shift toward infections by *Aspergillus* species, non-albicans *Candida* species, and previously uncommon hyaline filamentous fungi (such as *Fusarium* species, *Acremonium* species, and *Pseudallescheria boydi*), dematiaceous filamentous fungi (such as *Bipolaris* species and *Alternaria* species), and yeastlike pathogens (such as *Trichosporon* species and Malassezia species) *(52)*. These emerging pathogens are increasingly encountered causing life-threatening invasive infections that are often refractory to conventional therapies. Increasing use of antifungal prophylaxis may be linked to the emergence of these microorganisms as well.

Viral Infections

Overall, viruses account for relatively few HAIs. This number is likely to increase as viral diagnostic technology improves. Known HAI pathogens include VZV virus *(53,54)*, RSV *(55)*, influenza, and rotavirus *(56)*. Hepatitis B and hepatitis C have also been reported from other countries as healthcare-associated pathogens in children with cancer *(57,58)*.

CLINICAL MANIFESTATIONS

Fever is the most frequent manifestation of an infection including an HAI in the cancer patient. When fever occurs, especially in the setting of neutropenia, a diagnostic workup, including careful history and physical examination and bacterial and fungal cultures of blood, and any obvious sites of infection such as wounds, should be done before beginning therapy. BSIs most often present with fever with or without evidence of shock. Catheter-related bacteremias or fungemias may present with chills or rigors after flushing the catheter. If a tunneled CVC is in place, all lumens and ports should be cultured. In addition, if symptoms are present, a chest radiograph, and possibly sinus radiographs, should also be obtained. If no source of infection is identified by the diagnostic workup, a diagnosis of FUO may be made.

As noted earlier because of lack of inflammatory response in the neutropenic patient, signs and symptoms may be subtle, and pain and fever may be the only clinical manifestations of a serious HAI. Differentiating an infection from side effects of chemotherapy or radiation can sometimes be very difficult, and, not uncommonly, empiric treatment for an infection is started while waiting for further information.

SITES OF HEALTHCARE-ASSOCIATED INFECTIONS

Bloodstream Infections

BSIs account for a major proportion of HAIs and are associated with an extended hospital stay, extra costs, and excess mortality (59). The mean central line–associated BSI rate between 2006 and 2008 based on data collected by the NHSN from various participating oncology units ranged from 1.7 to 3.9 per 1,000 catheter days for permanent central lines and 2.0 to 4.6 for temporary central lines *(60)* (Table 57-2). In three prospective surveillance studies of HAIs in adult and pediatric hematology/oncology patients, 43% and 58% of HAIs were BSIs (8,11,61). From March 1995 through February 2001, a total of 22,631 cases of BSI were reported by 49 US hospitals participating in the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) Project (9). Among these cases, 2,711 isolates from 2,340 clinically significant episodes of BSI that met the surveillance definition of HAI were identified in adult patients with malignancies. Of all the recorded

TABLE 57-2

Distribution of Laboratory-Confirmed Permanent and Temporary Central Line-associated Bloodstream Healthcare-Associated Infection Rates by Type of Location (NHSN Data 2006 through 2008)

Permanent Central Line–associated Bloodstream Infection (PCLABSI) rate[a]				
Type of Location	*No. of Locations*[b]	*No. of PCLABSI*	*Permanent Central Line Days*	*Pooled Mean*
Specialty care areas				
Bone marrow transplant	21	235	60,546	3.9
Hematology/oncology	41	158	95,535	1.7
Long-term acute care	43 (33)	38	23,278	1.6
Pediatric hematology/oncology	7	75	32,255	2.3
Solid organ transplant	9	11	3,953	2.8

Temporary Central Line–associated Bloodstream Infection (TCLABSI) rate[c]				
Type of Location	*No. of locations*[b]	*No. of TCLABSI*	*Temporary Central Line Days*	*Pooled Mean*
Specialty care areas				
Bone marrow transplant	18 (17)	96	27,290	3.5
Hematology/oncology	33 (31)	117	51,950	2.3
Long-term acute care	67 (64)	260	149,298	1.7
Pediatric hematology/oncology	5	47	10,287	4.6
Solid organ transplant	12	66	32,591	2.0

[a] $\frac{\text{Number of PCLABSI}}{\text{Number of permanent central line days}} \times 1000$

[b] Number of locations meeting minimum requirements for percentile distributions if less than the total number of locations. If this number was <20, then percentile distributions were not calculated.

[c] $\frac{\text{Number of TCLABSI}}{\text{Number of temporary central line days}} \times 1000$

(Adapted from Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control* 2009;37(10):783–805.)

episodes, 61% were caused by gram-positive aerobic microorganisms, and 27% were caused by gram-negative aerobic microorganisms. The proportion of gram-positive microorganisms was 62% for BSIs in 1995 and 76% for those in 2000 ($p < .001$), indicating a shift from gram-negative to gram-positive infections that has been noted over the past two decades by other studies as well. The proportions of gram-negative pathogens during the same periods were 22% and 15%, respectively. The increasing use of tunneled CVCs and the concomitant increase in the number of CoNS infections are some of the factors believed to contribute to this shift toward gram-positive BSIs *(62)*. Another speculation to explain this shift is the widespread use of second- and third-generation cephalosporins for the empiric treatment of febrile neutropenia. Because these antibiotics have improved gram-negative coverage at the expense of gram-positive coverage, breakthrough healthcare-associated bacteremias are likely to be of gram-positive origin *(63)*.

Anaerobes were rarely isolated (3% of isolates), and the proportion remained stable throughout the study period. Fungi accounted for 10% of isolates, with a nadir of 6% in 1998 and a peak of 15% in 1995. Fungemia, most often with *Candida* species, is also increasing among oncology patients *(64)*.

Multiple reports note that patients with hematologic malignancies, such as leukemia and lymphoma, are at greater risk for healthcare-associated BSIs than patients with solid tumors are *(62,65,66)*. Mayo and Wenzel *(66)* noted that leukemia patients had an infection rate 15 times greater than that of patients with solid tumors. In their study, patients with solid tumors were at no greater risk for BSIs than patients without malignancies.

In the SCOPE project, among adult patients with malignancies, there were some differences in the etiology of healthcare-associated BSI among those who were neutropenic versus non-neutropenic (9) (Table 57-3). The microorganisms that were most frequently isolated from neutropenic patients were CoNS, *S. aureus*, *E. coli*, and enterococci. In non-neutropenic patients, the most common pathogens were CoNS, enterococci, and *S. aureus. Candida* species accounted for 9% and 8% of isolates recovered from neutropenic and non-neutropenic patients, respectively. Viridans group streptococci, which accounted for 3% of all isolates in neutropenic patients, were significantly more common in this group (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.87–7.60; $p < .001$). *E. faecium* was more frequently isolated from patients without neutropenia than it was from patients with neutropenia (6% vs. 2%; OR, 3.0; 95% CI, 1.75–5.04; $p < .001$). A total of 329 (14%) of all episodes were polymicrobial.

The risk factors for developing healthcare-associated BSIs include hematologic malignancies, prolonged hospi-

TABLE 57-3

Species Distribution of Predominant Pathogens in Bloodstream Healthcare-Associated Infections in Neutropenic and Non-Neutropenic Patients in the United States

Pathogen	*Total (n = 2711)*	*ANC < 1,000 neutrophils/μL (n = 798)*	*ANC ≥ 1,000 neutrophils/μL (n = 1913)*	*p*[a]
Gram-positive microorganisms				
All	1,639 (60.5)	487 (61.0)	1,152 (60.2)	.7
CoNS	818 (30.2)	252 (31.6)	566 (29.6)	.3
S. aureus	311 (11.5)	98 (12.3)	213 (11.1)	.4
Enterococci				
All	315 (11.6)	50 (6.3)	265 (163.9)	<.001
Enterococcus faecalis	125 (4.6)	25 (3.1)	100 (53.2)	.02
Enterococcus faecium	140 (5.2)	18 (2.3)	122 (6.4)	<.001
Streptococci				
All	163 (6.0)	73 (9.1)	90 (4.7)	<.001
VGS	38 (1.4)	23 (2.9)	15 (0.8)	<.001
Other	32 (1.2)	14 (1.8)	18 (0.9)	.1
Gram-negative microorganisms				
All	720 (26.6)	199 (24.9)	521 (27.2)	.2
E. coli	206 (7.6)	58 (7.3)	148 (7.7)	.7
Klebsiella species	173 (6.4)	43 (5.4)	130 (6.8)	.2
P. aeruginosa	119 (4.4)	29 (3.6)	90 (4.7)	.3
Enterobacter species	80 (3.0)	25 (3.1)	55 (2.9)	.8
Other enterobacteriaceae	56 (2.1)	14 (1.8)	42 (2.2)	.5
Other gram-negative microorganisms	87 (3.2)	30 (3.8)	57 (3.0)	.4
Anaerobes	93 (3.4)	38 (4.8)	55 (2.9)	.02
Fungi				
All	259 (9.6)	74 (9.3)	185 (9.7)	.8
Candida species	230 (8.5)	69 (8.6)	161 (8.4)	.9
Other	28 (1.0)	5 (0.6)	23 (1.2)	.3

ANC, absolute neutrophil count; CoNS, coagulase-negative staphylococci; VGS, viridans group streptococci.
[a]Patients with an ANC of ≤1,000 neutrophils/μL versus those with an ANC of ≥1,000 neutrophils/μL.
(Adapted from Wisplinghoff H, Seifert H, Wenzel RP, et al. Current trends in the epidemiology of healthcare-associated bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States. *Clin Infect Dis* 2003;36(9):1103–1110.)

talization, and bone marrow transplantation *(62)*. Patients with hematologic malignancies are at increased risk because of the intensive cytotoxic chemotherapy, which often renders them pancytopenic for long periods. Mayo and Wenzel *(66)* noted that more than 75% of healthcare-associated BSIs in leukemia patients occurred when the absolute neutrophil count was <100 cells/mm^3.

The prognosis of healthcare-associated BSI is related to many factors, including the microorganism causing the sepsis, the source of infection, the absolute neutrophil count, the bone marrow status, and the presence or absence of shock *(65)*. In general, the mortality rate of infections caused by gram-negative microorganisms is greater than that of infections caused by gram-positive microorganisms *(62)*. BSIs that are polymicrobial or that are associated with pulmonary or intra-abdominal infections also have a high mortality rate *(65)*. The overall mortality rate for the 2011 patients with a monomicrobial, healthcare-associated BSI followed in the SCOPE project was 32%, ranging from 16% in patients with BSI due to viridians group streptococci to 45% in patients with BSI due to *Candida* species (9). In general, the mortality rates were higher for neutropenic patients than they were for nonneutropenic patients. The mortality rate for patients with BSI due to *P. aeruginosa* was 36% (48% of neutropenic vs. 31% of non-neutropenic patients; $p = .2$); for *E. coli*, it was 35% (38% vs. 33%, respectively; $p = .6$); for vancomycin-resistant *E. faecium*, it was 34% (67% vs. 29%, respectively; $p = .05$); and for CoNS, it was 33% (34% vs. 32%, respectively; $p = .2$).

Respiratory Tract Infections

HAIs of the respiratory tract include pneumonia, sinusitis, pharyngitis, otitis, and rhinitis (see Chapters 22, 23, and 49). Of these, pneumonias are associated with a high morbidity and mortality. Of the 263 HAIs across seven pediatric oncology centers in Switzerland and Germany between 2001 and 2005, 20 (8%) and 21 (8%) were radiologically confirmed pneumonias and invasive pulmonary aspergillosis, respectively (8) (Table 57-1). In only 1 of the 20 cases of radiologically diagnosed pneumonia was a causal pathogen identified, a well-recognized limitation in the identification of pneumonias, especially in nonventilated patients.

A subset of healthcare-associated pneumonias (HAPs) is in mechanically ventilated patients and called "ventilator-associated pneumonia" (VAP). VAPs constitute a significant proportion of HAIs seen in intensive care units. Detailed evidence-based guidelines and recommendations regarding the prevention, diagnosis, and management of HAP and VAP are available from expert groups in the United States, Canada, and Britain *(67–69)*.

The top three identified pathogens in VAP identified by bronchoscopic techniques are *P. aeruginosa* (24.4%), *S. aureus* (20.4%), and the Enterobacteriaceae group (14.1%) *(70)*. These were identified in 24 studies (1989–2000) including 1,689 episodes and 2,490 pathogens, not limited to the oncology patient population.

Respiratory tract infections occur most commonly in patients with leukemia/lymphoma and those with solid tumors of the lung and head and neck regions (12,13). Postoperative pneumonias are more often diagnosed in solid tumor patients, because extensive surgical procedures are more often a part of their diagnosis or treatment (13).

Urinary Tract Infections

Overall, not specific to patients with malignancies, most hospital-acquired UTIs are associated with catheterization, and most occur in patients without signs or symptoms referable to the urinary tract. Catheter-associated bacteriuria is the most frequent HAI worldwide, accounting for up to 40% of HAIs in US hospitals each year.

UTIs have been reported to cause between 17% and 28% of HAIs in the oncology population (12,13) (see Chapter 20). Gram-negative microorganisms, particularly *E. coli, K. pneumoniae*, *P. aeruginosa*, and *Proteus mirabilis*, predominate. The most frequent gram-positive isolates are enterococci. Fungal microorganisms are unusual urinary tract pathogens (12,13).

Patients with cancer are at greater risk for healthcare-associated UTI than other hospitalized patients *(71)*. Those with underlying diagnoses of prostate, bladder, bone, joint, liver, ovarian, colorectal, or vulvar cancer are the most commonly afflicted (13). As with nononcology patients, urinary catheterization and manipulation of catheters are often instrumental in the development of healthcare-associated UTI *(71)*. International practice guidelines for the prevention, diagnosis, and treatment of catheter-associated UTI in adults from the Infectious Diseases Society of America (IDSA) were recently published *(72)*.

Surgical Site Infections

Surgical site infections accounted for approximately 20% of HAIs in cancer patients, according to reports from the 1980s (12,13), and 6% of all HAIs in the multicenter pediatric study published in 2008 (8) (see Chapter 21). Identification of infections of surgical sites is usually based on the presence of purulent drainage from the sites. However, special consideration must be given to the neutropenic patient who may manifest infection by serous drainage or erythema and induration alone (12). Patients with solid tumors are most likely to develop surgical site infections (12,13). This is due to the extensive surgical procedures involved in their diagnosis and treatment. Patients with carcinoma of the vulva or uterus, soft tissue sarcomas, or malignant melanoma are most susceptible. Other high-risk patients include those with gastrointestinal or head and neck malignancies (12,13).

S. aureus is the most common pathogen isolated from surgical site infections in the cancer patient (8,12,13). Others frequently noted include *E. coli*, CoNS, enterococci, and anaerobes (12,13).

We retrospectively investigated infections complicating limb-sparing surgery (104 procedures) in 103 children and young adults with bone malignancies and found a high incidence of infections (median, 4%; range, 0–13%), including local surgical site infections in 67% and secondary bacteremia in 21%. Patients who developed deep infections were more likely to undergo amputation (OR, 24.0; 95% CI, 5.1–114.0; $p < .001$) and were less likely to have good functional outcomes (OR, 0.02; 95% CI, 0.002–0.15; $p < .001$) *(73)*.

Gastrointestinal Infections

Little information is available about gastrointestinal HAIs in cancer patients (see Chapter 24). The diagnosis should be based on the development of clinical symptoms of diarrhea with or without the isolation of a known pathogen. It is often difficult to distinguish diarrhea associated with gastroenteritis from that caused by chemotherapy-related mucositis. Potential pathogens include *Salmonella* species, *Shigella* species, rotavirus, other viral agents, and *Clostridium difficile*. In general, surgical patients and those receiving antibiotics are at increased risk of developing *C. difficile*-associated diarrhea (see Chapter 37). These predisposing factors also apply to the oncology patient. *C. difficile*-associated enterocolitis constituted 9% of all HAIs in a prospective multicenter HAI surveillance study of pediatric oncology patients and 6% of all HAIs at a single transplant center *(74)*. Both groups observed that, unlike other site-specific infections such as BSI, the risk for *C. difficile*-associated enterocolitis was comparable between neutropenic and non-neutropenic patients, a finding likely explained by the overall high antibiotic exposure in both populations.

Fever of Unknown Origin

Although not officially recognized by the CDC as a reportable entity, healthcare-associated FUO is common in hospitalized adult (11) and pediatric (8) cancer patients. Despite intensive diagnostic workups and clinical symptoms suggestive of sepsis, pathogens are often not isolated. At St. Jude Children's Research Hospital, we have routinely included FUO in our surveillance, and it accounts for about one-third of HAIs in pediatric oncology patients. Including FUO as a separate, defined clinical entity, Engelhart et al. (11) described an overall rate of 8.2 per 1,000 days, with two-thirds of these episodes occurring during periods of neutropenia. These researchers recommended the inclusion of this entity routinely in studies of surveillance of HAIs in patients with cancer. A study comparing HAIs between pediatric and adult bone marrow or peripheral stem cell transplant recipients found the FUO rate higher among the pediatric patients (34 vs. 15 FUOs per 100 patients/transplants), a finding for which the investigators found no obvious explanation *(75)*.

DIAGNOSIS OF HEALTHCARE-ASSOCIATED INFECTIONS IN CANCER PATIENTS

Cultures for Bacteria, Fungi, and Viruses

The most meaningful cultures for bacteria and fungi are those of otherwise sterile body fluids, such as blood, spinal fluid, bone marrow, urine, and tissue biopsies. Cultures of specific surface lesions by swab (typically an inferior specimen in terms of sample yield), aspirate, or biopsy require correlation with clinical features, morphology, and type of microorganism isolated. Cultures of stool, oropharynx, and normal skin usually provide information only on microbial colonization rather than on the etiology of disease. In certain clinical settings, such as a patient with prolonged granulocytopenia with fever unresponsive to antibiotics, the isolation of *Aspergillus* species from the nares or *C. tropicalis* from the stool or the urine may raise the index of suspicion for invasive fungal disease.

Various techniques are used to diagnose catheter-related infections, including paired quantitative CVC and peripheral venous blood cultures and the difference in time to detection of blood cultures simultaneously drawn from these two sources *(76,77)* or from the two lumens of a double-lumen CVC *(78)*.

In terms of viral cultures, shell vial spin amplification cultures give a more rapid turnaround time than traditional viral cultures do for detection of CMV and the more common respiratory viruses including influenza A and B; parainfluenza 1, 2, and 3; RSV; and adenovirus. Respiratory viruses can be significant healthcare-associated pathogens, and molecular amplification techniques are increasingly replacing culture-based approaches for diagnosis of these infections. While the significance of herpes simplex and VZV isolates is easily discernible because of the typical lesions and illness associated with the overt infections, CMV isolates may be difficult to assess, because the disease patterns associated with this infection are varied, may be nonspecific, and range from asymptomatic latency to life-threatening disease. As mentioned earlier, differentiating a new-onset, viral HAI from reactivation of a latent infection can sometimes be difficult. Stool culture–based methods to diagnose viral gastrointestinal infections identify some adenoviruses, enteroviruses, and CMV. Because many enterovirus serotypes are noncultivable, and because enterovirus can be shed asymptomatically for several months, there is poor positive and negative predictive value for this agent in a stool specimen. All adenoviral serotypes that can be detected by culture are detected more sensitively by PCR. Culture-based yield for CMV is poor. All this points to the low yield of stool viral cultures and makes a case for pathogen-directed PCR-based approaches combined with clinical correlation.

Smears and Stains

Material obtained from infected sites may contain enough of the causative microorganism to permit recognition of the microbe with selective stains and microscopy. Bacterial stains include Gram stain for most bacteria and acid-fast stain for mycobacteria, *Nocardia* species, and *Cryptosporidium* species. While fungi are usually visualized directly by a Gram stain, a KOH (wet) mount, or a Calcofluor white stain, histopathologically or cytologically, stains such as methenamine silver, periodic acid-Schiff, or Papanicolaou stains are used. *Pneumocystis jiroveci* can be visualized by a Grocott-Gomori methenamine-silver nitrate, Calcofluor white, toluidine blue O, Giemsa, or monoclonal antibody stain. An India ink preparation can be made for *Cryptococcus neoformans* although this method has largely been supplanted by specific antigen detection methods. Rapid identification of viruses is based on tests that detect viral antigens, such as a direct fluorescent-antibody assay or enzyme immunoassay. These tests are currently used to detect respiratory viruses such as RSV, influenza, parainfluenza, and adenovirus; herpes simplex virus and VZV (lesional); and gastrointestinal pathogens such as rotavirus.

Tissue Biopsy

Biopsies or aspirates of various tissues may be obtained for histopathologic or cytopathologic examination, for microscopic examination of stained smears, and for culture, including skin biopsy (punch and excisional), lung biopsy (open biopsy and transbronchial), and liver and kidney biopsy (transcutaneous needle biopsy and open biopsy). In experienced hands, transthoracic needle biopsy of chest lesions is a generally safe and noninvasive tool for the diagnosis of pulmonary fungal disease *(79)*.

Antigen-Based Assays

There are several rapid antigen detection-based tests for RSV, influenza A and B, rotavirus, and adenovirus serotypes 40 and 41 based on enzyme immunoassays or direct fluorescent antigen assays. The rapid influenza antigen assay for diagnosis has a low sensitivity for the diagnosis of the 2009 H1N1 pandemic influenza strain. For fungi, the Platelia *Aspergillus galactomannan* antigenemia test (Bio-Rad Laboratories, Redmond, WA) is widely used and demonstrates an overall high sensitivity and specificity for the diagnosis of invasive aspergillosis in high-risk patient populations that are getting assayed serially.

Molecular Assays

Several molecular platforms that offer same-day detection of a panel of viruses, particularly respiratory viruses, are now commercially available and increasingly being used by centers that provide care for immunocompromised patients. PCR-based assays frequently identify respiratory virus infections not diagnosed by direct fluorescent- or culture-based tests *(7)* and have allowed characterization of viral infections such as those due to human metapneumovirus, rhinovirus, and coronavirus *(80,81)*. Molecular amplification techniques increasingly support outbreak investigations in establishing epidemiologic relatedness *(6,82,83)*.

Several new molecular assays offer faster pathogen identification than conventional culture-based bacterial and fungal assays. These include the GeneOhm StaphSR assay (BD Diagnostics) for identification of *S. aureus* and MRSA directly from blood cultures and the peptide nucleic acid fluorescence *in situ* hybridization (PNA FISH) assay (AdvanDx, Woburn, MA; bioMerieux, Durham, NC) for identification of *C. albicans* in smears made from positive blood cultures. The PNA FISH technology is also being applied

for the identification of other *Candida* species as well as gram-positive microorganisms such as enterococcus and *S. aureus*.

Radiography and Imaging

Radiography is most helpful in recognizing pneumonia. Serial chest radiographs are especially helpful in establishing healthcare-associated pneumonia. The absence of discernible infiltrates does not exclude significant infection of the pulmonary parenchyma in the neutropenic patient. A more sensitive diagnostic test for early diagnosis of chest disease, especially fungal disease, is computed axial tomography *(84,85)*. Even this test has limitations in the setting of a profoundly granulocytopenic host. Computed axial tomography of the liver, spleen, and kidneys is useful in identifying systemic fungal infections. The hypodense distinct lesions are highly suggestive of systemic candidiasis and aspergillosis *(86,87)*.

PREVENTION AND CONTROL

Prevention and control of HAIs in patients with neoplastic disease is one of the most important contributors to the overall success of treatment in this patient population. Not only do HAIs add to morbidity, mortality, and the overall cost of care, but they often necessitate modifications in dose and scheduling of antineoplastic therapies, potentially compromising the successful treatment of the patient's malignancy. The general principles of prevention of HAI and infection control that are applied to any hospitalized patient, including hand hygiene, remain the same for patients with neoplastic disease. Certain additional precautions are taken based on the immunosuppressed state of these patients and their ability to contract infections by opportunistic pathogens, such as environmental safeguards to minimize exposure to pathogens and antimicrobial prophylaxis during periods of risk. This is especially true in the very high-risk host, such as patients who have recently undergone bone marrow or peripheral stem cell transplantation or those with prolonged granulocytopenia. Special precautions to prevent such patients from acquiring infection by filamentous fungi, especially *Aspergillus* species, are extremely important. Although some preventive measures (e.g., sophisticated air-handling systems and total protected environment [TPE]) are labor intensive, consume a considerable amount of limited healthcare resources, and sometimes lack clear-cut supporting evidence, others (e.g., hand hygiene and appropriate aseptic techniques) are simple, inexpensive, and require very little of the busy healthcare worker's time, and their efficacy is firmly established. Another common principle to minimize HAI is regular review of the necessity of foreign bodies *in situ*, such as CVCs, urinary catheters, and endotracheal tubes, and minimizing their manipulations, such as by reducing CVC entries. Healthcare setups need to individualize their practices based on the availability of resources and a review of local problems.

Hand Hygiene

The importance of hand antisepsis in prevention of HAIs is well accepted *(88,89)*, and numerous professional societies and committees have published guidelines for appropriate hand hygiene practices. The biggest change in this field over the past decade has been the introduction of alcohol-based hand rubs. Guidelines on hand hygiene in healthcare settings are available both from the Healthcare Infection Control Practices Advisory Committee and the World Health Organization *(90,91)*.

WHO recommends alcohol hand rubs based on: (a) evidence-based, intrinsic advantages of fast-acting and broad-spectrum microbicidal activity with a minimal risk of generating resistance to antimicrobial agents; (b) suitability for use in resource-limited or remote areas with lack of accessibility to sinks or other facilities for hand hygiene (including clean water, towels, etc.); (c) capacity to promote improved compliance with hand hygiene by making the process faster and more convenient; (d) economic benefit by reducing annual costs for hand hygiene; and (e) minimization of risks from adverse events because of increased safety associated with better acceptability and tolerance than other products. Readers are encouraged to review the comprehensive WHO guidelines on hand hygiene in healthcare, which provide an excellent summary of the existing literature on this subject (92). Alternatively, the practice of hand washing with antimicrobial soap and water should be continued. Ready access at strategic locations of efficacious hand-hygiene products with low irritancy potential has been emphasized. Use of artificial fingernails or extenders by clinical care providers, especially those taking care of high-risk patients, is discouraged.

It seems clear that the simple act of hand hygiene greatly reduces the likelihood of transmitting pathogenic microorganisms to hospitalized patients on the hands of healthcare workers. What is also clear is that despite the presence of published guidelines and policies, adherence of healthcare workers to recommended hand-hygiene procedures has been poor, with mean baseline rates of 5% to 81% *(90)*. We encourage that institutions review these guidelines and, based on the resources available, select a hand-hygiene agent or agents and implement a hand hygiene policy. Periodic monitoring for compliance and focused interventions to improve it, based on the feedback generated, is critical to the success of this intervention.

Evidence-Based Guidelines and Recommendations for Prevention of Healthcare-Associated Infections

Comprehensive guidelines based on a review of current literature are available from professional societies and expert working groups on prevention, diagnosis, and management of various HAIs. These are applicable to the oncology patient population as well, and readers are encouraged to review the specific guidelines for details. To assist acute care hospitals in focusing and prioritizing efforts to implement evidence-based practices for the prevention of HAIs, the Society for Healthcare Epidemiology of America and the IDSA Standards and Practice Guidelines Committee appointed a task force to create a concise compendium of recommendations for the prevention of common HAIs *(93)*. This compendium is implementation-focused and differs from most previously published guidelines in that it highlights a set of basic HAI prevention strategies plus special approaches for use in locations and populations within the

hospital when infections are not controlled by the use of basic practices. In addition, it includes proposed performance measures for internal quality-improvement efforts. Summarized in this compendium are strategies to prevent central line–associated BSIs *(94)*, VAP *(67)*, catheter-associated UTIs *(95)*, surgical site infections *(96)*, MRSA *(97)*, and *C. difficile* infections *(98)*.

Specific to CVC, the big change in terms of prevention of central line–associated BSI in the past decade has been the concept of bundling a group of prevention practices rather than implementation of individual components that vary from site to site. Guidelines for the prevention of catheter-related BSIs recommended by a working group comprising numerous professional organizations have been published *(99)*. These include the use of antimicrobial- or antiseptic-impregnated CVCs in adults, recommendations for selection of catheter insertion sites, catheter care, and surveillance for catheter-related infections. Consideration should be given to establishing special intravenous therapy teams to ensure a high level of aseptic technique during catheter insertion and follow-up care. Policies and procedures for infusion therapy should be comprehensive, and those who perform manipulations of these devices should be thoroughly trained in appropriate infection-control techniques.

Updated guidelines for preventing infectious complications among hematopoietic cell transplantation recipients, cosponsored by various professional societies and organizations, are available and summarize the evidence basis for the current recommendations in this patient population (100). These include a summary of recommendations regarding room ventilation, construction, renovation and building cleaning, isolation and barrier precautions, and other environmental measures (see also Chapters 83 and 84).

Total Protected Environment Versus Care of the Allogenic Transplant Patient in the Outpatient Environment—A Wide Spectrum of Care

Because the causative agents of HAIs in patients with neoplastic diseases include endogenous and a wide variety of exogenous microorganisms, a comprehensive approach to preventing infection and colonization with hospital pathogens has been tried *(101,102)*. This comprehensive approach, TPE, has included the use of protective isolation (gowns, gloves, and masks for healthcare providers and visitors), selective decontamination of the digestive tract, rigorous antisepsis of the skin and perirectal area, and high-efficiency particulate air (HEPA)-filtered air supplied to the patient in a laminar or a turbulent fashion. TPE also includes provision of food and water low in microbial content, sterilization or high-level disinfection of objects before they are taken into the room, and frequent and thorough cleaning and disinfection of room surfaces.

A sterile patient environment cannot be achieved and maintained. Because the patient's endogenous flora and microorganisms in the room and in food and water can only be suppressed, not totally eliminated, a labor-intensive decontamination regimen must be continued throughout the isolation period. TPE is expensive and is beyond the capabilities of many hospitals providing care for patients with neoplastic diseases. Although a reduction in the incidence of infection has been associated with the use of TPE, it must be recognized that since the performance of these studies more than two decades ago, the treatment of infectious complications in neutropenic patients has improved considerably. Thus, a more relevant question is whether TPE would lessen infection-related mortality with the current availability of better treatment options. At this time, a comprehensive TPE approach is not a standard recommendation for patients with neoplastic disease. However, various components of this approach are followed by individual centers, especially those with a bone marrow transplant program.

On the other extreme, over the past two decades, some investigators have reported their experience managing highly immunosuppressed patients in an outpatient environment. The risk of HAI and financial costs of care are some of the factors that have prompted examining this approach. A review examined six published studies, including four comparative but nonrandomized analyses, describing the experience of home care for patients with cytopenia after high-dose therapy and stem cell transplantation *(103)*. The pooled statistics compiled in this review suggest that protective environments provided no benefit in decreasing mortality for the transplant patient.

In summary, there is significant variability between centers in terms of the infection control measures in place for patients with prolonged granulocytopenia, including stem cell transplant recipients. Few infection control and protective environment recommendations have been tested in randomized control trials. While such rigorous study designs to test the efficacy of all recommended infection control measures is not feasible, efforts should be made to re-examine those that are logistically intense and financially demanding.

Protective Isolation

Studies suggest that most bacterial infections in patients with granulocytopenia arise from the patient's own flora and that colonization by the causative microorganism in nearly half of the infections occurs only after admission to the hospital *(104)*. Contaminated hands of healthcare workers are thought to play a major role in the colonization of these patients. Protective isolation, using only gloves and gowns, has been shown to be effective in reducing infection rates in a pediatric intensive care unit, but patients with immunologic dysfunction were excluded from the study *(105)*. Protective isolation alone has been shown in one study *(106)* to be of no value in protecting patients with severe granulocytopenia. In a randomized clinical trial comparing the role of gown-and-glove isolation and strict hand washing in the reduction of HAI in children with solid organ transplantation admitted to a pediatric intensive care unit, Slota et al. *(107)* found that, while the rate of HAIs in both intervention groups was significantly reduced compared with the baseline rate, there was a trend toward a greater reduction in the gown-and-glove group than in the hand-washing group. While this study demonstrates the role of gown-and-glove isolation in certain specific clinical settings and indicates the possibility of some additional benefit of this intervention over simple hand washing, the latter intervention is undeniably relatively inexpensive and simple to implement. Until further studies demonstrating

the efficacy and cost-effectiveness of protective isolation in the routine care of patients with neoplastic diseases in various clinical settings are done, this intervention cannot be uniformly recommended. In the meantime, its use as a component of standard infection control procedures such as respiratory or enteric isolation in the setting of documented infections should be continued.

Air-Handling Systems

Guidelines for hospital room design and ventilation are available and should be followed *(108,109)*. While provision of clean air is important to any patient, additional measures to eliminate the risk of exposure to filamentous fungi such as *Aspergillus* species, are attempted, especially for high-risk hosts with prolonged granulocytopenia. Reported outbreaks of healthcare-associated invasive aspergillosis have been caused by concentration of conidia in hospital ventilation systems *(110)*, contaminated fireproofing materials *(111)*, and air contamination from construction *(47–50)*. One such measure is the use of HEPA filters. The modern HEPA filter, made of superfine spun-glass fibers less that 1 mm in diameter, was developed by the Army Chemical Corps and the Naval Research Laboratory in the years immediately after World War II. The maximum allowable penetration of a HEPA filter at any point in the media, frame, or gasket is 0.03% of the challenge concentration of monodispersed thermally generated dioctyl phthalate (DOP) having a count-median droplet diameter of $0.3 \pm 0.03\,\mu m$.

HEPA-filtered air has been used in many centers as a component of protective isolation to provide ultraclean air to patients during periods of granulocytopenia. In some studies, HEPA-filtered air was delivered to the patient in a unidirectional (formerly called "laminar flow") fashion, and in other studies, "life island" units that enclosed the patient's bed in a plastic canopy were used. Unidirectional airflow is not achieved in life island units. A concentration of about 2.12 microorganisms per cubic meter of air can be achieved in life island units and 0.21 microorganisms per cubic meter can be achieved in rooms with unidirectional flow, compared with approximately 106 microorganisms per cubic meter in conventional rooms. Although the efficacy of HEPA filters in preventing aspergillosis seems clear *(48,112,113)*, the effect on preventing other infections is less certain.

With proper installation, testing, and maintenance, ultraclean air can be maintained in the patient room. Patients with neoplastic diseases, however, must periodically leave this protected environment for a wide range of diagnostic and therapeutic procedures. Despite the lack of clear-cut data, for a subset of immunocompromised patients identified at high risk for aspergillosis, it is desirable to protect the respiratory tract from opportunistic pathogens during these periods. For this purpose, various masks or respirators are in use. High-efficiency masks have been successfully used for high-risk patients during periods when they are outside their hospital rooms *(114)*. A breakthrough in the manufacture of HEPA-filtered masks is the replacement of delicate fiberglass fibers with durable plastic fibers. This new technology has permitted the production of a durable, lightweight, comfortable mask that readily passes DOP leak tests and should provide the patient with air quality at least as good as that found in HEPA-filtered unidirectional-flow rooms. Another mask in clinical use is the N95 respirator. In the guidelines for Preventing Opportunistic Infections Among Hematopoietic Stem Cell Transplant Recipients published by the CDC, use of the N95 mask (particulate respirator) has been mentioned to prevent mold exposure during transportation near hospital construction or renovation areas because these respirators are regarded as effective against any aerosol *(115)*. For maximal efficacy of any face device, whether it be the HEPA mask or the N95, proper fit testing and training of the patient is very important. In this regard, unavailability of small masks poses a limitation for their use with infants and small children. In conclusion, while HEPA filters are important, especially in high-risk hosts, to prevent healthcare-associated aspergillosis, particularly if there is concurrent hospital renovation or construction, the correct and optimal installation and use of HEPA filters is relatively complex and expensive.

Other factors related to hospital air handling, including appropriate air exchanges and pressurization, are equally important in preventing healthcare-associated airborne infections, especially aspergillosis *(116)*. In a study assessing the ability of hospital air–handling systems to filter *Aspergillus*, other fungi, and particles after the implosion of an adjacent building, an encouraging observation was that even standard hospital air–handling systems with filtration exceeding minimum American Society of Heating, Refrigeration, and Air Conditioning Engineers standards have a significant safety buffer in filtering *Aspergillus* spores *(117)*. HEPA filters likely provide an additional level of safety. The design and maintenance of hospital ventilation systems is discussed in detail in Chapter 84.

Anaissie et al. *(51)* have submitted evidence to support the theory that hospital water distribution systems may be a potential indoor reservoir of *Aspergillus* species and other molds, leading to aerosolization of fungal spores and potential patient exposure. In a high-risk population such as bone marrow transplant patients, these researchers recommend the use of sterile (boiled) water for drinking and sterile sponges for bathing. In addition, they recommend cleaning of the floors of the patient shower facilities to reduce the air concentration of *Aspergillus* species and other pathogenic airborne molds *(118)*.

Antimicrobial Drugs

The concept of antimicrobial prophylaxis in patients with cancer to prevent infections in general, not necessarily HAIs, has been most widely studied in neutropenic patients. It is well accepted that infections in a healthcare setting can be of exogenous origin or of endogenous origin related to the patient's own residential microbial flora. The latter can be influenced by microorganisms acquired in the hospital environment as well as the antimicrobial pressure the patient is under. Initial trials of infection prophylaxis using combinations of nonabsorbable drugs such as aminoglycosides, polymyxins, and vancomycin were followed by studies of orally absorbable agents, primarily trimethoprim sulfamethoxazole (TMP-SMX) and quinolones. A review of studies of prophylaxis with TMP-SMX by the IDSA Fever and Neutropenia Panel found that, in most studies, there was some benefit in terms of lower infection rates in the TMP-SMX–treated group than in the placebo group *(119)*. Studies have shown the benefit of quinolone-based

prophylaxis in reducing the rates of febrile episodes and infections in neutropenic patients *(120–122)*. Fluoroquinolone prophylaxis reduces the risk of febrile episodes in neutropenic outpatients with solid tumors, including lymphomas, and is associated with a statistically insignificant, yet clinically important, decrease in mortality in all neutropenic patients. Prophylaxis with levofloxacin may reduce febrile episodes in neutropenic hematology patients and stem cell transplant recipients. As per the 2010 IDSA guidelines for the use of antimicrobial agents in neutropenic patients, fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC <100 cells/mm^3 for >7 days). With any prophylaxis strategy systematic surveillance to monitor for changes in patterns of antimicrobial resistance is critical and cannot be overstated (123).

Finally, with the increase in frequency of fungal infections in patients with neoplastic diseases, especially patients with hematologic malignancy, there has been considerable interest in the role of antifungal prophylaxis. A systematic meta-analytical review of the efficacy of antifungal prophylaxis in neutropenic chemotherapy recipients showed antifungal prophylaxis reduced overall morbidity, as evidenced by reductions in the use of parenteral antifungal therapy, superficial fungal infection, and invasive fungal infection, as well as reducing fungal infection-related mortality. These effects were most pronounced in patients with malignant disease who had prolonged neutropenia and HSCT recipients *(123a)*. There is no widely accepted standard for antifungal prophylaxis in patients with hematologic malignancies. In a randomized clinical trial in patients undergoing chemotherapy for acute myelogenous leukemia or myelodysplastic syndrome, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival. There were more serious adverse events possibly or probably related to treatment in the posaconazole group *(124)*. In another randomized clinical trial in patients with graft-versus-host disease who were receiving immunosuppressive therapy, posaconazole was found superior to fluconazole in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections *(125)*. The Infectious Diseases Working Party of the German Society for Hematology and Oncology recommends posaconazole in patients with acute myelogenous leukemia/myelodysplastic syndrome and for patients undergoing allogeneic stem cell transplantation with graft-versus-host disease for the prevention of invasive fungal infections and attributable mortality *(126)*. The 2010 IDSA guidelines for the use of antimicrobial agents in neutropenic patients also list recommendations for prophylactic, empiric and preemptive use of antifungal agents based on risk stratification of the host (123). As more aggressive antifungal therapy and prophylaxis is used, there has been increasing concern about a shift in fungal pathogens isolated from oncology patients. Of particular concern have been breakthrough cases of zygomycosis in patients receiving voriconazole.

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CHAPTER 58

Healthcare-Associated Infections in Solid Organ Transplant Recipients

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Infections remain a significant complication and a leading cause of mortality, particularly within the first year after transplantation. Most infections in transplant recipients are healthcare-associated and represent either opportunistic infections resulting from iatrogenic immunosuppression or infections resulting from conventional healthcare-associated pathogens. The incidence of several opportunistic infections (e.g., cytomegalovirus [CMV] and *Pneumocystis jirovecii* pneumonia [PJP]) has declined dramatically, largely because of the advent of effective prophylaxis. On the other hand, healthcare-associated infections (primarily due to bacteria) transmitted from environmental reservoirs or harbored as a result of endogenous colonization in healthcare-associated settings have emerged as leading infections in organ transplant recipients. In liver transplant recipients, 82% of the episodes of fever documented in consecutive patients over a 2-year period were healthcare associated, of which 62% were bacterial in origin (1). Fifty-three percent of all infections in heart transplant recipients in another study were healthcare-associated, and of these, 63% were bacterial *(2)*.

Paralleling the trends in healthcare-associated infections, antimicrobial resistance is increasingly recognized as a problem in the transplant setting. It is noteworthy, however, that the emergence of several of the antibiotic-resistant pathogens was first documented in transplant recipients *(3)*. For example, vancomycin-resistant enterococci (VRE) were initially discovered in liver transplant recipients at several institutions where they eventually became a more widespread problem.

Transplant recipients are uniquely vulnerable to colonization and infection resulting from healthcare-associated pathogens. Within the same institution, transplant recipients have been shown to have a significantly higher incidence of healthcare-associated infections than nontransplant patients *(4)*. The predilection of immunocompromised patients to *Legionella* infection is well recognized. However, it is notable that within this subgroup, transplant recipients have the highest risk *(5)*. Among patients undergoing surgical procedures at one institution where legionellosis was documented, renal transplant recipients had an attack rate of 50%, whereas the general hospital population experienced an attack rate of only 0.4% *(6)*. Transplant recipients exposed to tuberculosis during an institutional outbreak were more likely to contract *Mycobacterium tuberculosis* as compared with nontransplant contacts of the source case *(7)*. During a healthcare-associated outbreak of extended-spectrum β-lactamase–producing *Escherichia coli*, 67% of patients on the liver transplant service, but no other surgical patients on the same floor, were shown to be colonized or infected with the outbreak isolate (8).

This chapter discusses the potential sources of infections, unique risk factors according to the type of organ transplanted, and the treatment and prevention of infections in solid organ transplant recipients that may be acquired during or after transplantation.

SOURCES OF INFECTIONS IN RECIPIENTS

Donor-Derived Infections

Latent Infections in the Donor Viral infections latent in the donor have by far the greatest potential for transmission by the transplanted organ and exert a more profound clinical impact in the allograft recipient compared with many other donor-transmitted infections. Thus, serologic screening of the donor for hepatitis B virus (HBV), hepatitis C virus (HCV), CMV, EBV, and human immunodeficiency virus (HIV) is routinely recommended (9). Nonviral infections (e.g., toxoplasmosis) are also discussed here.

Hepatitis B Virus The risk of transmission of HBV varies according to the HBV serologic profile of the donor and the recipient and the type of organ transplanted (liver vs. nonliver). Transplantation of allografts from hepatitis B surface antigen (HBsAg)-positive donors carries the highest risk of HBV transmission and is recommended only in life-threatening situations. IgM antibody to hepatitis B core antigen (anti-HBc IgM) positivity indicates either recent or current infection; it should be managed as in HBsAg-positive donors. Anti-HBc IgG positivity in the absence of HBsAg poses a low likelihood of transmission of HBV. The liver may continue to harbor the replicative form of HBV in such donors with the potential of HBV transmission even in the presence of anti-HBs *(10)*. Donors with isolated anti-HBc positivity should be considered infectious, especially for the hepatic allograft. Indeed, 78% (18/23) of the liver transplant recipients from donors with isolated

anti-HBc experienced HBV transmission *(11)*. Transplantation of an anti-HBc–positive liver into a nonimmune recipient should be performed only if deemed medically urgent and under a prophylactic regimen of lamivudine with or without hepatitis B immune globulin (HBIG) *(12,13)*. However, the risk of HBV transmission for recipients of nonhepatic organs is low. None of the seven heart transplant recipients and 2.3% (1/42) of the renal transplant recipients who received organs from isolated anti-HBc–positive donors became infected *(14)*. General consensus is that the organs from anti-HBc positive donors should be used for recipients who are HBsAg positive or who have evidence of HBV immunity. The risk of HBV transmission from anti-HBc–positive donors to nonhepatic organ recipients can be further stratified based on the presence of HBV DNA in the serum at the time of transplantation (15) as the risk is considered negligible if serum HBV DNA is negative. The use of anti-HBc–positive nonhepatic allografts has not been associated with poor outcomes *(16,17)*. Anti-HBs–positive liver donors who are negative for both HBsAg and anti-HBc are generally considered unlikely to transmit HBV. Anti-HBs positivity is usually explained by HBV vaccination or administration of hepatitis B immunoglobulin. However, the potential for HBV transmission can still exist for donors with isolated anti-HBs positivity since HBV DNA may be detectable in the hepatic allografts *(18)*.

The most important measure to prevent HBV transmission is the administration of HBV vaccine to nonimmune transplant candidates. However, HBV transmission may occur even if recipients are immune to HBV (positive anti-HBs status). Transplantation of any organs from HBsAg-positive donors should be ideally avoided. If a recipient emergently needs an organ from HBsAg-positive donors due to life-threatening situations, the recipient should receive HBIG and prophylactic antiviral therapy with lamivudine for a minimum of 1 year with close monitoring of liver enzymes, HBsAg, anti-HBs, and HBV DNA. Liver transplant from an IgG anti-HBc–positive donor should be managed in a similar manner. HBV-immune candidates can receive extrahepatic organs from an IgG anti-HBc–positive donor without any prophylaxis; however, posttransplant surveillance for liver enzymes, HBsAg, anti-HBs, and HBV DNA are recommended. If potential candidates are not immune to HBV, HBIG, and/or lamivudine are typically administered. The duration of prophylaxis depends on the presence of the donor HBV DNA. If the donor HBV DNA at the time of transplant is negative, prophylaxis may be discontinued. If the donor HBV DNA is positive or unknown, HBIG for >3 to 6 months or lamivudine for >12 months should be continued (*13*,15).

Hepatitis C Virus Approximately 5% of all cadaveric organ donors are positive for antibody to HCV (anti-HCV), and 50% of these have detectable HCV viremia by PCR *(19)*. Nearly all the recipients from anti-HCV-positive donors become infected with HCV (20). Donor-derived HCV infection is associated with rapid progression of fibrosis and high mortality *(21)*. Transplantation of livers from HCV-positive donors into HCV-positive recipients has not been associated with a decrease in graft or patient survival up to 8 years *(22–24)*. Most transplant centers use HCV-positive extrahepatic organs only for HCV-positive recipients, because there are data suggesting that donor HCV-positive status is independently associated with decreased survival regardless of recipient HCV status *(25,26)*. The use of anti-HCV–positive organs in anti-HCV–negative recipients should be avoided; however, it may be considered in life-threatening situations. Unlike HBV, no effective measures to prevent HCV transmission are currently available.

Herpesviruses The donor allograft is a significant and an efficient source of transmission of CMV *(27,28)*. The morbidity from infection is greatest in CMV-seronegative recipients of CMV-positive allografts. Superinfection (i.e., infection with an exogenous strain of CMV in patients with prior evidence of CMV infection) has also been documented. Symptomatic CMV disease occurred more frequently in patients infected with the new CMV strain compared with those with reactivation of the latent virus *(29)*. Donor transmission (documented by molecular typing) has also been demonstrated with other herpesviruses, including herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), and human herpesvirus-6 (HHV-6) *(30–34)*. EBV-seronegative recipients of EBV-positive allografts are at highest risk of developing EBV-associated posttransplant lymphoproliferative disorder, especially among intestinal transplant recipients *(35,36)*. Transmission of herpesviruses from donors to recipients is not preventable; however, identification of recipients is at high risk (i.e., seronegative recipients) followed by use of antiviral prophylaxis (CMV, HSV) with or without monitoring of viral replication and close clinical follow-up with symptoms is crucial. Management issues of herpesviruses infection are discussed later in this chapter.

Human Immunodeficiency Virus Donor positivity for HIV by enzyme-linked immunosorbent assay (ELISA) is considered an absolute contraindication to organ donation. There is a remote possibility that HIV can be transmitted from donors who test negative for HIV antibody if the time of transplantation is during the window period or if the test is false-negative due to resuscitation-associated hemodilution.

Recently, transmission of HIV was reported in three organ recipients from a donor who had sex with men who tested negative for HIV antibody (*37*,*38*,39). Scrutinizing the donor's behavioral and medical risks of HIV in a limited time frame followed by weighing these risks against the benefits of transplantation are critically important (40). Use of special consent forms for transplantation of organs from high-risk donors has been utilized in many transplant centers. Although more sensitive nucleic acid amplification assays are available, the cost and delayed turnover time may prohibit their routine use.

Human T-Cell Lymphotrophic Virus Type 1/2 Human T-cell Lymphotrophic Virus Type 1/2 (HTLV-1/2) is a retrovirus with marked geographically variant prevalence from 0.035% to 0.046% in the United States blood donors to 30% in Southern Japan *(41,42)*. UNOS data revealed that the prevalence of HTLV-1 and HTLV-2 among the US organ donors is 0.027% and 0.046%, respectively *(43)*. Although HTLV-1 is associated with the development of acute T-cell lymphoma and HTLV-1-associated myelopathy, the majority of these patients remain asymptomatic. Only a few cases of documented transmission and development of HTLV-1-associated disease in solid organ transplant

recipients have been reported *(44,45)*. HTLV-2 does not appear to be associated with the clinical syndrome. The OPTN/UNOS Ad Hoc Disease Transmission Advisory Committee recently recommended against routine screening for HTLV-1/2 given the lack of routine availability of some commercial assays, a high false-positive rate leading to the waste of organs, favorable short-term follow-up of recipients of HTLV-1/2 screen positive organs, and low prevalence of the disease in the United States *(46)*.

Mycobacterium tuberculosis Transmission of *M. tuberculosis* to recipients receiving allografts from donors with active tuberculosis has been documented. Transmission of *M. tuberculosis* to two renal transplant recipients from a donor with unrecognized tuberculous meningitis at the time of organ retrieval has been reported *(47)*. Tuberculin- positive donors without clinically overt tuberculosis may also transmit tuberculosis. Tuberculin-positive living donors should receive chemoprophylaxis after appropriate workup to rule out active tuberculosis if delay of transplant is acceptable. It is recommended that the recipients of allografts from donors with latent tuberculosis or a history of tuberculosis should receive chemoprophylaxis for tuberculosis after transplantation *(47)*.

Toxoplasma gondii *Toxoplasma gondii*, because of its predilection for latency in muscle tissue, poses a substantial risk for transmission of toxoplasmosis in heart transplant recipients. In the absence of prophylaxis, 50% to 70% of the seronegative recipients of *T. gondii* antibody-positive allografts have developed toxoplasmosis *(48)*. Heart transplant donors and recipients should be serotested to determine the risk for toxoplasmosis. Because of the paucity of *Toxoplasma* cysts in noncardiac tissue, toxoplasmosis is rarely transmitted by the nonheart organs and pretransplant screening is controversial in this population *(49)*. Prophylactic use of trimethoprim-sulfamethoxazole significantly decreases the risk of developing toxoplasmosis posttransplant in heart transplant recipients (*50*,51). Some experts administer a higher dose of trimethoprim-sulfamethoxazole or a combination of pyrimethamine and sulfadiazine to high-risk patients (seronegative recipients of a seropositive heart).

Trypanosoma cruzi *Trypanosoma cruzi* is an endemic parasitic disease in Latin America (American trypanosomiasis). It is transmitted by the triatomine insect, but blood transfusion, maternal–fetal transmission, and organ transplant are also the major routes of transmission in a nonendemic area *(52,53)*. Donor screening should be performed for those who lived or traveled in an endemic area. Organs from donors positive for *T. cruzi* should not be utilized especially for heart transplant given its fatal outcomes *(54)*. If nonheart organs are utilized in emergent situations, aggressive monitoring with direct parasitological tests and/or PCR-based assays (51).

Other Pathogens Transmission of endemic fungi including *Histoplasma capsulatum* and *Coccidioides immitus* via donor allograft has been reported *(55,56)*. Although active fungal infections should be excluded prior to procurement, no consensus exists with regard to donor screening for latent fungal infection. West Nile virus (WNV), rabies, and lymphocytic choriomeningitis virus (LCMV) are the examples of emerging pathogens that have been reported to be donor derived *(57–59)*.

Acquired Infections in the Donor Life-sustaining measures in critically ill donors may render them susceptible to healthcare-associated infections with the potential for transmission to allograft recipients. Two recent studies comprising a large number of patients have shown that donor bacteremia did not portend a higher risk of infectious complications or compromise graft or patient survival *(60,61)*. The most frequent cause of the donor bacteremias in these studies was gram-positive bacteria, of which *Staphylococcus aureus* was the predominant pathogen. Most recipients of organs retrieved from bacteremic donors in the aforementioned studies received antimicrobial therapy. In the study by Lumbreras et al. *(60)*, specific antibiotics were administered to the recipients for 7 to 10 days on receipt of donor blood culture results. In the report by Freeman et al. *(61)*, 91% of the recipients received antibiotics for a mean of 3.8 days. These data suggest that with appropriately administered antibiotic therapy, organs from bacteremic donors can be successfully transplanted without incurring an additional risk for infection or allograft dysfunction in the recipient.

A similar dilemma exists regarding the feasibility of using organs from donors with bacterial meningitis *(62)*. Lopez-Navidad et al. *(62)* described the outcome in 16 recipients who had received organs from five patients with bacterial meningitis. The pathogens included *Neisseria meningitidis, Streptococcus pneumoniae,* and *E. coli*. With antibiotic administration ranging from 5 to 10 days, infection caused by the aforementioned bacteria was not documented in any of the recipients. Thus, patients with brain death attributable to bacterial meningitis caused by these bacteria can also be suitable organ donors, if the donor and the recipient receive appropriate antibiotic therapy. An exception, however, is donors with a less commonly encountered bacterial infection, that is, *M. tuberculosis*. Unrecognized active *M. tuberculosis* infection in the donor can be efficiently transmitted to the recipient with deleterious sequelae. Moreover, caution must be exercised when transplantation from donors with a presumptive diagnosis of bacterial meningitis is considered.

Donor organs colonized with *Candida* or *Aspergillus* may transmit the fungi to lung and heart–lung transplant recipients. Karyotypic analysis of the *Candida albicans* isolates demonstrated identical strains from the donor lung and *C. albicans* isolates causing disseminated infection in a lung transplant recipient *(63)*. Donor organs have also been documented to transmit other fungal infections (e.g., *Cryptococcus neoformans* and *Histoplasma capsulatum*) *(64)*.

Contamination during Organ Procurement

Contamination during harvesting and preservation of the allograft has been reported to occur in 2% to 23% of the kidney allografts. Although some bacteria (e.g., *Staphylococcus epidermidis,* diphtheroid species, and *Propionibacterium acnes*) present little risk of infection to the allograft recipient, more virulent pathogens (e.g., gram-negative rods, particularly *Pseudomonas aeruginosa*; *S. aureus*; and

fungi) cultured from the donor or the preservation fluid can lead to serious infections (e.g., mycotic aneurysm and anastomotic rupture) in kidney transplant recipients *(64–66)*.

Blood Products

Although CMV infection has been shown to be transmitted by blood products in organ transplant recipients, the risk is small and has not been shown to correlate with the number of blood products transfused *(33)*. Over a 13-year period, only 2.6% (3/112) of CMV-seronegative recipients who received CMV negative renal, heart, lung, or liver allografts were documented to develop transfusion-associated CMV infection *(67)*. Furthermore, transfusion, compared with donor-transmitted CMV infection, has been associated with a lower frequency of symptomatic disease and, therefore, has a less profound clinical impact *(68)*. Nevertheless, the use of CMV seronegative blood products or leukoreduced blood product for recipients who are seronegative for CMV should be considered. Finally, the use of leukoreduced blood product further reduced the risk of CMV transmission.

Since 1990, all blood products in the United States have been routinely screened for HCV. Consequently, the risk of posttransfusion HCV has declined from 8% to 10% to <1% currently.

Environmental Reservoirs and Sources

Environmental sources are significant sites for acquisition of a number of infectious agents, particularly healthcare-associated pathogens in transplant recipients (Table 58-1). Most cases of *Legionella* in solid organ transplant recipients are healthcare-associated *(69)*. The source of posttransplant legionellosis in all studies where an environmental link was sought was the hospital's potable water distribution system *(5)*. Restriction fragment length polymorphism patterns documented that the hospital's central hot water supply was the source of legionellosis in a hospital where 14 cases were documented in transplant recipients over an 8-year period *(70)*. Healthcare-associated legionellosis in heart–lung transplant recipients at one institution was linked to a contaminated ice machine *(71)*.

Outbreaks of invasive aspergillosis in transplant recipients have been linked to construction or demolition activity within or near a hospital; contaminated or poorly maintained ventilation ducts, grids, or air filters; and other dust-generating activities that may aerosolize *Aspergillus* spores. Accommodation of marrow transplant recipients outside of rooms with laminar air flow and high-efficiency particulate air (HEPA) filters during periods of neutropenia have been shown to be a risk factor for invasive aspergillosis *(72)*. A seasonal variation in the incidence of invasive aspergillosis, coinciding with a high outdoor concentration of airborne spores in late summer or fall and a lower concentration in the winter months, has also been observed. The prevailing belief that *Aspergillus* is predominantly an airborne pathogen acquired via inhalation has recently been challenged. It has been proposed that *Fusarium* and *Aspergillus* can be detected in hospital water systems, and aspiration, as opposed to inhalation of *Aspergillus,* may be the mode of acquisition of healthcare-associated invasive aspergillosis in susceptible hosts *(73)*.

The prevailing assumption has been that *P. jirovecii* infection arises from reactivation of endogenous infections

TABLE 58-1

Mode of Acquisition of Major Pathogens in Transplant Recipients

Pathogen	*Mode of Acquisition*
Viruses	
Cytomegalovirus	
Seronegative recipient	Donor transmission, rarely transfusions
Seropositive recipient	Reactivation and donor transmission
Herpes simplex virus	Reactivation, rarely donor transmission
Varicella zoster virus	Reactivation, rarely donor transmission
Human herpesvirus-6	Reactivation and donor transmission
Hepatitis C virus	Reactivation, unless donor anti-HCV positive
Hepatitis B virus[a]	Rarely donor transmission
Adenovirus	Donor and healthcare-associated transmission
Respiratory viral infections	Healthcare-associated and community acquisition
Bacteria	
Staphylococcus aureus	Endogenous colonization, healthcare-associated transmission
Vancomycin resistant enterococci	Healthcare-associated transmission, endogenous gastrointestinal colonization
Pseudomonas aeruginosa	Healthcare-associated environmental acquisition
Enterobacteriaceae	Endogenous colonization, healthcare-associated transmission
Legionella	Environmental acquisition
Mycobacterium tuberculosis	Reactivation, donor transmission, healthcare-associated transmission
Fungi	
Candida	Endogenous infection (liver transplants), donor transmission (lung transplants)
Aspergillus	Environmental acquisition
Pneumocystis jirovecii	Reactivation, possibly healthcare-associated transmission
Cryptococcus neoformans	Primarily reactivation
Protozoa	
Toxoplasma gondii	Donor transmission, rarely reactivation

[a]HBsAg-positive donors can transmit hepatitis B virus (HBV) but are not considered acceptable organ donors. Rarely anti-HBs–positive donors (particularly of hepatic allografts) can transmit HBV.

acquired in childhood. However, healthcare-associated patient-to-patient transmission and environmental contamination of *P. jirovecii* has also been documented *(74,75)*. A cluster of renal transplant recipients who developed PJP shared the same strain confirmed by multilocus DNA sequence typing *(76,77)*. *P. jirovecii* DNA has been demonstrated in more than 50% of the air samples from the hospital rooms of *P. jirovecii*–infected patients *(78)*. It remains to be determined whether isolation of patients with PJP decreases the incidence of PJP, though such trials would be difficult in the current era of routine anti-PJP prophylaxis.

VRE and methicillin-resistant *S. aureus* (MRSA) have become established as endemic pathogens in many institutions and are increasingly recognized as significant microorganisms in transplant recipients. At many centers, VRE, MRSA, or *Clostridium difficile* are currently the most frequent etiologic agents of infections in transplant recipients. Although patient-specific variables (e.g., severity of illness, intensity of antimicrobial use, and length of hospital stay) are risk factors for acquisition, environmental contamination and, more importantly, person-to-person transmission are also considered significant factors in the healthcare-associated spread of these bacteria. Equipment and surfaces in the vicinity of patients colonized and infected with VRE have been shown to become contaminated with VRE; VRE could be recovered for at least 7 days from the surfaces of countertops and after 30 minutes from the stethoscopes *(79)*. Furthermore, epidemiologic studies have documented healthcare-associated VRE transmission by molecular typing techniques *(80)*. Likewise, pulse-field gel electrophoresis demonstrated that 43% of the MRSA isolates causing invasive infections at a transplant unit shared the same pattern, suggesting healthcare-associated transmission *(80)*.

C. difficile is currently the most common cause of infectious diarrhea in transplant recipients. Liver transplantation was identified as the most significant independent risk factor for *C. difficile* acquisition in one report *(81)*. Although the precise mode of transmission of *C. difficile* has not been determined, environmental contamination and healthcare-associated transmission are the likely mode of transmission of *C. difficile*; however, airborne dispersal of spores could be another important source *(82,83)*. *C. difficile* was recovered from 9% to 51% of the environmental cultures; objects contaminated with feces (e.g., bed pan, toilet seats, sinks, and scales were most likely to yield *C. difficile*) *(84)*. Positive hand cultures were documented in 59% of the hospital personnel caring for the patients with *C. difficile,* implicating hands of hospital personnel as a likely mode of transmission *(85)*. Prudent use of antimicrobial agents and measures to curtail healthcare-associated transmission are key toward effective prevention of infections caused by these pathogens.

RISK FACTORS FOR INFECTIONS

Surgical factors, intensity of immunosuppression, and variations in local and systemic host response are among the variables that determine not only the type but also the site and the severity of infections in different types of organ transplant recipients (Table 58-2).

TABLE 58-2

Risk Factors for Infection with Major Healthcare-Associated Pathogens in Transplant Recipients

Pathogen	*Risk factors*
Fungi	
Aspergillus	
Lung transplantation	Single-lung transplant, CMV infection, airway ischemia, hypogammaglobulinemia, pretransplant and posttransplant *Aspergillus* colonization, bronchial stent
Liver transplantation	Poor allograft function, renal failure (particularly a requirement for dialysis), retransplantation
Heart transplantation	Isolation of *Aspergillus* species in respiratory tract cultures, reoperation, CMV disease, posttransplant dialysis
Renal transplantation	Augmented immunosuppression, graft failure requiring hemodialysis
Candida	
Liver transplantation	Prolonged operation time, high transfusion requirement, renal failure, repeat operation, retransplantation, choledochojejunostomy
Pancreatic transplantation	Diabetes, exocrine enteric drainage
Pneumocystis jirovecii	Augmented immunosuppression, allograft rejection, CMV infection, low CD4 count
Viruses	
Cytomegalovirus	Donor CMV seropositivity, Augmented immunosuppression (particularly, antilymphocyte agents), allograft rejection, HHV-6 infection
Bacteria	
Vancomycin-resistant enterococcus	Rectal colonization prior to transplant, previous antibiotic use, biliary complications, prolonged hospitalization, surgical reexploration, allograft nonfunction
Methicillin-resistant *Staphylococcus aureus*	Nasal *S. aureus* carriage, prolonged hospitalization, ICU stay
Legionella	Contaminated hospital potable water system, humidifiers, and ice machines
Mycobacterium tuberculosis[a] (risk factors for early-onset tuberculosis)	Nonrenal transplantation, history of prior *M. tuberculosis* (positive tuberculin test or old active tuberculosis on chest radiographs), OKT3 use
Pseudomonas aeruginosa	Donor colonization (lung transplants), cystic fibrosis

[a]Early-onset tuberculosis implies infection occurring within 12 months of transplantation.
CMV, cytomegalovirus; HHV-6, human herpesvirus-6; ICU, intensive care unit.

Liver Transplantation

Liver transplant recipients, by virtue of having hepatic failure and malnutrition before transplantation, represent severely compromised hosts. Many of these patients have concomitant renal failure as a result of hepatorenal syndrome. Renal failure, particularly the requirement for dialysis, was an important predictor of early infections and adversely affected survival after liver transplantation (86,*87*).

Liver transplant recipients are uniquely susceptible to invasive candidiasis. Most cases originate from endogenous sources; deficient reticuloendothelial function and translocation across the gut mucosa are considered important pathogenetic factors predisposing to invasive candidiasis *(88)*. Vascular and anastomotic complications are also significant risk factors for infectious morbidity in liver transplant recipients. Duct-to-duct biliary anastomosis compared with Roux-en-Y choledochojejunostomy is associated with a lower incidence of infections, because the latter involves the breach of the bowel integrity and sacrificing the sphincter of Oddi, which may promote reflux of bowel contents into the biliary tree *(89)*. Hepatic artery thrombosis may lead to the development of hepatic infarcts with subsequent gangrene and abscess formation. The clinical presentation is usually acute or fulminant, although hepatic artery occlusion may occasionally be occult and present with a clinical picture of unexplained fever and relapsing subacute bacteremia. Hepatic artery thrombosis may also lead to liver abscesses by compromising the biliary vascular supply. Impaired arterial flow to the hepatic allograft preferentially affects the biliary tree because of the biliary tract's almost total reliance on the hepatic arterial blood supply. Hepatic artery thrombosis may thus lead to biliary tract ischemia and biliary leaks, eventually resulting in intrahepatic abscess formation.

The biliary tract may be a source of infection even with an intact vascular supply. Biliary composition is altered during liver transplantation, leading to supersaturation with cholesterol and sludge and stone formation that may predispose to infections (e.g., cholangitis). T tubes, commonly used to protect duct-to-duct biliary anastomoses, are prone to microbial colonization and form a nidus for the deposition of biliary sludge.

Portal vein thrombosis was shown to be the most significant independent predictor of early bacterial infections after liver transplantation *(90)*. Recurrent viral HCV hepatitis has been documented in nearly 50% of the patients undergoing liver transplantation for end-stage liver disease resulting from HCV. HCV is considered an immunosuppressive and an immunomodulatory virus. Patients with HCV recurrence were significantly more likely to develop late-occurring infections, particularly fungal infections after liver transplantation *(91)*.

Renal Transplantation

Urinary tract and postoperative surgical site infections are two of the most frequent and serious healthcare-associated infections in renal transplant recipients. Urinary tract infections occur in more than 50% of patients during the first 3 months after transplantation and are the most frequent source of bacteremia during this time. In the absence of antimicrobial prophylaxis, surgical site infections have been reported in up to 20% of patients. Organ/space surgical site infections after renal transplantation have been shown to adversely affect graft survival.

Surgical site infections in renal transplant recipients are usually due to staphylococci or gram-negative bacilli *(92,93)*. Staphylococcal infections were associated with incisional surgical site infections and occurred earlier, whereas those due to gram-negative bacilli occurred later; were organ/space surgical site infections; and often led to bacteremia, graft loss, or death. Prolonged urinary catheterization, a surgical site hematoma, a reopened surgical site, and a cadaveric donor graft are risk factors for healthcare-associated urinary or surgical site infections in renal transplant recipients *(94,95)*. Renal trauma with nephrectomy and graft contamination during transportation may likely account for a higher risk of infection in cadaveric compared with living allograft recipients. Bacteriuria occurring in the late posttransplant period is usually benign and rarely symptomatic; however, late-onset (>6 months) urinary tract infections were significantly associated with an increased risk of graft loss *(96–98)*. Antimicrobial prophylaxis has proven highly effective in reducing the rate of urinary tract and surgical site infections in renal transplant recipients. A single perioperative dose of antibiotics led to a reduction in the incidence of surgical site infections from 25% to 2% *(99)*. Prophylaxis with trimethoprim-sulfamethoxazole has been shown to significantly lower the incidence of urinary tract infections, bacteremias, and infections caused by gram-negative bacilli and *S. aureus* when compared with placebo *(100)*. Currently, no recommendations are made for screening and treatment of asymptomatic bacteriuria in renal transplant recipients *(101)*.

Heart and Lung Transplantation

Heart and lung transplant recipients are uniquely susceptible to healthcare-associated bacterial pulmonary infections, particularly in the first month after transplantation. Bacterial pneumonia has been reported in 35% to 48% of the lung and heart–lung transplant recipients *(102,103)*. Impaired mucociliary clearance, loss of cough reflex, postoperative pain with splinting, and donor tracheal colonization are some factors contributing to a high risk of postoperative pneumonia in lung transplant recipients.

Multiple drug-resistant strains of *P. aeruginosa* and *Burkholderia cepacia* complex are of particular concern in patients undergoing lung transplantation for cystic fibrosis. Although panresistant *P. aerguinosa* colonization was associated with worse survival (88.6% vs. 96.6% at 1 year) than sensitive *P. aeruginosa* colonization, their survival is comparable to CF patients in the UNOS registry (86% at 1 year) *(104)*. Thus, panresistant *P. aeruginosa* colonization should not be considered as a contraindication to lung transplant. Among *B. cepacia* complex, most transplant centers consider *B. cenocepacia* (*B. cepacia* complex genovar III) colonization or infection to be a contraindication for lung transplant given its worse outcomes compared with nongenovar III *B. cepacia* complex (*105*,*106*,107). In a retrospective study of 75 cystic fibrosis lung transplant recipients, 1-year survival rates are 92%, 89%, and 29% in noninfected patients, those with *B. cepacia* complex species other than *B. cenocepacia*, and those with *B. cenocepacia*, respectively (107). Although the infected lung is removed during transplantation, residual colonization of the airway, nasopharynx, and sinuses remains a potential

nidus for subsequent infection. Typically, a course of antimicrobial prophylaxis is given to prevent development of posttransplant lung infections based on the result of bacterial cultures from donor- and recipient-bronchus at the time of procurement.

Circulatory support devices (e.g., intraaortic balloon pump and left ventricular assist devices) are required in many potential heart transplant recipients, and their prolonged placement is a major risk factor for bacterial colonization and subsequent healthcare-associated infections after transplantation. Sternal surgical site infections occur in 5% to 20% of heart and heart–lung transplant recipients; staphylococci, *Enterobacteriaceae,* and *P. aeruginosa* are the most common causative microorganisms. Sternal surgical site infections may directly extend into the mediastinum and predispose to mediastinitis or mycotic aneurysms at the suture sites. Mediastinitis occurs in 2% to 9% of the heart and heart–lung transplant recipients; *S. aureus, P. aeruginosa,* and *C. albicans* have been the most commonly reported microorganisms *(108–111)*. An unusual cause of mediastinitis in transplant recipients is *Mycoplasma hominis (112)*.

Pancreatic Transplantation

Surgical site infections, abscesses, or urinary tract infections occur in 7% to 50% of the pancreatic transplant recipients *(113–116)*. Organ/space surgical site infections are a significant cause of graft loss and mortality in these patients. The postoperative infection rates and the causative pathogens depend primarily on the technique used for the drainage of exocrine secretions of the pancreas. Enteric drainage (diversion into the small bowel) and bladder drainage are the main approaches used for drainage of exocrine secretions. Infection rates are generally higher with enteric drainage (which facilitates contamination with gastrointestinal bacteria); however, in a recent retrospective review of pancreatic transplant recipients, bladder drainage was associated with higher risk of bacterial infections *(117)*.

Whereas aerobic and anaerobic enteric flora predominates in abscesses associated with enteric drainage, microorganisms in infections in which the viscus has not been opened are usually from the skin flora. *Candida,* however, is a common pathogen in all types of surgical site infections, including those using bladder drainage. A high incidence of *Candida* urinary colonization, because of diabetes in these patients, along with the nonacidic environment in the bladder created by the exocrine pancreatic secretions facilitate *Candida* colonization.

Small-Bowel Transplantation

Unique features predisposing to infections in small-bowel transplant recipients are the fact that the contents of the transplanted organ are nonsterile and that these patients require a higher intensity of immunosuppressive therapy to prevent graft rejection *(118–122)*. Virtually all small-bowel transplant recipients experience at least one episode of infection; the number of infectious episodes per patient may range from 1 to 11 (median, 5) *(119)*. Multivisceral transplant recipients and those undergoing colonic segment transplantation with small-bowel transplantation are more likely to develop infections *(119)*. It is noteworthy that small-bowel transplant recipients remain susceptible to infections, even in the late posttransplant period (i.e., more than 6 months after transplantation) *(119,123)*.

Small-bowel transplant recipients, particularly CMV-seronegative recipients of seropositive grafts, are uniquely vulnerable to CMV infection and to recurrent episodes of CMV disease *(118)*. CMV disease in recipient-negative donor-positive patients has been shown to adversely affect outcome in these patients. Consequently, some transplant centers do not use CMVseropositive small-bowel grafts for CMV-seronegative recipients *(122)*. Notably, a small-bowel graft is involved in 81% to 90% of the patients with CMV disease *(118,122)*.

Bacterial translocation in small-bowel transplant recipients predisposes these patients to intra-abdominal infections (peritonitis and abscesses). Selective decontamination of the gut after transplantation has been proposed to reduce early postoperative infections in small-bowel transplant recipients *(120)*.

TIME TO ONSET

The relative frequency, types of infection, and the specific pathogens encountered after transplantation generally have a predictable time of onset. Thus, infections in transplant recipients must be evaluated in the context of time elapsed since transplantation. These data also have implications relevant for the institution of prophylaxis and the duration of prophylaxis.

Infections During the First 30 Days

Most infections occurring within 30 days of transplantation are a consequence primarily of surgical or technical complications related to transplantation, healthcare-associated acquisition, and rarely reactivation of latent infections (e.g., herpesviruses) in the recipient. Bacterial infections are by far the most frequently occurring infections during this period; vascular catheter-related infections, healthcare-associated pneumonia, *C. difficile* infection, and surgical site infections are the most common types. Fungal infections likely to be encountered in the first month after transplantation include candidiasis and aspergillosis. Nearly 75% of the cases of invasive candidiasis and aspergillosis in liver transplant recipients occur within the first month and virtually all within 2 months of transplantation *(88,124)*. More recently, however, delayed occurrence of *Aspergillus* infections has been noted; 55% of the cases of invasive aspergillosis in liver transplant recipients occurred after 90 days of transplantation *(125)*. Liver transplant recipients are uniquely susceptible to invasive candidiasis; disruption of the integrity of the bowel and gastrointestinal translocation are the proposed mechanisms. The only significant viral infection occurring within the first 30 days of transplantation is that due to the HSV. However, there is accumulating evidence to suggest that HHV-6 may also be a pathogen in the early posttransplant period *(126)*. HHV-6 infection characteristically occurs earlier than CMV and may cause fever of unknown origin and idiopathic cytopenia during this period.

Infections Occurring between 30 and 180 Days

Although healthcare-associated infections may continue to pose a threat in patients requiring prolonged hospitalization, most infections occurring between 30 and 180 days after transplantation are opportunistic infections related to the effects of immunosuppression. The foremost pathogen in transplant recipients during this time period is CMV; however, infections resulting from *M. tuberculosis, P. jirovecii*, *T. gondii*, and *Nocardia* are also likely to be encountered during this interval. Clinically and histopathologically manifest recurrences of HCV hepatitis usually occur within 6 months of transplantation. In the absence of immunoprophylaxis for HBV, recurrence of HBV infections in the recipient occur a median of 3 months after transplantation.

Infections Occurring 6 Months or Later

Infectious diseases in the last posttransplant period are typically community-acquired infections similar to those occurring in the general population. However, patients requiring aggressive immunosuppression for recurrent or chronic rejection and those with poorly functioning allografts (e.g., liver transplant recipients with recurrent viral HBV or HCV) continue to be at risk for opportunistic infections. Posttransplant lymphoproliferative disorder, varicella-zoster virus (VZV) infections, cryptococcosis, and infections resulting from dematiaceous fungi typically occur 6 or more months after transplantation.

VIRAL INFECTIONS

Herpesviruses

Cytomegalovirus CMV has been recognized as one of the most significant pathogens in organ transplant recipients (*127*,*128*,129,*130*). Depending on the pretransplant CMV serostatus of the recipient, three distinct epidemiologic patterns of CMV infection exist. Primary infection occurs when a seronegative recipient acquires CMV, either from the transplanted allograft or less commonly from blood products. Reactivation infection results from endogenous reactivation of the latent virus. Superinfection implies acquisition of a new strain of CMV in a patient seropositive for CMV before transplantation. Because 50% to 70% of the general population is seropositive for CMV, most infections in transplant recipients represent reactivation infections. However, the clinical impact of CMV is by far greatest in the context of newly acquired or primary infection. Primary CMV acquisition is associated with a higher rate of CMV infection and symptomatic disease, earlier onset of CMV infection posttransplantation, higher incidence of recurrence, greater risk of dissemination, and higher mortality *(131,132)*. Symptomatic disease, CMV hepatitis, invasive fungal infections, and death in liver transplantation were more likely to occur when primary infection in the recipient was acquired from the donor organ compared with acquisition from transfusions *(68)*. The time to onset of CMV infection after transplantation is also shorter with donor versus transfusion-associated CMV infection *(68)*. Superinfection, as compared with reactivation infection, is also associated with a higher incidence and severity of symptomatic CMV disease *(133)*.

Risk Factors CMV serologic status of the recipient and donor is the most significant factor influencing the rate and severity of CMV infection. Eighty percent to 100% of the seronegative recipients of a seropositive donor allograft (D+/R–) acquire CMV infection after transplantation. The risk of CMV infection is lowest (<10%) in seronegative recipients of seronegative organ donors. CMV-seropositive recipients have an intermediate risk (40% to 60%) for developing CMV infection. The intensity and type of immunosuppression are also important determinants of the risk of CMV infection *(134)*. Antilymphocyte preparations (e.g., OKT3, thymoglobulin) are extremely potent reactivators of CMV. Primary immunosuppressive agents (e.g., cyclosporine and tacrolimus), on the other hand, are not efficient reactivators, but, when CMV reactivation occurs, they interfere with the host's ability to limit viral replication *(134)*.

Primary infection with HHV-6, which is considered an immunomodulatory virus, has been proposed to be a risk factor for subsequent CMV invasive disease *(135,136)*. Intraoperative hypothermia is a common complication of liver transplant surgery. In a study in liver transplant recipients, intraoperative hypothermia was an independently significant risk factor for early CMV infection and active warming using a convective heating device appeared to curtail this risk *(137)*. Human leukocyte antigen matching and retransplantation have also been shown to be risk factors for CMV infection *(131,138)*.

Pathogenesis CMV-specific major histocompatibility complex (MHC)-restricted cytotoxic T cells are pivotal in host defense against CMV; clinically significant CMV occurs predominantly among patients without an adequate T-lymphocyte response. Humoral immunity, on the other hand, is an ineffective host defense against CMV, although it may modify (or temper) the severity of infection. Tumor necrosis factor-alpha has been shown to be a powerful promoter of CMV *(134,139,140)*. Any physiologic stimulus for tumor necrosis factor-alpha release (e.g., OKT3, sepsis, and rejection), therefore, has the potential to activate CMV.

CMV is considered an immunosuppressive virus that may facilitate superinfection with opportunistic pathogens (e.g., fungi, gram-negative bacteria, and *P. jirovecii*) *(131,141)*. Other indirect sequelae of CMV infection include acute and chronic allograft rejection, bronchiolitis obliterans in lung transplant recipients, atherogenesis in heart transplant recipients, and glomerulopathy in renal transplant recipients.

Epidemiology and Clinical Features The overall incidence of CMV infection ranges between 40% and 90% in organ transplant recipients. Without prophylaxis, the highest incidence of CMV infection has been documented in lung or heart–lung transplant recipients (60–98%) and the lowest (40–50%) in renal transplant recipients. Liver and heart transplant recipients have an intermediate risk of CMV infection (50–67%). The frequency of symptomatic disease resulting from CMV ranges from 8% to 15% in renal, 20% to 35% in liver, 27% to 30% in heart, and 55% to 60% in lung transplant recipients. The incidence of CMV infection in small-bowel transplant recipients approaches that in lung transplant recipients *(118)*. Small-bowel transplant patients also appear to be uniquely susceptible to recurrent episodes of CMV infection *(118)*.

Traditionally, most CMV infections have occurred between 4 and 6 weeks. In patients receiving prolonged antiviral prophylaxis, onset of CMV infection has been noted to be delayed *(142–145)* as antiviral prophylaxis only inhibits viral replication and does not eradicate latent infection. A febrile mononucleosis syndrome characterized by fever, arthralgias, myalgias, leukopenia, and atypical lymphocytosis is the most common symptomatic disease caused by CMV, although localized or disseminated tissue invasive disease may also occur. Predilection to involve the transplanted allograft is a peculiar characteristic of CMV. CMV hepatitis occurs most commonly in liver transplant recipients, CMV pneumonitis occurs most commonly in lung transplant recipients, and CMV enteritis occurs most commonly in small-bowel transplant recipients. It is proposed that the transplanted allograft may provide a sequestered site for latently infected cells, because MHC mismatches at these sites may prevent the generation of virus-specific cytotoxic T-cell responses *(146)*.

Diagnosis The diagnosis of CMV infection has traditionally been made by viral isolation. These culture-based assays are considered obsolete because of their low sensitivity and time-consuming nature. Conventional cultures take up to 4 weeks. The shell vial assay uses a monoclonal antibody to detect a 72-kDa immediate early CMV antigen and allows detection of CMV within 16 to 24 hours *(147)*. The currently available tests not only allow rapid and reliable diagnosis of CMV infection but also may detect viral shedding at an earlier stage. The pp65 antigenemia assay detects CMV-infected leukocytes with monoclonal antibodies directed against the 65-kDa lower matrix phosphoprotein *(148,149)*. The CMV antigenemia assay is more sensitive and allows earlier detection of CMV than shell vial culture does. Furthermore, results of the antigenemia assay can be quantitated; the number of antigen-positive cells has been shown to correlate with the likelihood of CMV disease and can also be used to monitor response to antiviral therapy. The major drawback of the antigenemia assay is the need for immediate processing of blood samples. Detection of viral DNA by PCR in the plasma or whole blood is also very sensitive for the diagnosis of CMV, and it has been considered the gold standard given its high sensitivity and rapid turnover time. Although the PCR assays are not fully standardized, they have emerged as the preferred diagnostic tests for CMV.

Prevention

Matching Donors and Recipients by Serologic Status Attempts to decrease the morbidity associated with primary donor-acquired CMV infection have included the use of CMV-seropositive donor organs only for seropositive recipients. Although a decrease in graft loss and mortality attributable to CMV was noted in one report *(150)*, others have not shown a significant impact with such an approach. Widespread adoption of this approach, however, is not feasible given the limited organ donor pool.

Prophylaxis Two approaches exist for CMV prophylaxis: universal prophylaxis and preemptive therapy (129). Universal prophylaxis requires administration of antiviral prophylaxis to all organ transplant recipients except for seronegative recipients from seronegative donors for typically 3 to 6 months. The advantage of this strategy includes relatively easy implementation and favorable effects on "indirect effects" such as rejection and opportunistic infections; however, drug costs, their adverse effects, late-onset disease, and emergence of drug-resistant CMV may be potential issues *(3,142,151,152)*. Preemptive therapy requires periodic monitoring of CMV replication for early identification of CMV infection with prompt treatment to prevent asymptomatic infection from progressing to CMV disease. It decreases the cost and adverse effects; however, continuous CMV monitoring can be logistically difficult and viral load thresholds for initiating antiviral therapy have not been precisely defined. Preemptive therapy is typically administered until resolution of CMV viremia. Both strategies are efficacious to reduce the rate of CMV disease *(153,154)*, although superiority of one approach over the other has not been incontrovertibly documented. Although not approved for use in liver transplant recipients, valganciclovir is the most commonly used antiviral agents for prophylaxis of CMV.

Herpes Simplex Virus HSV infections in transplant recipients present as mucocutaneous lesions resulting from reactivation of the latent virus. However, visceral or disseminated HSV infection can be donor-transmitted and may have a fulminant presentation with a grave outcome without antiviral therapy. HSV hepatitis is the most frequently documented site of disseminated HSV infection; its incidence (cases per thousand) is reported to be 2.11 in renal, 2.23 in heart, and 4.81 in liver transplant recipients. In a report comprising 12 cases of HSV hepatitis in solid organ transplant recipients, 33% were due to primary HSV infection believed to be acquired from the donor *(155)*. The median time to onset of HSV hepatitis was 18 days, although it occurred as early as 5 days posttransplantation *(155)*. This characteristic time of onset is in contrast with CMV hepatitis, which usually occurs 30 to 40 days after transplantation. Clinical manifestations of HSV hepatitis include fever, leukocytosis, thrombocytopenia, and marked elevation of hepatocellular enzymes. Mortality from primary visceral HSV infection in seronegative recipients was 75%; hypotension, disseminated intravascular coagulation, metabolic acidosis, low platelet count, and high creatinine were significant predictors of mortality *(155)*.

HSV accounted for 41% of all non-CMV isolates from the respiratory tract in lung transplant recipients; 80% of the isolates were deemed clinically significant and were associated with pneumonitis *(156)*. Another clinical presentation of HSV, predominantly reported in intubated lung and cardiac transplant recipients, is HSV tracheobronchitis that manifested as fever, bronchospasm, leukocytosis, and difficulty weaning. Paradoxically, HSV tracheobronchitis had a more severe presentation and worse outcome in immunocompetent compared with immunosuppressed patients *(157)*. It was proposed that this may be due to a more exuberant local immune response in the immunocompetent patients *(157)*.

Low-dose acyclovir (200–400 mg orally three times daily) generally used for a month posttransplant is highly effective as prophylaxis for HSV in transplant recipients *(158)*. At one institution, HSV hepatitis was documented

in 12 of 3,536 solid organ transplant recipients before the routine use of acyclovir prophylaxis and in none of the 1,144 patients since the use of acyclovir prophylaxis *(155)*. Longer duration of acyclovir can be considered for organ recipients who develop frequent recurrences of HSV lesions.

Varicella-Zoster Virus Up to 70% of the pediatric and 5% of the adult transplant recipients have been reported to be seronegative for VZV *(159,160)*. Exposure to VZV infection may result in primary varicella in these susceptible patients. Donor-derived primary varicella infection was also reported in a cardiac transplant recipient whose donor suffered from varicella 2 weeks prior to transplant *(34)*. Median time to onset of varicella was 2 years after transplantation in one report *(160)* and 2.4 years in another *(161)*. Visceral dissemination, frequently documented in transplant recipients, is the primary cause of mortality in patients with VZV. Hepatitis, pneumonitis, pancreatitis, gastroenteritis, or meningoencephalitis are the most commonly documented sites of visceral dissemination. Varicella may initially present with acute abdominal pain, and in the absence of skin lesions can defy early recognition. It is notable that up to 16% to 18% of the pediatric transplant recipients may have recurrent varicella infections *(161,162)*.

All transplant candidates susceptible to VZV should receive varicella vaccination prior to transplantation. Varicella-zoster immunoglobulin (VZIG) is recommended for susceptible transplant recipients exposed to varicella within 96 hours. VZIG, however, is not entirely protective; in up to one third of the patients with varicella, lesions have occurred despite VZIG prophylaxis. Since the production of VZIG was discontinued, VariZIG is the only immunoglobulin currently available in the United States under an investigational new drug application. Exposed susceptible organ recipients should be isolated in Airborne and Contact Precautions from day 10 to day 21 (day 28 if receiving VZIG or VariZIG) to decrease the risk of transmission to other susceptible patients. Some centers use high-dose oral acyclovir or valacyclovir for the duration of the incubation period of varicella (i.e., 2–3 weeks after exposure of susceptible patients to varicella). Use of varicella vaccine is not recommended in transplant recipients *(163)* (see also Chapter 43).

Human Herpesvirus-6 HHV-6 is a large double-stranded DNA virus that is antigenically distinct from other human herpesviruses. Its closest phylogenetic relative is CMV; nucleotide sequencing has revealed 66% DNA homology between CMV and HHV-6. On the basis of genomic DNA sequences, cell tropism, and protein expression, two distinct variants of HHV-6, designated as variant A and variant B, have been described *(164,165)*. The two variants differ in virulence; the HHV-6A variant is intrinsically more virulent and neurotropic than the HHV-6B variant *(126)*. Most infections in transplant recipients are due to the HHV-6B variant *(126)*.

Most HHV-6 infections are believed to result from endogenous reactivation of the recipient's latent virus; however, donor transmission has also been documented. Although the precise incidence and clinical sequelae of HHV-6 infection after transplantation remain to be fully elucidated, HHV-6 infection has been reported in 31% to 55% of solid transplant recipients *(126)*. The usual timing of onset is between 2 and 4 weeks posttransplantation. Bone marrow suppression, interstitial pneumonia, encephalopathy, and fever of unknown origin are the most commonly reported clinical manifestations of HHV-6 *(126,166–168)*. Diagnosis for acute or reactivation infection is based on the detection of viral nucleic acids by polymerase chain reaction (PCR) in noncellular samples such as serum or plasma. It is worth noting that PCR can detect latent HHV-6 in peripheral blood mononuclear cells or chromosomally integrated HHV-6. The antiviral susceptibilities of HHV-6 resemble those of CMV *(169–171)*. HHV-6 is sensitive to both ganciclovir and foscarnet and resistant to acyclovir at achievable serum concentrations. The role of prophylaxis for HHV-6 has not yet been fully discerned. Active HHV-6 infection does not require antiviral treatment except for patients with encephalitis and other tissue-invasive diseases.

Hepatotropic Viruses

Hepatitis C Virus End-stage liver disease resulting from HCV has been documented in up to 50% of the patients undergoing liver transplantation in recent years. Up to 95% of the patients with pretransplant HCV infection remain viremic after transplantation, as demonstrated by the presence of HCV RNA in the blood. Clinically and histologically manifest recurrence occurs in 30% to 70% of patients with pretransplant HCV, generally within 1 to 12 months after transplantation *(172–174)*. Progression to cirrhosis has been observed in 15% to 20% of patients 1 to 3 years after initial transplantation. Despite significant morbidity associated with HCV, survival rates in patients with and without HCV recurrence have not been different *(173)*.

The prevalence of HCV positivity in hemodialysis patients ranges between 5% and 54% *(175)*. The number of blood units transfused, the duration of hemodialysis, and the type of dialysis (hemodialysis as opposed to peritoneal dialysis) correlated with a higher incidence of HCV infection in renal transplant candidates *(175–177)*. After transplantation, chronic liver disease has been reported in 10% to 60% of renal transplant recipients and occurred significantly more frequently in patients with HCV compared with those without HCV *(176–178)*. Earlier studies showed pretransplant HCV infection did not adversely affect the graft or patient survival after renal transplantation *(178,179)*; however, a more recent study suggested that pretransplant HCV infection was independently associated with patient and graft survivals *(180)*.

Although most posttransplant HCV infections are due to recurrence of pretransplant HCV, *de novo* infections resulting from acquisition from the donor organ or transfused blood products have been reported. A 35% rate of acquired HCV-RNA infection was reported in 89 liver transplant recipients, most of whom were transplanted before the routine screening of blood products for anti-HCV *(172)*. Routine screening of blood products has led to a significantly lower acquisition rate of HCV (i.e., 2.5–4%). HCV has also been transmitted by organs from anti-HCV–positive donors (see the section "Sources

of Infections in Recipients"). HCV infection is also considered a significant risk to the personnel involved in the care of HCV-infected transplant patients. The seroprevalence of HCV (7%) in healthcare workers directly involved in the care of liver transplant patients was significantly higher when compared with those not associated with liver transplantation (0.5%) or in volunteer blood donors (0.3%) *(181)*. None of the transplant personnel had hepatitis or a history of transfusion *(181)*. The risk of acquiring HCV after needle stick injuries may be as high as 10%. Serum immunoglobulin is not protective against HCV and is not recommended (also see Chapter 73).

A number of variables are believed to influence the rate and severity of recurrent HCV hepatitis after transplantation, including the level of pretransplant viremia, genotype of the virus, and the intensity of posttransplant immunosuppression *(173,182,183)*. HCV genotype 1b has been associated with more severe recurrent HCV infection after liver transplantation *(173)*.

Corticosteroids have been shown to result in a several fold increase in the HCV-RNA level. Finally, allograft rejection and steroid-resistant rejection requiring lymphocyte-depleting agents can lead to a higher incidence and earlier onset of recurrent HCV hepatitis after liver transplantation *(183,184)*.

Effective prophylaxis against HCV in transplant recipients is not available. It has been shown that polyclonal immunoglobulin preparations against HBsAg administered to liver transplant patients for HBV were also protective against HCV *(185)*. Among the patients who had HCV infection before transplantation, the incidence of HCV viremia after transplantation in the patients receiving HBIG was significantly lower than in those who did not receive HBIG (54% vs. 94%, $p = .001$). This protective effect may have been due to the presence of anti-HCV in HBIG *(185)*. Prophylaxis with interferon-alpha, administered for 6 months posttransplantation in liver transplant recipients, delayed the occurrence of HCV but decreased neither the incidence nor the severity of recurrent HCV hepatitis *(186)*. The majority of liver transplant recipients receiving posttransplant antiviral therapy with pegylated interferon alfa-2b and ribavirin developed adverse effects *(187)*, and this approach was not practical. Nonhepatic organ transplant candidates with chronic hepatitis C infection should undergo evaluation (i.e., liver biopsy) for therapy prior to transplant *(13)*.

Hepatitis B Virus

The clinical impact of HBV is of greatest importance in the context of liver and renal transplantation. In studies in which long-term immunoprophylaxis was not used, the reinfection rate of the hepatic allograft with HBV was virtually 100% with progression to liver failure and death in as little as 2 to 2.5 years. Anti-HBs immunoprophylaxis has significantly altered the natural history of HBV after liver transplantation. In a large study assessing the outcome in HBsAg-positive patients undergoing liver transplantation for HBV-related cirrhosis, the overall risk of HBV recurrence after 3 years was 67% (188). HBV recurrence was documented a mean of 3 months posttransplant in 78% to 90% of patients who did not receive long-term immunoprophylaxis; recurrence was significantly less (56%) and delayed, occurring a mean of 8 months posttransplant, in patients receiving long-term anti-HBs immunoprophylaxis (188). HBV adversely affects graft and patient survival; survival at 3 years was 54% in patients with HBV recurrence and 83% in those who remained HBsAg negative after transplantation (188).

Several factors influence the recurrence of HBV after transplantation. The risk of recurrence is greater for patients with markers for active replication of HBV before transplantation (e.g., those seropositive for HBeAg or HBV DNA) (188,*189*). The risk of HBV recurrence was 83%± 6% in liver transplant recipients seropositive for HBV DNA compared with 58% ± 7% in those with neither HBV DNA nor HBeAg detectable at the time of transplantation (188). Fulminant HBV (as opposed to chronic HBV infection) is associated with a lower rate of recurrence. Recurrence was observed in 17% of patients with fulminant HBV compared with 67% in those with chronic HBV cirrhosis (188). Patients with fulminant HBV tend to have lower levels of HBV DNA or replicative HBV. Coinfection with hepatitis delta virus decreases the risk of recurrence in HBV infection after transplantation (188). Delta virus is a naturally occurring inhibitor of HBV replication, and hence, HBV DNA levels in delta virus coinfected patients are lower.

Strains of HBV that fail to produce HBeAg because of mutations in the precore region of the HBV genome (also known as precore mutants or HBeAg-deficient mutants) have been identified *(190)*. Such patients have high levels of viral DNA in the absence of HBeAg. Patients infected with the precore mutants pretransplant, as opposed to the wild-type virus, have a greater risk of hepatic graft loss resulting from early recurrence *(190)*.

A unique and particularly aggressive syndrome of recurrent HBV infection observed in 12% to 20% of patients with HBV recurrence is fibrosing cholestatic hepatitis, characterized by marked cholestasis and hypoprothrombinemia but only modest increases in serum transaminases *(191)*. Fibrosing cholestatic hepatitis is more likely to occur in patients with pretransplant HBV replication and results in rapid death in almost all cases. A paucity of inflammatory response in this syndrome suggests that the virus may be directly cytopathic.

HBV infection also follows an aggressive clinical course after renal transplantation. Progression of liver disease to cirrhosis and death, however, occurs considerably later than in liver transplantation (i.e., 6–8 years after transplantation). Chronic active or persistent hepatitis occurred in 76% of HBsAg-positive patients undergoing renal transplantation compared with 31% in HBsAg-negative patients.

The most effective approach to prevent recurrent HBV in high-risk patients is the use of combination therapy with antiviral agents and HBIG in addition to pretransplant antiviral therapy. Prophylaxis with the use of lamivudine monotherapy is not recommended because of the reappearance of HBsAg after liver transplantation in 32% to 50% of the patients. Combination therapy with HBIG and lamivudine prevents HBV recurrence in more than 90% of the patients undergoing liver transplantation for HBV (192,*193*). Newer antiviral agents including adefovir dipivoxil, tenofovir, and entecavir have also been available for lamivudine-resistant HBV. Discontinuation or tapering of HBIG may be considered in low-risk patients (i.e., undetectable HBV DNA at the time of transplant). Periodic monitoring of HBsAg and HBV DNA is also critical for early detection of recurrent graft infection.

Other Viruses

BK Virus BK virus (BKV) has emerged as a significant pathogen in renal transplant recipients. BKV is a polyomavirus that is acquired during childhood. Renal and uroepithelial cells are the main sites of latency. Seroprevalence rates in the general population range from 70% to 90%. BKV-induced nephropathy has been reported in 1% to 10% of the renal transplant recipients with allograft loss occurring in nearly half of those patients *(194,195)*. This entity was encountered only rarely before the mid-1990s. Although precise reasons for the emergence of BKV as a significant pathogen are unclear, use of novel, more potent immunosuppressive agents (e.g., tacrolimus, mycophenolate mofetil, and sirolimus) is considered to play a role. Donor transmission has been reported; however, most cases of BKV nephropathy occur as a result of reactivation of the latent virus.

The usual time to onset of BKV nephropathy is 28 to 40 weeks posttransplantation. Its typical manifestations resemble those of acute rejection and include a modest rise in creatinine that fails to respond to antirejection therapy. The hallmark of BKV replication is decoy cells, which are urinary epithelial cells bearing ground-glass intranuclear inclusions. Decoy cells, however, lack sensitivity and specificity for the diagnosis. Screening for BKV replication in urine should be performed at least quarterly (ideally monthly) during the first 2 years and whenever renal dysfunction occurs *(194,196)*, followed by quantitative plasma PCR for BKV if viuria is detected. Some centers use plasma PCR for screening. Patients with sustained high-degree BKV viremia should undergo allograft renal biopsy to guide further therapy. The mainstay of therapy is judicious reduction of immunosuppression, but may not always be successful. Specific antiviral therapy for BKV is not available; however, cidofovir, fluoroquinolones, IVIG, and leflunomide have been used anecdotally. Given the high seroprevalence in the general population, specific infection control measures are not deemed necessary.

Adenovirus Adenovirus infections have been documented in up to 10% of the pediatric and 1% to 15% of adult transplant recipients *(197–200)*. Symptomatic disease is more common and generally more severe in pediatric compared with adult patients after transplantation; 60% of the children and 27% of the adult transplant recipients with adenoviral shedding have been shown to have disease resulting from adenovirus *(197–199)*. The precise mode of transmission of adenovirus infections has not been determined, although both donor transmission and healthcare-associated transmission have been proposed to occur *(197–199)*. In pediatric liver transplant recipients, most severe disease occurred in seronegative children *(198)*, and donor serology was positive in five of six patients evaluated, suggesting that donor transmission is a likely source of infection. Healthcare-associated acquisition is also a consideration, because several patients with the similar adenovirus strains were found temporally clustered in one report *(197)*. Accordingly, Contact and Droplet Precautions as well as disinfection of environment are strongly advised.

Adenovirus infection typically occurs in the donor allograft. Hepatitis in liver transplant recipients, pneumonitis in lung transplant recipients, and hemorrhagic cystitis in renal transplant recipients are the most common invasive forms of adenovirus disease. Serotypes 5 and 11 were the most frequent serotypes causing hepatitis and hemorrhagic cystitis, respectively, in transplant recipients. Diagnosis is suggested by the detection of microabscesses with smudgy intranuclear targeted inclusions in histopathologic specimens *(201)*. Immunohistochemistry and culture can be used to confirm adenovirus infection. Reduction of immunosuppression and supportive care are the critical parts of treatment. No antiviral agents have been studied in controlled trials; however, cidofovir has been used for severe adenovirus infections in solid organ transplant recipients *(202,203)*.

Respiratory Viruses The impact of respiratory viral infections (e.g., respiratory syncytial virus [RSV], influenza, parainfluenza virus, human metapneumovirus [hMPV]) has been recognized in solid organ transplant recipients (204). Although clinical manifestations are similar to those in immunocompetent patients, progression from upper tract infection to lower tract infection is relatively rapid, and respiratory viral infections are associated with allograft rejection in lung transplant recipients *(205,206)*. In a case–control study of 100 lung transplant recipients, 8 of 50 (16%) patients with respiratory tract infections developed acute rejection, whereas none of 50 patients without respiratory tract infections developed acute rejection *(206)*. Early diagnosis and prompt initiation of treatment (if available) are the key to prevent allograft damage. Organ transplant recipients with respiratory symptoms especially in the early posttransplant period should have a nasal swab and/or bronchoscopic aspirate sent for viral culture, rapid antigen testing (RSV, influenza), and PCR-based assays *(207)*. Treatment consists of general supportive care and prompt initiation of antiviral agents if available. In a multicenter study of influenza A H1N1 infection in solid organ transplant recipients, early administration (within 48 hours of symptom onset) of antiviral agents was associated with a decrease in admission to hospital and ICU, need for mechanical ventilation, and death (*207a*). Although the duration of treatment with antiviral agents for influenza is typically 5 days in general population, some experts recommend continuation of antiviral agents until patients stop shedding virus from their respiratory secretion *(207,208)*. Aerosolized ribavirin with antibody-based therapy such as IVIG and palivizumab are recommended for treatment of severe RSV infection based on experience in hematopoietic cell transplant recipients *(209,210)*. Vaccination is the most effective method for prophylaxis; however, it is only available against influenza in the form of trivalent inactivated vaccine or live attenuated influenza vaccine. Organ transplant recipients should not receive live attenuated influenza vaccine given the potential safety concern *(211)*. Antiviral chemoprophylaxis may also be considered as alternative.

BACTERIAL INFECTIONS

Staphylococci

Staphylococci, particularly *S. aureus*, are increasingly recognized as pathogens in transplant recipients and have emerged as the leading cause of bacterial infections in liver, heart, kidney, and pancreatic transplant recipients at many centers *(212–216)*. This increase largely parallels

the more widespread rise in gram-positive infections in the healthcare-associated setting in recent years. Forty-nine percent of the bacteremias in liver transplant recipients in one report were due to *S. aureus (215)*. Although intravascular catheters, accounting for 54% of all MRSA bacteremias, were the predominant source, wound infections, healthcare-associated pneumonia, intraabdominal abscess, and peritonitis were also documented as sources of MRSA bacteremia *(215)*. Over one-half of the *S. aureus* infections occur in the intensive care unit setting *(215)*. Requirement of invasive procedures, mechanical ventilation, continuous need for intravenous access, and overall debilitated condition of the patients in the intensive care unit provide conditions conducive to the development of healthcare-associated *S. aureus* infections. *S. aureus* infections generally occur very early after transplantation. In a study in liver transplant recipients, nearly one third of such infections occurred within the first week of transplantation; the median time to onset was 16 days (39). *S. aureus* is also the most frequent cause of endocarditis in organ transplant recipients *(216)*. Notably, 74% of the cases of endocarditis were associated with previous hospital-acquired infection, especially venous access device and wound infections *(216)*.

S. aureus colonization of the anterior nares has been shown to be a significant predictor of infections resulting from *S. aureus* in liver transplant patients *(80)*. Overall, nasal carriage was documented in 67% of the patients; infected patients were significantly more likely to be nasal carriers of *S. aureus* compared with the noninfected patients. Pulsefield gel electrophoresis documented that the isolates causing infections matched the isolates from the anterior nares in all cases *(80)*. Furthermore, 43% of infected patients shared the isolates with the same restriction pattern, indicating cross-transmission in the healthcare-associated setting *(80)*. Eradication of nasal carriage by mupirocin, however, has not been shown to prevent *S. aureus* infections in liver transplant recipients *(217)*. Although 87% of the colonized patients were successfully decolonized, recolonization occurred in 37% *(217)*. Healthcare-associated transmission leading to exogenous colonization and colonization at nonnasal sites unaffected by nasal administration of mupirocin likely accounted for the failure of mupirocin to decrease *S. aureus* infections *(217)*. Recently, an active surveillance program using nasal and rectal swabs for cultures in the peritransplant period followed by targeted infection control interventions including isolation precautions and cohorting of patients colonized with *S. aureus* were shown to be effective in reducing new acquisition of *S. aureus* and infection in liver transplant recipients (218).

Enterococci

Enterococci, which are normal inhabitants of the gastrointestinal tract, are of greatest relevance in liver transplant recipients. Most enterococcal bacteremias in these patients result from complications related to the biliary tree. Roux-en-Y choledochojejunostomy (which facilitates reflux of enteric bacteria into the biliary tree) and biliary strictures have been shown to be independent risk factors for enterococcal bacteremia after liver transplantation *(219)*.

VRE have emerged as healthcare-associated pathogens of grave concern, particularly after liver transplantation. VRE infections were documented in 11% to 16% of the liver transplant recipients *(220–222)*. Notably, VRE was the most frequently isolated pathogen in infected liver transplant recipients in one study *(221)*. Infections were documented a median of 10 to 42 days after transplantation *(220,221)*. Intra-abdominal infections and catheter-related infections were the frequent sites of VRE infection. VRE fecal carriage before transplantation; previous antibiotic use (vancomycin); biliary complications; prolonged hospitalization and intensive care unit stay; surgical reexploration; surgical complications during transplantation, including hypotension; and primary nonfunction of the allograft have been identified as significant risk factors for VRE infections *(220,221,223,224)*. Mortality in the infected patients ranges between 16% and 50%. Intensive care unit stay before transplantation, hemodialysis, liver failure, and shock have been shown to be independent predictors of mortality in patients with VRE infections *(221,224)*. Treatment consists of removal or debridement of infected sources and antibiotics (i.e., daptomycin, linezolid, quinupristin-dalfopristin, tigecycline) effective against VRE.

VRE colonization once established is often a persistent event; spontaneous conversion to VRE-negative carriage is uncommon. In liver transplant recipients, 18% of recipients who were not colonized with VRE acquired VRE within a mean of 12 days posttransplant (225). These patients, therefore, remain at risk for invasive infections and a threat for healthcare-associated transmission (225). A variety of gut decontamination regimens have been tried; however, none have been shown to be consistently effective. Consequently, infection control practices to prevent healthcare-associated acquisition and cross-transmission and judicious use of antimicrobial agents, particularly vancomycin, are critically important in curtailing VRE infections (see also Chapter 33).

Mycobacterium tuberculosis

The incidence of tuberculosis in solid organ transplant patients ranges from 0.35% to 5% in the United States and Europe *(226–228)*. However, in highly endemic areas (e.g., India and Pakistan), tuberculosis may develop in 5% to 15% of the transplant patients. The median time to onset after transplantation is 9 months and ranges from 0.5 to 144 months *(226,228)*. Tuberculosis occurs significantly later after transplantation in renal compared with nonrenal transplant recipients. Disseminated disease occurs in nearly one-third of the transplant recipients with tuberculosis *(226)*. The gastrointestinal tract is the most frequent extrapulmonary site of tuberculosis in transplant recipients. Other reported extrapulmonary sites of involvement include the skin and osteoarticular tissue, central nervous system, kidneys, and urogenital tract.

Tuberculin reactivity has been documented in 20% of the transplant recipients with tuberculosis, and chest radiographs with evidence of old active tuberculosis were documented in 12% of the patients *(226)*. These patients are more likely to develop tuberculosis earlier after transplantation than those without a history of tuberculin reactivity or abnormal chest radiograph before transplantation. Most tuberculosis infections in transplant recipients represent reactivation of old dormant disease. However, healthcare-associated acquisition and donor transmission are also well-documented modes of transmission. Tuberculosis has

been shown to be transmitted both by living and cadaveric organ donors. Tuberculosis, involving the renal allograft, was documented 35 and 39 days after renal transplantation in two recipients of the same donor who died of hypoglycorrhachic lymphocytic meningitis of unknown etiology; the donor's cerebrospinal fluid culture was positive for *M. tuberculosis* 3 weeks after death *(47)*. One renal allograft recipient of this donor died of disseminated tuberculosis, whereas the second recovered, although rejection secondary to antituberculosis therapy necessitated allograft nephrectomy *(47)*. Two recipients of a single-lung transplant from a common donor had the same *M. tuberculosis* isolate as demonstrated by restriction fragment length polymorphism *(229)*. Tuberculosis involving a hepatic allograft was documented in a pediatric transplant recipient who received a living related lateral segment hepatic allograft from the mother *(230)*. Pulmonary tuberculosis was detected concomitantly in the mother who was apparently asymptomatic at the time of donation of the hepatic segmental graft.

A healthcare-associated outbreak involving 10 renal transplant patients was documented from one institution; eight of these cases were clustered within a 5-month period *(7)*. The source case was a renal transplant recipient who was exposed to tuberculosis at another hospital. Tuberculosis was not suspected in the source case on admission, thus delaying the isolation precautions. Restriction fragment length polymorphism documented transmission of *M. tuberculosis* from the index case to five renal transplant recipients. The median incubation period for tuberculosis in this outbreak was only 7.5 weeks, and death occurred in 5 of 10 patients a median of 8 weeks after diagnosis *(7)*. It is noteworthy that the exposed transplant recipients were more likely to contract tuberculosis compared with the nontransplant contacts of the source case *(7)*. Overall mortality in organ transplant recipients with tuberculosis is approximately 30% *(226)*. Disseminated compared with localized tuberculosis, prior rejection, and OKT3 receipt were significant predictors of mortality in transplant recipients with tuberculosis.

All transplant recipients should have a tuberculin skin test administered before transplantation unless they had a history of tuberculosis or previous positive test (231,*232*). Isoniazid prophylaxis should be considered for the transplant recipients with the characteristics outlined in Table 58-3 regardless of the tuberculin skin test reactivity. Isoniazid chemoprophylaxis initiated during liver transplant candidacy was safe and effective in one study *(233)*. Rifampin is alternative to isoniazid; however, its interaction with calcineurin inhibitors usually precludes its use posttransplant *(234)*. Other reports recommend that chemoprophylaxis for latent tuberculosis be deferred until after transplantation. Tuberculin skin test reactivity *per se* is a controversial indication for prophylaxis in transplant recipients. The rate of tuberculosis among skin-test positive liver transplant candidates and recipients who receive no chemoprophylaxis has been estimated to be 1,585.3 cases per 1,000,000 person-years *(235)*. Tuberculosis has been documented in up to 2% of the tuberculin skin-test–negative liver transplant recipients *(236)*. It has been proposed that clinical or radiographic evidence of previous tuberculosis may more reliably identify high-risk patients as compared with the tuberculin skin test result. Although the interferon-gamma release assay has been used as an alternative in immunocompetent patients *(237)*, its utility in solid organ transplant recipients has not been tested extensively.

TABLE 58-3

Indications for Chemoprophylaxis with Isoniazid in Organ Transplant Recipients

I. Tuberculin skin reactivity ≥5 mm before transplantation
II. Patients with the following characteristics, regardless of tuberculin skin test reactivity:
    1. Radiographic evidence of old active tuberculosis and no prior prophylaxis
    2. Prior history of inadequately treated tuberculosis
    3. Close contact with an infectious case
    4. Receipt of an allograft from a donor with a history of tuberculosis or tuberculin reactivity
III. Newly infected persons (recent tuberculin skin test converters)

Legionella

Legionellosis has been reported in 2% to 9% of solid organ transplant recipients with pneumonia; however, at certain institutions, 25% to 38% of the bacterial pneumonias have been due to *Legionella (5). Legionella pneumophila* and *Legionella micdadei* are the most common species implicated; however, *Legionella bozemanii*, *Legionella birminghamensis*, *Legionella dumoffii*, and *Legionella cincinnatiensis* have also caused infections in transplant recipients.

Inhalation of aerosols containing *Legionella* has been proposed as the mode of transmission for this microorganism. However, aspiration of water contaminated with *Legionella* is considered the most likely and underrecognized mode of transmission *(238,239)* and *Legionella*-contaminated potable water distribution systems as the predominant source of legionellosis *(5)*. Molecular fingerprinting methods have linked *L. pneumophila* infection in transplant recipients to hospital drinking water *(240)*. Ice machines *(71)* and ultrasonic humidifiers *(241)* have also been shown to be the sources of *Legionella* infection after transplantation. Pneumonia is the predominant clinical manifestation of legionellosis, although pericarditis, necrotizing cellulitis, peritonitis, hepatic allograft infection, and hemodialysis fistula infections have been reported after transplantation *(5)*. Nodular pulmonary densities and cavitation (reported in 50–70% of the pulmonary infections in some reports) are characteristic radiographic features but may not be invariably present. *Legionella* are fastidious microorganisms that do not grow on standard bacteriologic media. Selective media containing dyes and antimicrobial agents are needed for optimal growth. Urinary antigen is both sensitive and specific for the detection of *Legionella* and may also be diagnostically useful for detecting *Legionella* in body fluids (e.g., pleural fluids).

It is recommended that hospitals performing large numbers of transplants should routinely culture the hospital water supply for *Legionella,* perhaps once a year (*242*,243). If such cultures are positive, specialized *Legionella* laboratory tests, especially culture on selective media and urinary antigen tests, should be made routinely available

in the clinical microbiology laboratory. Two disinfection methods for the water supply have emerged as cost effective: superheating the water to 70°C and flushing the distal outlets or the installation of copper–silver ionization units *(244)*. Hyperchlorination is no longer recommended because of the expense, erratic efficacy, corrosive damage to the piping, and the carcinogenic potential of ingested chlorine (see also Chapter 36).

Nocardia

Infections resulting from *Nocardia* species may occur in 0.6% to 4% of organ transplant recipients; the median time to the onset of nocardiosis after transplantation ranges between 2 and 8 months. Nocardiosis most commonly occurs in lung transplant recipients; the incidence was up to 3.5% in a recent large single-center study *(245)*. Pulmonary disease is the most common manifestation and central nervous system involvement occurs in 17% to 38% of these patients. Brain abscesses are usually multiple; meningitis is rare and usually associated with an abscess. An important clue to central nervous system nocardiosis is concomitant skin or subcutaneous lesions from which *Nocardia* species can be readily isolated.

Nocardia is a soil microorganism whose primary portal of entry is the lung. There is evidence to suggest that healthcare-associated transmission of nocardiosis may occur *(246–252)*. Cases of *Nocardia* infection clustered in time have been reported in renal transplant units. An epidemic strain of *Nocardia* common to the infected patients and environmental dust samples from the unit housing the patients but distinct from environmental isolates elsewhere in the hospital was documented to cause seven infections in a renal transplant and dialysis unit *(252)*. Respiratory isolation of the cases of nocardiosis during outbreaks has been recommended by some *(249,252)*. There was an outbreak of *N. farcinica* surgical site infection that was traced to a colonized anesthesiologist *(247)*. Trimethoprim-sulfamethoxazole used as prophylaxis for PJP is also effective against nocardiosis; however, breakthrough infections particularly among solid organ recipients receiving low-dose trimethoprim-sulfamethoxazole have been reported *(245)*.

FUNGAL INFECTIONS

Aspergillus

Invasive aspergillosis remains a devastating fungal infection in all types of transplant recipients (253,*254*). It has, however, unique clinical characteristics and risk factors in different types of solid organ transplant recipients.

Epidemiology

Lung Transplantation Lung transplant recipients are more likely than other solid organ recipients to develop infection with *Aspergillus*. Up to 23% of lung transplant recipients develop invasive aspergillosis *(255)*. Risk factors for *Aspergillus* infection after lung transplantation include CMV infection, single-lung transplantation *(256)*, relative ischemia at the anastomosis *(257)*, hypogammaglobulinemia *(258)*, colonization of the airways with *Aspergillus (259,260)*, and placement of a bronchial stent *(261)*. Most cases of invasive aspergillosis in lung transplant recipients occur within the first 9 months posttransplantation. A unique form of invasive aspergillosis occurring in lung transplant recipients is ulcerative tracheobronchitis, which usually occurs in the first 2 to 3 months.

Liver Transplantation The incidence of invasive aspergillosis in liver transplant recipients ranges from 1% to 8% *(254,262–265)*. The infection was most often diagnosed between 2 and 4 weeks after transplantation; however, it has recently been shown that the infection occurs in the late posttransplant period *(125)*. Indeed, 55% of the infections now occur after 90 days of transplantation. Advance in surgical technique, antifungal prophylaxis practice, and delayed onset of CMV infection are proposed as possible explanations. A poorly functioning hepatic allograft and renal insufficiency, particularly the requirement for hemodialysis, are considered important risk factors for invasive aspergillosis in liver transplant recipients. Approximately 25% of the cases of invasive aspergillosis in liver transplant recipients occur after retransplantation *(263)*. Rarely, the *Aspergillus* infection is confined to the surgical site (producing necrotizing fasciitis) or intra-abdominal sites in liver transplant recipients.

Heart Transplantation Invasive aspergillosis occurs in 1% to 14% of heart transplant recipients *(266)*. The median time to development of invasive aspergillosis in these patients is 1 to 2 months. Most infections originate in the lungs, and 20% to 35% disseminate to other organs.

Renal Transplantation Invasive aspergillosis has been reported in 0.7% to 4% of the patients undergoing renal transplantation *(266–268)*. Cases of invasive aspergillosis in renal transplant recipients have usually been pulmonary infections and occasionally disseminated disease. Augmented immunosuppression and graft failure requiring hemodialysis are risk factors for invasive aspergillosis in renal transplant recipients.

Diagnosis Early diagnosis is critically important in reducing the mortality from invasive aspergillosis. *Aspergillus* can be cultured from sputum in only 8% to 34% and from bronchoalveolar lavage fluid in 45% to 62% of patients with invasive pulmonary aspergillosis *(269)*. Respiratory cultures, therefore, may not detect aspergillosis before significant vascular invasion has occurred. Furthermore, a positive culture with *Aspergillus* may indicate colonization. Serum galactomannan assay, however, may potentially be more useful. It has been shown to have a sensitivity of 50% to 90% and specificity of 81% to 93% for the diagnosis of invasive aspergillosis *(269–271)*. Furthermore, the galactomannan assay may be positive as long as 28 days before clinical and radiographic signs of invasive aspergillosis become apparent *(270)*. The efficacy of the galactomannan assay may be improved significantly by using a bronchoalveolar lavage specimen *(272,273)* with sensitivity of 67% to 100% and specificity of 91% to 98%. High-resolution thoracic computed tomography (CT) may be able to raise the index of suspicion for invasive pulmonary aspergillosis soon after the development of symptoms and before culture results are available. Such imaging in neutropenic patients

whose fever persisted for more than 2 days despite empiric antibiotic treatment showed findings highly suggestive of invasive pulmonary aspergillosis 5 days earlier than the use of chest roentgenograms *(274)*.

Prevention and Prophylaxis Outbreaks of aspergillosis have been linked to construction activity within or near a transplant unit and to contaminated or poorly maintained ventilating ducts, grids, and air filters. Outbreaks associated with construction activity in bone marrow transplant recipients have been curtailed by use of laminar air flow units with HEPA filtration. Not all solid organ transplant recipients require antifungal prophylaxis. Current recommendation is to administer antifungal agents to high-risk patients only such as lung transplant recipients and high-risk liver transplant recipients (253). Targeted prophylaxis with a lipid formulation of amphotericin B and echinocandins has proven effective for high-risk liver transplant recipients *(275–277)*, and itraconazole or voriconazole are commonly used for antifungal prophylaxis following lung transplantation. Some centers employ aerosolized lipid polyenes in lung transplant recipients, which limit systemic exposure to the drug, and therefore, fewer adverse effects; however, unequal distribution to the native lung in case of single-lung transplantation and lack of efficacy for systemic fungal infections are concerning *(278)*.

Candida

Invasive candidiasis is the most frequent fungal infection in solid organ transplant recipients *(88,279)*. The incidence of *Candida* infections is highest in liver transplant recipients. Virtually all *Candida* infections are healthcare-associated although the source may vary depending on the type of organ transplant recipients. Whereas in liver transplant recipients candidiasis results from endogenous (generally gut) colonization, donor organs are the potential source in heart–lung and lung transplant recipients. Karyotypic analysis has demonstrated *Candida* infection originating in the donor lung as a cause of disseminated disease in a lung transplant recipient *(63)*.

In the earlier studies in liver transplant recipients, 15% to 20% of the patients were documented to have invasive candidiasis *(264,280)*. Intra-abdominal infections, with or without subsequent dissemination, are the usual clinical manifestations. Prolonged operation time, retransplantation, greater transfusion requirements, high serum creatinine, and CMV infection were the proposed risk factors for *Candida* infections (Table 58-2). More recently, however, many transplant centers have documented a decline in the incidence of invasive candidiasis, even in the absence of specific antifungal prophylaxis *(73,124,164,211,213,281)*. More conservative immunosuppression but, more importantly, improvement in surgical technique likely accounts for this decline. After pancreatic transplantation, *Candida* infections occur in 15% to 30% of the patients and manifest predominantly as surgical site or bloodstream infections. The incidence of infections was almost twofold higher for enteric-drained than for bladder-drained pancreatic transplantations *(282)*. In heart–lung or lung transplant recipients, the clinical pattern of *Candida* infections may range from tracheobronchitis to systemic invasive disease. Invasive candidiasis in these patients may also result in anastomotic dehiscence, mediastinitis, and mycotic aneurysm. The anastomotic site is particularly vulnerable because of poor blood supply and the presence of suture material. Invasive bronchial infection can then result in breakdown of the anastomosis. In kidney transplant recipients, candiduria occurs in 11% of these recipients *(283)*. Although asymptomatic candiduria is typically treated with antifungal agents, little evidence exists to support this practice. Persistent symptomatic candiduria warrants imaging studies to exclude the possibility of fungus ball and abscess.

The precise patient population to be targeted, optimal regimen, and duration of antifungal prophylaxis for *Candida* remains controversial. Currently, fluconazole is commonly used for prophylaxis at many liver, pancreatic, and small-bowel transplant centers *(284)*. In liver transplant recipients, it is common practice to administer antifungal prophylaxis using fluconazole in patients at risk for developing invasive candidiasis. High-risk recipients are defined those with ≥2 of the following factors: choledochojejunostomy anastomosis, preoperative renal insufficiency, retransplantation, administration of at least 40 units of cellular blood products, early abdominal reexploration for bleeding or graft dysfunction, and perioperative colonization with *Candida* species *(264)*. Low-risk recipients do not require antifungal prophylaxis. Only 2% of these patients developed invasive candidiasis that could be preventable by fluconazole in a prospective observational study *(285)*. In lung transplant recipients, given the relatively high incidence of invasive pulmonary aspergillosis and rarity of invasive pulmonary candidasis, antifungal prophylaxis should be targeted toward the prevention of aspergillosis. The risk of invasive candidiasis is considered too low to warrant prophylaxis in kidney or heart transplant recipients. A major concern with routine azole antifungal prophylaxis is the emergence of azole-resistant *Candida* species *(286)*. Azole-resistant invasive *Candida glabrata* infection occurred in 4% (4/101) of the liver transplant recipients receiving fluconazole prophylaxis and was the direct cause of death in one patient *(286)*. The routine use of fluconazole is expected to have the potential of selecting fungi innately resistant to fluconazole (e.g., *Aspergillus*).

Pneumocystis jirovecii

P. jirovecii has long been classified as a protozoan microorganism on the basis of morphologic features and lack of growth on fungal media. However, gene sequencing of *P. jirovecii* suggests that the microorganism is indeed a fungus.

Lung transplant recipients are at greatest risk of developing pulmonary infection with *P. jirovecii*; in the absence of prophylaxis, PJP may develop in up to 80% of the patients *(287)*. Not all of these patients, however, are symptomatic. Up to 40% of the lung transplant recipients have been shown to have normal chest radiographs, be asymptomatic, and have the microorganism detected on routine posttransplant bronchoscopy. Several factors may account for the high incidence of *P. jirovecii* infection in lung transplant recipients. First, local defense mechanisms are impaired as a result of lung denervation. Second, it has been hypothesized that an incompatibility exists between the immune effector cells and parenchymal cells in the

allograft lung. Infiltrating lymphocytes and mononuclear phagocytes recruited to the infected allograft are derived from the recipient and, therefore, express different MHC antigens than do the donor-derived parenchymal cells *(102)*. Finally, surveillance bronchoscopy may increase the chance of early detection of occult infection. *P. jirovecii* infection in lung transplant recipients usually occurs in the fourth month after transplantation. Up to 25% of the cases may occur more than a year after transplant; these patients had usually received more intense immunosuppressive therapy.

The incidence of infection with *P. jirovecii* in patients not receiving PJP prophylaxis is 2% in renal transplant recipients, 5% in heart, and 9% in liver transplant recipients. Most infections occur between 3 and 6 months after transplantation. Between 10% and 20% of the cases occur >6 months posttransplantation, usually in those receiving augmented immunosuppression for rejection *(219)*. Other risk factors for PJP include use of corticosteroids and antilymphocyte therapy (e.g., alemtuzumab) *(288,289)*, CMV infection *(29)*, allograft rejection *(290)*, and low CD4 count (291). Mycophenolate mofetil has been shown to have *in vitro* activity against *P. jirovecii*; however, this has not been confirmed in human studies *(292)*.

Unlike HIV-infected patients, PJP in transplant recipients is rarely diagnosed by examination of an induced sputum sample. Virtually all cases require bronchoalveolar lavage for diagnosis. Coinfection with CMV or bacteria (especially in lung transplant recipients) is common.

Prophylaxis with oral trimethoprim-sulfamethoxazole has proven highly efficacious and is recommended for all transplant recipients *(293,294)*. The recommended dose is either 160/800 mg (double-strength) daily or every other day, or 80/400 mg (single-strength) daily.

A more controversial issue in prophylaxis of *P. jirovecii* infection in transplant recipients is the duration of prophylaxis. The duration of prophylaxis should be based on the type of allograft, immunosuppressive regimen (e.g., corticosteroid, antilymphocyte agents), and other risk factors (e.g., CMV infection, rejection) for *P. jirovecii* infection. The risk of *P. jirovecii* infection is the highest in the first 6 months posttransplant regardless of the type of allograft, and it declines substantially after this period. Prolonged or lifelong prophylaxis may be indicated in lung or small-bowel transplant recipients and any organ recipients with those risk factors *(294)*. An additional advantage of trimethoprim-sulfamethoxazole prophylaxis is that it is also effective against other microorganisms such as *Nocardia, Listeria, Toxoplasma,* and *Legionella* in transplant recipients, and the majority of transplant centers offer life-long prophylaxis unless an adverse effect is concerning.

Nebulized pentamidine, dapsone, and atovaquone are alternative prophylactic agents in patients intolerant of trimethoprim-sulfamethoxazole. Breakthrough infections, however, have been reported in such patients. Neither drug has significant interactions with cyclosporine or tacrolimus.

Cryptococcus neoformans

The incidence of cryptococcosis in organ transplant recipients ranges from 0.3% to 5.0% *(295)*. The infection usually develops in the late period after transplantation: the median time to onset was 21 months and some cases are detected 4 or more years after transplantation *(296)*. Cryptococcosis is considered to be a reactivation of latent disease; however, primary infection or transmission from donor organs may occur *(297–299)*. Given the low incidence of cryptococcosis in transplant recipients and the delayed and often unpredictable time of onset after transplantation, primary antifungal prophylaxis is not usually considered necessary in transplant recipients.

Endemic Mycosis (Histoplasmosis, Coccidioidomycosis, and Blastomycosis)

Histoplasmosis has been infrequently reported in transplant recipients. In endemic regions, 0% to 0.4% of transplant recipients developed histoplasmosis *(300,301)*. The prevalence of disseminated histoplasmosis rose to 2.1% during an outbreak associated with construction activity near a hospital in Indianapolis (302). The median time to onset is 17 months after transplantation *(300)*. The modes of infection include primary acquisition from inhalation, reactivation of latent disease, and infected allografts *(55,303)*. Disseminated disease occurs in more than 75% of the transplant recipients developing histoplasmosis. Culture of *H. capsulatum* remains the gold standard of diagnosis but is often delayed. The antigen detection using serum and/or urine has proven useful in providing a more rapid diagnosis of histoplasmosis in transplant recipients *(300)*, despite lower sensitivity compared with AIDS patients *(304)*. Given the low incidence of posttransplant histoplasmosis, pretransplant screening for prior histoplasmosis and secondary prophylaxis is not currently recommended *(305)*.

Coccidioidomycosis in transplant recipients has been described predominantly from the centers in Arizona and southern California. The risk of overt infection in solid organ transplant recipients in Arizona is about 3% per year, with an overall prevalence of 4.5% for heart transplant recipients *(306)* and 6.9% for renal transplant recipients *(307)*. In liver transplant recipients in Los Angeles, 0.6% of patients developed overt coccidioidomycosis *(308)*. The usual time to onset is 2 to 6 months posttransplant *(306–308)*. However, cases have also been reported in the first 4 weeks posttransplantation. Sometimes, this early infection may manifest as fever, a sepsis-like syndrome, or an aggressive pneumonia *(308)*. A subacute presentation occurring several to many months after transplantation, however, is a more common finding. Some patients have disseminated disease with arthritis, meningitis, or skin lesions *(309)*.

Transplant candidates who reside in or travel to endemic areas should be screened for coccidioidomycosis before transplantation. Patients at high risk of developing coccidioidomycosis posttransplant include those with detectable titers of coccidioidal antibodies on complement fixation tests, those with radiographic evidence of prior pulmonary infection, and those with a history of active coccidioidomycosis. Prophylactic fluconazole (400 mg/day) should be considered for these patients posttransplant *(305,310)*.

Blastomycosis is rarely reported in transplant recipients and its incidence was 0.14% in one study *(311)*. Given its low incidence and the lack of a sensitive screening test, pretransplant screening is currently not recommended *(305)*.

Mucormycosis

The incidence of mucormycosis complicating organ transplantation ranges between 0.3% and 5% *(312)*. The usual time to onset is 5 months after transplantation (interquartile range, 6 weeks to 12 months) *(313)*. Most cases are due to *Rhizophus* and *Mucor* species. Pulmonary disease has been observed in 48% of the cases and is the most common clinical presentation. Mucormycosis can be healthcare-associated; the usual portal of entry is believed to be pulmonary. Adhesive bandages have been incriminated as a source of surgical site infections in transplant recipients.

PROTOZOAL INFECTIONS

Toxoplasma gondii

Heart transplantation poses the highest risk for transmission of *T. gondii* because of the parasite's predilection to invade muscular tissue. Fifty percent to 75% of seronegative recipients of seropositive cardiac allografts may develop primary *T. gondii* infection *(48). T. gondii* infections are distinctly unusual in noncardiac transplant recipients *(314)*.

Most symptomatic infections occur within 3 months of transplantation. Meningoencephalitis, brain abscess, myocarditis, and pneumonitis are the usual clinical manifestations. Demonstration of tachyzoites in tissue sections establishes the diagnosis of acute infection. An immuno-peroxidase stain is both sensitive and specific. Significant changes in antibody titer may not occur in transplant recipients with acute toxoplasmosis. Conversely, a rise in IgM and IgG titers is frequent after heart transplantation without evidence of clinical disease. Modalities for posttransplant prophylaxis in heart transplant recipients were discussed earlier in this chapter.

APPROACH TO MAJOR HEALTHCARE-ASSOCIATED INFECTIONS IN TRANSPLANT RECIPIENTS

Pulmonary Infiltrates

Pulmonary infiltrates, including those resulting from pneumonitis, remain a serious and frequently encountered complication in transplant recipients. In heart transplant recipients, pulmonary infections have been documented in 28% to 40% of patients (*2,212*). Fifty-one percent (36/71) of all pulmonary infections in heart transplant recipients in one report were healthcare-associated in origin; 32% (23/71) were opportunistic, and only 17% (12/71) were community acquired. The latter usually occur in the late posttransplant period (>1 year) (2). Nearly one half of all pneumonias in these patients are bacterial in origin. Prolonged intubation, reintubation, and high-dose corticosteroids were significant risk factors for pneumonia in heart transplant recipients.

The differential diagnosis of pulmonary infiltrates in lung and heart–lung transplant recipients, among other entities, includes acute rejection. Acute rejection may develop in up to 60% of these patients, and most of these episodes occur within the first 3 months. Bronchiolitis obliterans is a significant late-occurring complication in lung transplant recipients. Rejection and/or infection, particularly resulting from CMV, are proposed to be the leading risk factors.

After liver transplantation, pneumonia occurs in 13% to 34% of patients. Forty-four percent of the liver transplant recipients requiring intensive care unit admission developed pulmonary infiltrates in one study; pulmonary edema (40%), pneumonia (38%), atelectasis (10%), and acute respiratory distress syndrome (8%) were the documented causes *(315)*. Acute respiratory distress syndrome has been reported in 5% to 17% of liver transplant recipients. Large-volume transfusions, liver failure, retransplantation, and sepsis are considered factors predisposing to acute respiratory distress syndrome in these patients *(315)*. Bacteria account for 40% to 67% of all pneumonias in liver transplant recipients. In the earlier reports, viral pneumonitis (CMV or HSV) was documented in 15% to 20% of the pulmonary infections. This incidence, however, has declined to <5% in the more recent reports *(234)*. Pneumonias are less common after renal transplantation (occurring in 8% to 16% of the patients) but are nevertheless a significant complication in these patients.

Healthcare-associated bacterial pneumonitis is the predominant cause of pneumonia in all types of solid organ transplantation, particularly in the first month after transplantation; *P. aeruginosa,* Enterobacteriaceae, and *S. aureus* are the bacteria usually implicated. Legionellosis has been reported in 2% to 9% of solid organ transplant recipients with pneumonia *(5)*. After the first month, opportunistic pathogens emerge as the etiology of pneumonia. Fungal pneumonias in transplant recipients are predominantly due to invasive aspergillosis. Although isolation of *Candida* species from respiratory cultures is common, *Candida* pneumonitis is a rare entity *(63)*. It may present as tracheobronchitis in lung transplant recipients. Other less frequent causes of pulmonary infection include cryptococcosis, mucormycosis, coccidioidomycosis, histoplasmosis, nocardiosis, and infections due to dematiaceous fungi. CMV and to a lesser degree HSV account for most cases of viral pneumonitis. Whereas 5% to 20% of renal, liver, and heart transplant patients develop CMV pneumonitis, the incidence in heart–lung and lung transplant recipients is higher and ranges from 10% to 50%. It is believed that the host immune response is more important for the development of CMV pneumonitis than viral replication is *(29)*. Pneumonia resulting from RSV generally occurs in pediatric patients and may occur 3 weeks to 2 years after transplantation. Up to 20% to 50% of the cases of RSV are healthcare associated. Early identification and isolation of cases, however, is crucial to prevent healthcare-associated spread.

Given the diversity of likely causes and the immunosuppressive state in transplant recipients, early and aggressive pursuit of the etiology of pulmonary infection with initiation of broad-spectrum antibiotics are warranted. Although the radiographic appearance of the lesion is never diagnostic, a number of entities may have distinctive or suggestive radiographic characteristics. Nodular pulmonary infiltrates of infectious etiology in liver transplant recipients were most frequently due to *Aspergillus* or *Cryptococcus* in one study *(316)*. However, *S. aureus, Nocardia,* tuberculosis, PJP, CMV, mucormycosis, *Bartonella henselae,* and coccidioidomycosis may present similarly in

transplant recipients. Noninfectious causes of pulmonary nodules include metastatic carcinoma, pulmonary calcification, and lymphoproliferative disorders. Pulmonary infarcts, rounded atelectasis, and pulmonary varix in cardiac transplant recipients and acute or chronic rejection in lung transplant patients may have a nodular appearance. Cavitary pneumonia in transplant recipients may be due to *Aspergillus, Cryptococcus, Nocardia, Legionella, M. tuberculosis, Rhodococcus equi,* or other fungi.

CT offers a number of advantages over conventional radiographs, including detection of additional lesions, precise morphology of the lesion, and delineation of mediastinal lymphadenopathy. Bacterial pneumonia presents more focal features compared with viral or pneumocystis pneumonia *(317)*. CT in patients suspected of having aspergillosis has often revealed lesions that appeared nonspecific or were not visualized on routine x-ray examination.

Isolation or detection of *Legionella, Nocardia, Cryptococcus, M. tuberculosis,* or *P. jirovecii* in the sputum or respiratory secretions is diagnostic of pulmonary infection resulting from these pathogens. However, smears and cultures of sputum or respiratory secretions may be diagnostic in fewer than 50% of patients. In a patient with focal air space disease and nondiagnostic noninvasive tests, the choice lies between empiric antibacterial therapy or a diagnostic procedure; we recommend early bronchoscopy with bronchoalveolar lavage. In patients with focal nodular infiltrates, percutaneous needle aspiration is superior to bronchoalveolar lavage with a diagnostic accuracy of 70% to 90%. In patients with diffuse pulmonary infiltrates, bronchoalveolar lavage with or without transbronchial biopsy is the preferred approach. Transbronchial biopsy is particularly valuable for the diagnosis of rejection in lung transplant recipients and for the differentiation of allograft rejection and CMV pneumonitis in these patients. Open lung biopsy should be reserved only for patients with progressive disease refractory to antimicrobial agents in whom bronchoalveolar lavage or percutaneous needle aspiration is nondiagnostic.

Healthcare-Associated Bacteremias

Although the incidence of bacteremia may vary, identifiable portals of entry and defined pathogens exist for most solid organ transplant recipients with bacteremia. The frequency of bacteremia varies from 5% to 10% in kidney, 8% to 11% in heart, 8% to 25% in lung, 5% to 20% in pancreatic, and 10% to 25% in liver transplant recipients *(318,214,319–322*). Ninety-four percent (75/80) of all bacteremias in liver transplant recipients, 56% (15/27) in renal transplant recipients, and 78% (13/18) in heart transplant recipients were healthcare-associated in one study *(318)*. Besides catheter-related infections, pneumonia in heart and heart–lung transplant recipients, urinary tract infections in renal transplant recipients, abdominal and biliary infections in liver transplant recipients, and surgical site and urinary tract infections in pancreatic transplant recipients have been shown to be the most common identifiable sources of bacteremia *(214,318)*. Aerobic gram-negative bacilli constituted 48% to 62% of the bacteremic isolates in renal transplant recipients, 44% to 49% in liver transplant recipients, 39% to 41% in heart transplant recipients, and 17% to 52% of lung transplant recipients *(318,320,322)*. *E. coli, Acinetobacter baumanii, P. aeruginosa*, *Klebsiella species,* and other Enterobacteriaceae were the predominant gram-negative bacteria *(320)*.

The sources and pathogens causing bacteremias in transplant recipients appear, however, to have undergone a striking evolution in the recent years. Many transplant centers documented the emergence of gram-positive cocci (enterococci and staphylococci) as foremost pathogens in transplant recipients in the mid-1990s *(215)*. However, the proportion of gram-negative bacteremias doubled from 25% in 1989 to 1993 to 52% in 1998 to 2003 in one center *(323)*. Within the hospital, intensive care units are the most common site of acquisition of healthcare-associated bacteremias. Ninety-three percent of the bacteremias in one report were healthcare-associated, and 52% occurred in the intensive care unit setting *(215)*. Indeed, intensive care unit stay has been shown to be an independent predictor of bacteremic compared with nonbacteremic infections in liver transplant recipients *(87)*. Patients developing bacteremia in the intensive care unit were also more likely to die than those not in the intensive care unit *(87)*; this likely reflected the greater severity of illness of the patients hospitalized in the intensive care unit. A recent study also confirms that septic shock and the need for mechanical ventilation, common factors for ICU stay, were independently associated with mortality *(320)*.

In small-bowel transplant recipients, 72% of patients had at least one episode of bloodstream infection *(119)*. Intravascular catheters accounted for 43% of these infections and were the most frequently identifiable portal of entry. Sixty-two percent of all bloodstream infections were due to gram-positive bacteria *(119)*. In another report, 45% of all bacterial infections and 72% of all bacteremias after small-bowel transplantation were due to staphylococci *(121)*.

Most VRE infections originate from an abdominal or biliary source; 38% to 68% of these infections have been associated with bacteremia *(221,224)*. Vancomycin resistance was an independent predictor of mortality in liver transplant recipients with enterococcal bacteremia *(221)*. A noteworthy observation is the predilection of VRE to cause endovascular complications, including mycotic aneurysms and endocarditis *(221)*. Delayed metastatic complications, including endocarditis and osteomyelitis, have also been documented in transplant recipients with MRSA bacteremia. Prophylaxis and infection control measures pertinent to these infections are discussed in the sections on staphylococci and enterococci.

Intra-Abdominal Infections

Intra-abdominal abscesses, peritonitis, and biliary infections are a significant complication after liver transplantation. Intrahepatic abscesses usually occur within 30 days of transplantation; technical problems involving the implanted allograft (e.g., hepatic artery thrombosis, biliary leak, and, rarely, tear of the donor liver) are the primary risk factors. Nearly one half of patients with intrahepatic abscesses may be bacteremic *(89)*. Peritonitis after liver transplantation is typically related to biliary anastomotic leaks or, less frequently, bowel perforation *(89)*. Aerobic enteric gram-negative bacteria, enterococci, anaerobes, and, *Candida* species are the causal pathogens in most

intra-abdominal abscesses and peritonitis. An unusual cause of abdominal abscesses in liver transplant recipients is *M. hominis*.

Cholangitis has been documented in 4% to 15% of patients after liver transplantation, with most episodes occurring within 30 days of transplantation. Biliary strictures and biliary leaks are significant predisposing risk factors. Enterococci are characteristically the most common pathogen, whereas anaerobes are encountered rarely. Biliary strictures (e.g., in patients with primary biliary cirrhosis and in those with previous bile duct surgeries) often necessitate Roux-en-Y anastomosis, which is associated with a high rate of intrahepatic and biliary complications. Sterile intra-abdominal fluid collections are common after liver transplant surgery. Diagnosis of peritonitis or abscess, thus, requires percutaneous or open drainage and culture. Cultures from abdominal drains often reflect colonization and are not reliable in diagnosing the infection or its etiology.

Central Nervous System Mass Lesions

Although mild neurologic complications may occur in 10% to 47% of organ transplant recipients, 1% to 8% of such patients have major neurologic sequelae or central nervous system lesions. Brain abscesses are among the most serious central nervous system lesions in these patients *(324)*. The frequency of brain abscesses was 0.36% in kidney, 0.63% in liver, and 1.17% in heart and heart–lung transplant recipients *(325)*. Most brain abscesses in solid organ transplant recipients are fungal and represent a healthcare-associated complication *(324,325)*. Although *Aspergillus* is the most common cause of brain abscesses in organ transplant recipients, less frequently encountered fungal pathogens include *Mucorales, Candida* species, and dematiaceous fungi. Central nervous system lesions resulting from *T. gondii* have been reported mainly in heart transplant recipients.

Selby et al. *(325)* showed that two distinct groups of solid organ transplant recipients existed with regard to timing and susceptibility to brain abscesses. One group, comprising predominantly liver and renal transplant recipients, developed brain abscesses a median of 24 days post-transplant. Ninety-five percent of these patients were in the intensive care unit and were ventilator dependent; brain abscesses in this setting were exclusively fungal. In the second group, abscesses developed a median of 264 days after transplantation, occurred almost exclusively in heart transplant recipients, and were due to *T. gondii* and *Nocardia*.

Most patients (up to 75%) with fungal brain abscesses have been shown to concurrently have pulmonary lesions resulting from the same fungus *(324)*. A brain biopsy may not be required in such cases.

In the absence of an extraneural focus, brain biopsy should be considered, given the diversity of causal fungal pathogens in such lesions *(324)*.

CONCLUSIONS

Improvement in surgical techniques, the advent of modern immunosuppressive drugs, the availability of rapid and reliable diagnostic modalities, and effective prophylaxis against a number of pathogens have undoubtedly led to a decrease in infectious morbidity and improved outcome in transplant recipients in recent years. Increasing documentation of the emergence of antimicrobial resistance in several key pathogens in transplant recipients, however, is worrisome. Strategies for antimicrobial prophylaxis must comprise approaches that are not only efficacious but minimize the emergence of resistance. Finally, for therapy and prevention to be effective, classic opportunistic infections typically encountered in these patients must be considered, and the emerging trends in new infectious agents and the changing epidemiology of these complicating infections must be understood.

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CHAPTER 59

Infection Prevention and Control in Hematopoietic Stem Cell Transplant Patients

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BASIC CONCEPTS OF HEMATOPOIETIC STEM CELL TRANSPLANTATIONS

Bone marrow or hematopoietic stem cell transplantation (HSCT) is a lifesaving therapy for many malignancies and genetic or acquired hematologic syndromes. Worldwide, over 25,000 allogeneic and 30,000 autologous HSCTs were performed in 2009 (1). HSCTs are the transfer of hematopoietic stem cells from one individual to another (allogeneic HSCT) or the return of the previously harvested cells to the same individual (autologous HSCT) (1). HSCT is used in the treatment of numerous conditions, including hematologic and other malignancies and nonmalignant disorders (i.e., bone marrow failure syndromes, congenital immunodeficiencies, enzyme deficiencies, and hemoglobinopathies) (1,*2*). Prior to transplantation, the recipient's own marrow is fully or partially ablated to allow the engraftment of new bone marrow (1,*2*). Recipients receive a conditioning regimen that usually includes high-dose chemotherapy with or without total body radiation. After the conditioning regimen is completed, the graft is infused. At this point, the host is usually granulocytopenic and the peripheral neutrophil count has reached its nadir. The patient remains granulocytopenic and profoundly immunosuppressed until the donated or reinfused stem cells engraft. The time to engraftment depends on a number of factors and usually takes 2 to 4 weeks. Recovery of marrow function is accompanied by a prolonged, progressive restoration of the recipient's immunologic competence *(*1,*2)*.

The most serious complication of allogeneic transplantation is graft versus host disease (GVHD), which occurs when immunologically competent cells target antigens on the recipient's cells *(3,4)*. The potential immunologic phenomena that accompany foreign cell transplantation are minimized by closely matching the human leukocyte antigen (HLA) of the donor and recipient *(5,6)*. In patients undergoing allogeneic HSCT, additional immunosuppression, such as cyclosporine, corticosteroids, and antithymocyte globulin, or other therapies, may be required to minimize the immunologically mediated complications, such as GVHD *(3–5,7–9)*. Some degree of GVHD is desirable, because it produces a graft versus tumor effect, which results in lower relapse rates *(10)*. GVHD occurs in acute or chronic forms and primarily affects the skin, liver, and gastrointestinal tract *(3,4)*.

High-risk HSCT for GVHD includes stem cell source (unmatched or unrelated donor–recipients), types of manipulation to the stem cells, and conditioning regimens. For instance, nonmyeloablative conditioning regimens, also known as reduced-intensity conditioning (RIC) regimens, have been increasingly used *(2,11)*. In these procedures, patients undergo less aggressive chemotherapy or immune-suppressive therapy prior to allogeneic transplant, so there is not complete ablation of the bone marrow *(11)*. This strategy decreases chemotherapy-related toxicities such as mucositis and end-organ toxicity and the ability to treat older or sicker patients. However, as the recipient's bone marrow is not fully ablated, the risk for GVHD has become a significant problem *(9,12–14)*.

The recipient serves as his own donor in autologous HSCT transplants. Bone marrow stem cells are collected prior to treatment for the underlying disease. The most serious complication of this type of HSCT is relapse of the underlying disease. Purging is a technique that eliminates malignant cells from the recovered marrow and is used to prevent this complication.

In the past, bone marrow stem cells were obtained directly from the marrow space by repeated aspiration from the iliac crest. More recently, stem cells circulating in the peripheral blood are collected as there may be more rapid engraftment and, in some studies, higher recipient disease-free survival *(15–18)*. The major limitation of allogeneic peripheral blood stem cell transplantation is the high risk of developing GVHD, since approximately a 10-fold greater number of T cells can be found in peripheral blood grafts than in the bone marrow *(19)*. Umbilical cord blood grafts, collected from the umbilical vessels in the placenta at the time of delivery, may also be used for HSCT. Umbilical cord blood graft cells are considered naïve hence associated with lower GVHD risk *(20)*. The major disadvantages of blood as the HSCT source are the limited cell dose and delayed engraftment (1,*21*).

RISK FACTORS FOR INFECTION

Risk factors for infection among HSCT recipients can be classified as endogenous, including those related to the host and recipient, and exogenous, including those related

to administered conditioning regimens and high-dose steroids for GVHD and the environment of care.

Host and Pretransplant Factors

The patients' overall state of health is often compromised at the time of transplant with a predisposition to infection from either their underlying illness or any previous treatments received *(22)*. Age considerably increases the risk of GVHD in allogeneic transplantation, and therefore the risk of infection *(23)*. The recipient's underlying disease may be associated with immune function impairment; for instance, chronic lymphocytic leukemia and multiple myeloma are associated with deficient humoral immunity *(24,25)*. The more advanced the patient's underlying disease at the time of transplant, the higher the risk of infection may be (1). The intensity of previously administered regimens may also influence the host's immunity (1).

Transplant-Related Factors

Types of conditioning regimens, transplant source, and donor–recipient matching are the major transplant-related variables that dictate the risk for infectious complications. Conditioning-related mucositis and degree or/and duration of cytopenias represent the major risk factors for infection during the pre-engraftment period. Nonmyeloablative conditioning regimens have been associated with lower infection risk compared to fully ablative regimens, in part because of shorter duration of neutropenia and less mucosal damage (26). The above observations appear most likely in the early period after HSCT. However, during the late posttransplant period, mostly correlating with GVHD, the risks for late (after engraftment) viral and fungal infections persist (26,*27*). In addition, stem cell source may impact the risk for infectious complications: lower in peripheral blood graft and higher in cord blood transplants, in part, due to slower engraftment in the latter *(28)*. The type of transplant may also affect the risk of infection: higher risk with unmatched or unrelated allogeneic (in part due to higher risk for GVHD and associated treatments) and lower risk with autologous or matched related allogeneic HSCT (1). Stem cell manipulation, such as T-cell depletion, may lead to higher rates of infections (1,*29–31*).

Environmental Factors

During the preparative and early posttransplant periods, HSCT recipients are usually hospitalized; hence, the hospital environment represents a major potential source for infections. The source can be related to the facility and the physical environment, the care provided including treatments and equipment, and personnel, visitors, and other human interactions.

Based on serial surveillance cultures and cultures from normally sterile body sites obtained over a 2-year period among patients with acute myeloid leukemia, most infections developed from the patients' endogenous flora; however, 47% of patients became colonized with healthcare-associated microorganisms *(32)*. Ultimately, 39/43 (91%) patients who developed bacteremia were colonized with the implicated microorganism prior to developing a bloodstream infection *(32)*.

Healthcare workers' hands are another potential source of microorganisms. Schimpff et al. *(32)* found that the hands of 43 out of 126 (34%) healthcare workers caring for leukemic patients were colonized with gram-negative microorganisms or *Staphylococcus aureus*. Hands can become contaminated by lotions or contaminated soaps *(33)*. For example, 12 of 25 (48%) HSCT recipients became colonized or infected (9 of 25; 36%) with *Paecilomyces lilacinus* after exposure to a contaminated, pharmaceutically prepared skin lotion *(34)*. Healthcare workers and other patient contacts transmit microorganisms in other ways. Contact with such infected or colonized visitors and staff, many of whom may be asymptomatic, increases the risk of respiratory viral infections. Clearly, the season of the year the patient receives their HSCT and transplant-related care would dictate the risk of developing these infections *(35–38)*.

Treatments and the environment can also lead to infections in this population. For instance, institutional water is a potential source of microorganisms such as gram-negative rods, *Pseudomonas* species, *Legionella* species, and *Mycobacterium* species and fungi *(39–45)*.

At another institution, seven of eight immunocompromised patients developed *Pseudomonas aeruginosa* septicemia *(46)*. The microorganism was also isolated from mouthwash used by the patients, the water, and two sinks *(46)*.

One outbreak of *Stenotrophomonas maltophilia* infections among allogeneic HSCTs was linked to a single room on the unit, although no source was found *(47)*.

Heating and air conditioning systems can aerosolize and facilitate the spread of *Aspergillus conidia.* Arnow et al. *(48)* demonstrated that the mean concentration of *A. fumigatus* and *A. flavus* spores in the air correlated with the incidence of invasive aspergillosis (IA). When the *Aspergillus* concentration was 0.02 colony-forming units (CFU)/m^3 of air, the incidence of invasive *Aspergillus* infections among high-risk patients was 0.3% *(48)*. However, when the *Aspergillus* concentration rose to 1.1 to 2.2 CFU/m^3 of air, the incidence of *Aspergillus* infections among high-risk patients rose to 1.2% *(48)*. Notably, it is not entirely clear what the minimum concentration of *Aspergillus* spores in the air is to cause disease. Rhame et al. *(49)* reported that 5.4% of HSCT recipients developed IA when the mean concentration of *A. fumigatus* was 0.9 CFU/m^3. Sherertz et al. *(50)* did not identify any cases of IA when 0.0009 CFU/m^3 of *Aspergillus* was measured in air samples. Thio et al. (51) noted that air samples obtained on units that house high-risk patients must be obtained using appropriate high-volume samples. Multiple outbreaks of *Aspergillus* infection reported in the literature have illustrated the risks associated with construction and/or renovation and suboptimal maintenance, cleaning, and protection of the environment. Patients housed outside of a high-efficiency particulate air (HEPA)-filtered laminar airflow environment are at a 10-fold higher risk for developing healthcare-associated *Aspergillus* infection *(50)*.

By the time HSCT recipients return home, their immune systems have been partially reconstituted, although environmental sources remain an ongoing potential source of infection. Clearly, the variety of exposures and variables makes it very difficult to study the effect of environmental factors for an infection after discharge. Prospective, well-designed studies are required to be able to make any further conclusions.

Risk Periods of Infectious Complications

The risk periods for infectious complications are traditionally divided into pre- and postengraftment. The former includes the time from initiation of the conditioning regimen to the infusion of the transplant and extends through engraftment. The latter starts from engraftment and is commonly divided into the early (up to 100 days after HSCT) and late phases (>100 days after HSCT).

Pre-Engraftment Host Risks

The major risk factors during the pre-engraftment period include mucositis and neutropenia associated with the administered chemotherapy and skin breakdowns from central venous catheters (1). Infections appear at a median of 6 days after the transplant, with 10% of the infections occurring in the pretransplant period *(52)*. During this early period after HSCT, most patients develop neutropenic fever and 35% to 71% of patients may develop an infection, with an estimated overall infection rate during this period of 18 infections per 1,000 patient days *(52–54)*. Engels et al. *(54)* reported that 30% and 55% of autologous and allogeneic HSCT recipients, respectively, developed infections during the early phase of HSCT ($p < .01$), and the risk of infection correlated with the severity of neutropenia. Among 35 autologous HSCT recipients with early infectious complications, the following factors were found to be independent mortality predictors: male gender, total body irradiation, low pretransplant albumin, and mucositis or diarrhea *(53)*.

Neutropenia Innate immunity is disrupted early in HSCT manifested primarily by the conditioning-associated neutropenia that occurs in the immediate posttransplant period and that coincides with the period when the patient's natural barriers to infection are most likely to be breached *(22)*. In addition to being decreased in numbers, the neutrophils are functionally impaired and display decreased chemotaxis *(22)*. The risk of infections is related to both the duration and degree of neutropenia, with the risk of infection increasing sharply when the absolute neutrophil count (ANC) falls below 500 mm^3 *(55)*. In one study, the risk of serious infections was 5 and 43 infections per 100 admissions when the ANC was above and below 500 cells/mm^3, respectively *(55)*. Granulocytopenia allows for otherwise minor localized infections to disseminate. Prolonged neutropenia may predispose to infections due to pathogens resistant to multiple antimicrobial agents (e.g., *S. maltophilia*, *Acinetobacter* species), which may in part be due to the selective pressure of antibiotic therapy administered earlier in the course of the neutropenia.

Mucositis Conditioning-related oral and gastrointestinal mucositis occur in the vast majority of patients undergoing HSCT *(56–58)*. Additionally, it can be induced by regimens used to prevent GVHD *(59)*. Breaches are created in the normal mucosal barrier of the oropharynx and gut that results in translocation of bacteria or fungi (mainly *Candida* species) *(60,61)*. Mucositis-associated candidemia and viridans *Streptococcus* bacteremia post-HSCT are well described *(61–69)*. In a prospective study involving severe oral mucositis among autologous HSCT recipients, severe mucositis was associated with higher rates of fever and microbiologically confirmed infection, duration of antibiotic administration, and use of total parenteral nutrition (TPN) *(70)*.

Postengraftment Host Risks

Several factors influence the degree of immunosuppression experienced after HSCT following recovery of neutrophil function. In allogeneic HSCT, the presence of GVHD greatly increases the risk of infection by prolonging the impairment in cellular immunity, by virtue of GVHD itself and the associated treatments *(71)*. After the resolution of neutropenia, defects in acquired immunity become apparent as the spectrum of infections switches to include those ordinarily prevented by intact humoral and cellular immunity. Both allogeneic and autologous HSCTs are associated with quantitative decreases in lymphocyte counts *(72)*. Furthermore, $CD8^+$ suppressor cell populations recover sooner than the $CD4^+$ helper cells *(22)*. Thus, although the absolute lymphocyte count recovers to normal by the second month posttransplant, cellular immunity remains impaired by an abnormal $CD8^+/CD4^+$ ratio for at least a year after transplantation *(72)*. In certain cases, the immune deficiency state can be prolonged for several years after transplantation (1). In addition, B-cell recovery may take up to 6 months posttransplant (1). In fact, an association between chronic GVHD and pneumococcal infections has been reported *(73,74)*. Notably, Witherspoon et al. demonstrated that HSCT recipients 180 days posttransplant without chronic GVHD, had antibody responses indistinguishable from those of normal donors compared to patients with chronic GVHD *(75)*. Other infections can occur during this period primarily due to impaired cell-mediated immunity, including infections caused by *Aspergillus* species, CMV, VZV, and *Pneumocystis jiroveci* (1)

INCIDENCE AND PREVALENCE OF HEALTHCARE-ASSOCIATED INFECTIONS

The incidence and prevalence of healthcare-associated infections among patients undergoing HSCT have not been well studied. In an early study, 12% of patients hospitalized in an oncology center developed a healthcare-associated infection *(76)*. The highest incidence of healthcare-associated infections occurred among patients with acute myelogenous leukemia, 30.5 per 1,000 patient days *(76)*. Among patients with acute lymphocytic leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, and breast cancer, the reported rates were lower, 16.7, 13.4, 5.4, and 3.3 per 1,000 patient days, respectively. Carlisle et al. performed a prospective observational study over a 42-month period among neutropenic patients with leukemia and solid organ malignancies, of whom 8% had undergone an HSCT *(77)*. Four hundred and forty-four infections were identified among 920 patients during 9,582 days of neutropenia. Overall, 48.3 infections occurred per 100 neutropenic patients (46.3 infections per 1,000 days of risk). The rates of site-specific healthcare-associated infections per 100 neutropenic patients were 13.5 for bloodstream infections, 5.7 for urinary tract infections, 5.5 for respiratory tract infections, and 3.4 each for skin and gastrointestinal infections. In 88% of infections, pathogens were identified; 35% of pathogens were classified as gram-positive cocci,

27% as gram-negative bacilli, 18% as *Candida* species, 9% as gram-positive bacilli, 6% as viruses, and 4% as *Aspergillus*. Dettenkofer et al. *(78)* reported 48% of 351 German HSCT recipients developed healthcare-associated infections. The most common cause of infections were catheter-related bloodstream infection, pneumonia, and gastroenteritis *(78)*. The main pathogens were coagulase-negative staphylococci (36.3%), *Clostridium difficile* (20.4%), and enterococci *(78)*.

Infections that occur more than 3 months after HSCT have not been well studied, as the vast majority of those patients have been discharged by that time. Hoyle and Goldman canvassed 18 of 22 centers performing HSCT in the United Kingdom to determine the prevalence of infections that developed at least 3 months after transplant *(79)*. Six percent of HSCT recipients were readmitted for a serious infection. The most common microorganisms causing serious infections included cytomegalovirus (CMV), *Pneumocystis jirovecii*, *Streptococcus pneumoniae*, *Pseudomonas* species, and *Aspergillus* species *(79)*. Other groups have shown that 6 months or more after HSCT, recipients remain at increased risk for *S. pneumoniae* infections and *Pseudomonas* pneumonia *(80,81)*. More prospective studies are needed to determine the risk of healthcare-associated infection among recipients of HSCTs and bridge the inpatient/outpatient care model that is being adopted by many HSCT centers.

SITE-SPECIFIC INFECTIONS

Bacteremia and Catheter-Related Infections

Bacteremia or bloodstream infection (BSI) is reported to be the most common infections in HSCT recipients. The incidence is estimated to be 38.6% per 100 patients based on a 249 episodes of bacteremia occurring over 4 years among 172 patients followed longitudinally *(82)*. In this series, 82% of these infections occurred within 30 days of HSCT, whereas 18% occurred after this time period. The most common microorganisms included coagulase-negative staphylococci and viridans streptococci *(82)*. Similarly, Almyroudis et al. *(83)* demonstrated that 170 BSI occurred among 298 HSCTs. Twenty-two percent of all HSCT recipients developed a BSI during the pre-engraftment period, while 19.5% developed a BSI after engraftment *(83)*. The most common pathogens during pre-engraftment and postengraftment were viridans streptococci, *Enterococcus faecium*, and coagulase-negative staphylococci *(83)*. All except one patient in this study had an indewelling intravascular catheter *(83)*.

In a study from Spain, intravascular catheters were the source of BSI in 44% of HSCT recipients *(84)*. Vascular access catheters are used in HSCT patients for an extended period of time. Most HSCT recipients have central venous access especially in the pretransplant phase and the pre-engraftment phase for delivery of conditioning regimens, stem cells, and other supportive treatments *(85,86)*. However, it is difficult to determine the risk of infection because of variations in the definitions of infection employed, host and treatment factors as mentioned above, and the types of catheters used. In a study of 123 patients who underwent HSCT, 139 double- or triple-lumen catheters were placed and a catheter-related infection occurred in 22 (15.8%); 127 of the 139 catheters were placed and remained in place for a mean of 65 ± 55 days *(87)*. The most common microorganisms causing BSI in most series were gram-positive bacteria, especially coagulase-negative staphylococci *(78,85,88–90)*. HSCT recipients with tunneled catheters are also at risk for catheter-related bloodstream infection, most commonly due to coagulase-negative staphylococci *(91–93)*. Among 242 HSCT recipients with indwelling, tunneled catheters who had daily blood cultures drawn, 5.28 patients per 1,000 catheter days developed a catheter-related bloodstream infection and 2.59 per 1,000 catheter days developed an exit site infection. Sixty-five percent of these infections occurred during neutropenia *(94)*. Although subcutaneous ports are believed to be associated with lower infection rates, studies are needed to document this finding in HSCT patients *(95)*.

Risk factors for healthcare-associated BSIs among HSCT recipients include an allograft from a matched unrelated or partially matched family donor, GVHD prophylaxis without methotrexate (MTX), presence of a tunneled catheter, and duration of TPN. A Dutch multicenter study on high-dose chemotherapy followed by peripheral stem cell transplantation in high-risk breast cancer patients demonstrated that factors predictive of BSI were duration of neutropenia >10 days, use of catheter for both stem-cell apheresis and high-dose chemotherapy, and use of TPN *(85)*. An outbreak of catheter-related polymicrobial bloodstream infections among 13 HSCT outpatients was reported in one study *(96)*. Risk factors included use of predrawn saline flush solution in which multiple doses were obtained from single-dose preservative-free vials *(96)*.

The Centers for Disease Control and Prevention (CDC) has developed guidelines for the prevention of catheter-related BSI, and these should be followed for all HSCT patients with intravascular catheters *(97)*. Recommendations in these guidelines should be followed when catheters are inserted and maintained. Given that many patients are discharged home with indwelling catheters, education regarding prevention of catheter-associated infection should be provided to patients and caregivers, including the recommendation that contact with tap water at the catheter site should be avoided *(97)* (see also Chapter 17).

Pneumonia

Pulmonary complications occur during the early and late periods after HSCT and are associated with significant morbidity and mortality. They can be either noninfectious or infectious in origin. For infectious processes, the source may be from endogenous reactivation, acquired from the environment or from person-to-person contact. The most common early-onset complication is interstitial pneumonitis, occurring in 10% to 40% of patients and usually associated with CMV coinfection *(98,99)*. During the first 100 days after HSCT, only 20% of pneumonias are caused by bacteria, and these are usually due to gram-negative bacilli *(91)*. Sinopulmonary infections caused by other microorganisms and obstructive airway disease associated with chronic GVHD are among the late-onset problems.

HSCT patients are at a higher risk than general hospital patients for developing healthcare-associated pneumonia, and 40% to 60% develop adverse pulmonary sequelae *(100,101)*. Pulmonary fungal infections, primarily *Aspergillus* species, develop in up to 16% of allogeneic HSCT patients *(102,103)*. Healthcare-associated pneumonia in immunocompromised hosts can be caused by inhalation of aerosols carrying *Legionella* species or *Aspergillus* species, or exposure to individuals with RSV, influenza, or parainfluenza virus. These microorganisms are important pathogens in HSCT recipients, and outbreaks of healthcare-associated pneumonia have been documented *(104–110)*. Among nonbacterial causes of pneumonia in recipients of allogeneic HSCTs, CMV pneumonia has the highest mortality rate, 91% *(111)*. Diffuse interstitial pneumonia caused by CMV during the postengraftment period occurs in 30% to 40% of the cases *(22)*.

Gastrointestinal Infections

Gastrointestinal illness in HSCT patients can be both an infectious and noninfectious process. HSCT patients can develop gastrointestinal symptoms from the conditioning regimen, radiation, acute GVHD, or medications *(112–114)*. A number of microorganisms including viruses, bacteria, protozoa, and helminthes can cause gastrointestinal infection *(112,115–118)*. Diarrhea may be caused by endogenous reactivation such as with CMV or acquired by various mechanisms such as respiratory transmission (e.g., adenovirus, influenza H1N1), ingestion (e.g., *Salmonella*), or contact transmission (e.g., *C. difficile*). The likely etiology of diarrhea following HSCT depends on the timing after transplantation *(119)*. Early after transplantation, intestinal damage due to chemotherapy is a common cause. Later onset, 20 to 100 days after HSCT the differential diagnosis includes acute GVHD *(120)*. In a cohort of 296 HSCT patients with diarrhea, Cox et al. *(121)* found that infectious pathogens accounted for only 13% of cases, whereas acute GVHD accounted for 48%. No etiology was identified in 39% of diarrheal episodes. Among patients with infections, the most common infecting microorganisms identified were viruses (12/126 patients; 9.5%) and *C. difficile* (6/126 patients; 4.8%). Another study reported identification of an infectious cause of diarrhea in up to 40% of episodes *(122)*. Of the 31 patients where a pathogen was identified, 12 (39%) had adenovirus, 12 (39%) had *C. difficile*, and 9 (29%) had rotavirus. More importantly, the mortality rate was 55% among patients with a pathogen isolated and only 13% among those patients who did not develop infectious diarrhea ($p < .0001$). Likewise, Blakey et al. *(116)* identified the cause of diarrhea in children undergoing HSCT. Enteric pathogens caused diarrhea 52% of the time; 14% of cases of diarrhea were caused by *C. difficile*. Interestingly, other *Clostridial species* including cytotoxin-negative *C. difficile* and *C. innocuum* were excreted in 90% of diarrheal episodes when no enteric pathogen was identified.

Typhlitis or neutropenic enterocolitis is a complication following chemotherapy that is commonly found in patients with hematologic cancer and patients undergoing autologous HSCT *(123,124)*. One study demonstrated that 75% of patients with typhlitis had at least cultured blood growing at least one microorganism at some time during their illness *(125)*.

If infectious diarrhea is suspected in HSCT patients, Contact Precautions should be applied, because many of these pathogens such as adenovirus, rotavirus, and *C. difficile* can be healthcare-associated (126,127).

Details about specific microorganisms can be found below.

Sinusitis

Approximately 1.7% of HSCT patients, most commonly allogeneic grafts, develop sinusitis *(128,129)*. Among 41 cultures of the paranasal sinuses obtained from 18 HSCT patients with sinusitis, the most common microorganisms identified were gram-negative bacteria (56.7%), gram-positive bacteria (26.7%), and fungi (16.6%) *(130)*. With the increasing use of high-risk HSCT and new cytotoxic chemotherapy, more cases of sinusitis due to less frequently identified pathogens have been reported including invasive fungi such as *Aspergillus* species, the Zygomycetes, and other filamentous microorganisms, which is a potentially lethal complication of HSCT-induced neutropenia. A mortality rate of 62% is reported despite appropriate antifungal therapy and surgical debridement *(128)*.

MICROORGANISMS

We review those microorganisms that require infection prevention and control interventions or have implications for healthcare workers or the environment. Certain infections characteristically occur at different time periods following HSCT. This pattern, however, has evolved as the management of HSCT patients had changed, including the use of prophylactic antibiotics and antiviral agents. The risk of developing a blood-borne infection (HIV; hepatitis A, B, C, D, E, G, and H; malaria; Chagas' disease; etc.) also exists in this population.

Infections in the early posttransplant period are usually due to the host's own flora colonizing the skin and mucous membranes and the urogenital or alimentary tracts. Medical therapies and the hospital environment, however, may alter the profile of microorganisms that colonize individual patients. Owing to the liberal use of broad-spectrum antibiotics in HSCT units, acquisition of highly resistant microorganisms, such as vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant gram-negative rods, and *S. maltophilia*, is common. The profound immunosuppression allows these patients to acquire potentially pathogenic microorganisms from sources that are of little concern in other hosts, such as uncooked foods and water. Free-living microorganisms, such as *Pseudomonas* species, normally colonize fresh fruits and vegetables and plants; institutional water sources are potential sources of microorganisms such as *Pseudomonas* species, *Legionella* species, fungi, and *Mycobacterium* species *(39)*. Similarly, construction and renovation in and around healthcare institutions have been associated with infection due to *Aspergillus* spp. and other molds (51). During the neutropenic phase immediately following transplantation, pathogens whose removal is dependent on phagocytic function predominate. It is estimated that 60% of febrile episodes in neutropenic patients are accompanied by bacteremia, but there have been important shifts in the microorganisms responsible

for these infections *(131)*. In the 1970s, gram-negative septicemia often caused by *P. aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*, and *Klebsiella* species resulted in high mortality of febrile neutropenic patients *(132,133)*. More recent prophylactic regimens have led to the emergence of fluoroquinolone resistant gram-negative rods and fungi. Driven by the extensive use of prophylactic and empiric antibiotic regimens active against gram-negative microorganisms, gram-positive microorganisms have now emerged as the most common pathogens *(134)*. Gram-positive microorganisms now account for 60% of bacteremias in HSCT centers *(134,135)*. Most of these infections are caused by *Staphylococcus epidermidis* and other coagulase-negative staphylococci. Wade et al. *(134)* found that the incidence of *S. epidermidis* infections increased from 2.0 per 1,000 patient days in 1972 to 14.6 per 1,000 patient days in 1979. Increased use of long-term indwelling venous catheters has also been implicated in the increase in gram-positive infections *(134,135)*. Streptococci, in particular alpha-hemolytic strains, commonly found in the oral flora have been recovered with increasing frequency owing to the poorer activity of fluoroquinolones against these microorganisms *(54)*. Furthermore, many gram-positive bacteremias, especially those due to *S. epidermidis*, now occur after engraftment *(136)*. The proportion of gram-positive and gram-negative bacterial infections varies from study to study due to the variation of timing of study period, antibiotic prophylaxis use, and type of center performing transplantation. Between 2004 and 2007, Cattaneo et al. *(137)* performed a prospective surveillance study in Italy analyzing microbiological isolates of all infectious episodes at a hematology unit that also included autologous HSCT recipients. Gram-negative bacteria caused 49.3% of infections, gram-positive bacteria caused 40.9% of infections, and fungi caused 8.9% of infections in this series *(137)*. These authors used levofloxacin for antibacterial prophylaxis in patients with expected neutropenia more than 7 days.

Viral Infections

Respiratory Virus Infections

Respiratory viruses cause infections in approximately 19% of HSCT patients each season (generally considered to be from November to May in the Northern Hemisphere). Respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza virus, adenovirus, picornaviruses, coronavirus, human metapneumovirus, and rhinovirus have been described as agents that affect HSCT patients *(138,139)*. These viruses commonly cause upper respiratory tract infections and can lead to serious lower respiratory tract infections associated with significant morbidity and mortality in this population. Adenovirus can lead to disseminated visceral syndromes *(140)*. Suspicion for respiratory virus infection should be maintained throughout the year, because parainfluenza and adenovirus occur year-round. While respiratory viruses are frequently acquired in the community, hospital transmission is well described. One group reported that 48% of these types of infections were acquired within the hospital *(138)*. A study of HSCT patients with respiratory symptoms who had cultures and direct fluorescent antibody examination of nasopharyngeal wash/throat specimens demonstrated that the most common community-acquired respiratory agent was RSV (35%), followed by parainfluenza virus (30%), rhinovirus (25%), and influenza (11%) *(141)*. Adenovirus was not included in the study because of the difficulty in differentiating new infection from reactivation of latent disease. Patients with radiographic evidence of pneumonia underwent bronchoalveolar lavage; 49% of patients with RSV had pneumonia and 22% of patients with parainfluenza had pneumonia, but pneumonia due to influenza and rhinovirus was uncommon (<10% of patients). In contrast, a more recent study reported the results of direct immunofluorescence assays performed on respiratory specimens from 179 HSCT patients who had 392 episodes of upper respiratory illness *(142)*. Of the 68 (38%) in whom virus was detected, respiratory syncytial virus was detected in 18 patients (26.4%), influenza A or B in 28 (41.2%), and parainfluenza in 7 (10.3%). Fourteen patients (20.6%) had multiple viruses isolated. RSV pneumonia developed in 55.5% of the patients with RSV upper respiratory infections. One of the 15 patients (6.7%) with RSV pneumonia died. Influenza pneumonia was diagnosed in three patients (7.3%). These investigators report a lower mortality than previously reported.

HSCT recipients or candidates who have symptoms of respiratory tract infection should be placed on Droplet Precautions and sometimes on both Droplet and Contact Precautions to avoid transmitting to other patients (127,143). Optimal isolation precautions should be modified after the causative agent is identified and the epidemiology understood (143). In some cases, prolonged shedding of virus is described requiring prolonged use of barrier precautions *(144–148)*. Diagnosis and the cause of upper respiratory infections should be established in HSCT patients, because they can progress to serious complications, some can be treated with antiviral agents, and others require precautions and rarely prophylaxis of exposed healthcare workers (143). HSCT candidates with upper respiratory tract symptoms, if possible, should postpone conditioning therapy until symptoms resolve (143) (see Table 59-1).

Adenovirus Adenoviruses are nonenveloped, double-stranded DNA viruses 70 to 90 nm in diameter *(149)*. At least 7 human adenovirus subgroups, including 52 serotypes, have been documented *(150)*. The incidence of disease in HSCT patients ranges from 5% to 27% in different studies *(151–157)*. Among HSCT recipients, especially children, the common serotypes that cause disease are 31 in subgroup A; 7, 11, 34, and 35 in subgroup B; 1, 2, 5, and 6 in subgroup C; and 4 in subgroup E *(158)*. One group found that subgroup B serotype 35 was the most prevalent adenovirus strain in their institution, and half of the adult patients infected with this strain had the same serotype recovered from cultures prior to HSCT *(152)*. Most of reported cases were diagnosed during the first 100 days posttransplant; however, the onset of adenoviral disease after 100 days has also been reported *(152,154,159)*. HSCT patients who develop adenovirus infections can present with upper and lower respiratory tract illness, acute hepatitis, gastrointestinal disease, acute hemorrhagic cystitis, nephritis, conjunctivitis, and central nervous system disease *(140,149,159–164)*. Patients who have recently undergone transplantation have an increased risk of severe disease (OR = 2.7) *(165)*.

TABLE 59-1

Prevention and Control Strategies for Respiratory Virus Infections

	Measurements
Transmission-based precautions	HSCT recipients with respiratory symptoms due to suspected respiratory virus infections should empirically be placed on Contact plus Droplet Precautions. After identification, precautions should be adjusted. - Droplet Precautions for influenza, parainfluenza and adenovirus - Droplet plus Contact Precautions for RSV - Prolonged shedding of virus is described in HSCT patients requiring prolonged use of barrier precautions Obtain nasopharyngeal swabs, throat swabs, or aspirates for culture, PCR, or rapid antigen testing to help determine whether patients have stopped shedding virus.
Hand hygiene	Healthcare personnel and visitors should disinfect hands with an alcohol-based gel, or if hands are visibly soiled, with soap and water.
Laboratory diagnosis	Hospitalized HSCT recipients with signs or symptoms of a respiratory virus infection should be promptly tested to identify respiratory viruses. - Appropriate samples include nasopharyngeal washes, swabs, aspirates, and bronchoalveolar lavage fluid. - In outbreak setting, prioritize and reduce turnaround time for diagnostic tests.
Visitor screening	Consider a daily screening of all persons who enter the unit for URI symptoms during hospital or community outbreaks of respiratory virus infections. - Visitors with URI symptoms should be asked to defer their visit to the unit until their symptoms resolve. - Visitors with infectious conjunctivitis should be restricted from direct patient contact until drainage resolves.
Personnel	- Personnel with URI symptoms should be restricted from patient contact and reassigned to nonpatient care duties until symptoms resolve.
Active surveillance	- Active surveillance of HSCT recipients may occur during respiratory virus season.
Outpatient setting	During hospital or community outbreak - Triage screening at the entrance of outpatient center. - HSCT recipients or family members with symptoms compatible with respiratory virus infections should be separated from other patients and don a mask. - HSCT recipients should be educated to use respiratory hygiene/cough etiquette.
Specific measurements	Influenza - HSCT recipients who are more than 4–6 mo after transplantation should receive a yearly inactivated influenza vaccine. - Personnel and close contacts of HSCT recipients should receive a yearly influenza vaccine at the start of the influenza season, preferably with trivalent inactivated influenza vaccine rather than with live attenuated influenza vaccine. - HSCT recipients less than 4–6 mo after transplantation should receive chemoprophylaxis with neuraminidase inhibitors during community influenza outbreaks that lead to healthcare-associated outbreaks. - Influenza postexposure prophylaxis is recommended for all influenza-exposed HSCT recipients who are less than 24 mo after transplantation or who are more than 24 mo after HSCT and substantially immunocompromised regardless of vaccination history, because of their likely suboptimal immunological response to influenza vaccine. RSV - During an outbreak of healthcare associated RSV infection, restrict healthcare personnel who care for RSV-infected patients from giving care for uninfected patients. Adenovirus - Recommendations for isolation Precautions depend on type of syndrome ◦ Gastroenteritis patients should be placed on Contact Precautions for at least the duration of illness. ◦ Cases with respiratory illness, conjunctivitis, or disseminated infection should be placed on Contact and Droplet Precautions. - Environmental disinfection with hospital-approved disinfectants

(Data from references 126 and 127.)

Disseminated adenovirus infection, in which two or more organ systems are involved, is associated with a 60% mortality rate *(140,163,166)*. The mortality rate may be as high as 70% in patients with pneumonia and disseminated disease *(154,167,168)*. Lymphopenia (<300 per μL) is one of the significant risk factors for severe disease, because lymphocytes play an important role in clearance of adenovirus viremia *(154,169,170)*. Receipt of an allogeneic transplant, presence of GVHD, and receipt of concurrent immunosuppressive therapy are risk factors for disseminated infection *(163,171)*. In addition, others have reported that the incidence of adenovirus is higher in children than adults *(172)*.

The diagnosis of adenovirus infection has traditionally been made by isolation of the virus in culture or by documentation of adenovirus in tissue. PCR is emerging as a promising diagnostic modality that provides a more rapid diagnosis and can be a monitoring tool for the virus *(156,173–176)*.

Because they are nonenveloped viruses, adenovirus are highly resistant to chemical and physical agents and can remain infectious at room temperature for prolonged periods of time, up to 49 days on plastic and up to 35 days on metal *(150,177)*. They are stable at low pH and resistant to gastric and biliary secretions allowing them to replicate and achieve high viral loads in the gastrointestinal tract *(150)*.

Transmission can occur by inhalation of aerosolized droplets, direct and indirect contact, fecal–oral spread, or exposure to infected tissue or blood (126,*159*). In general, type-specific immunity develops after a self-limited, 2-week illness, although latent infection may be established in lymphoid tissue *(149)*. Outbreaks have been reported primarily in pediatric HSCT patients *(167,178–180)*. The clinical presentation described in these outbreaks is diarrhea *(178–180)*.

Because the microorganism can be transmitted from person to person, attention to infection control practices is important. Recommendations for isolation precautions in a hospital setting depend on the type of clinical syndrome (126). Patients with diarrhea should be placed on Contact Precautions for at least the duration of illness (127). Since immunocompromised hosts may have asymptomatic shedding of adenovirus for months after infection, precautions should be continued for the duration of hospitalization or viral shedding to prevent transmission (126). For respiratory disease, conjunctivitis, or disseminated infection, Droplet and Contact Precautions should be maintained for at least the duration of illness (126,127).

Environmental cleaning with approved disinfectants such as a chlorine-based product, ethyl alcohol, or ethanol mixed with quaternary ammonium compounds is important to prevent spread of the microorganism (126). High-level disinfectants maybe used for instruments when applicable *(181)*.

Influenza Influenza is a segmented RNA virus with three subtypes, A, B, and C. The former two most commonly cause infection in humans. The virus is characterized by its hemaglutinin (H) and neuraminisase (N) moieties. Beyond the hemaglutinin and neuraminidase, minor genetic variations occur annually so that hosts can be susceptible to any strain that emerges each year *(182)*. Influenza causes a febrile syndrome characterized by the sudden onset of fever, myalgias, cough, and sometimes gastrointestinal complaints *(182–184)*. It can lead to viral pneumonia, encephalitis, myocarditis, rhabdomyolysis, and other disseminated processes *(185–190)*. Secondary bacterial infections with *S. pneumoniae*, *S. aureus,* and methicillin-resistant *S. aureus* (MRSA) are well described *(191–194)*. Immunocompromised patients receiving HSCT are considered to be at high risk for healthcare-associated influenza. Hospital outbreaks of influenza often occur during community epidemics and can be explosive among hospitalized high-risk patients and have been documented with the same frequency among neutropenic and nonneutropenic and autologous and allogeneic HSCT recipients *(195)*. Whimbey et al. *(195)* found that almost one-third (29%) of the hospitalized adult HSCT recipients had influenza type A cultured after developing respiratory symptoms. Hospital transmission was responsible for 60% of these 68 infections. Seventy-five percent of the cases were complicated by pneumonia and 17% (1/6) of these patients died *(195)*.

Pandemic H1N1 influenza, which emerged in 2009, has also been associated with morbidity and mortality in HSCT patients *(145,196–198)*. Five of thirteen HSCT recipients infected with H1N1 influenza had lower respiratory tract involvement that occurred when they were profoundly neutropenic *(196)*. Only one patient with lower respiratory tract infection survived, whereas all with upper respiratory tract infections were alive at follow up through 100 days *(196)*.

Infection prevention and control of influenza in the HSCT population can be challenging, because many of these patients have prolonged infection and viral shedding. Gooskens et al. *(144*) evaluated eight immunosuppressed patients with prolonged influenza virus infection. Virus was shed for more than 2 weeks and it was found that shedding was associated with lymphocytopenia, lower respiratory tract infection, and development of drug resistance during oseltamivir treatment *(144)*. Although patients who received antiviral treatment had clinical improvement, lymphocyte reconstitution was required for complete viral clearance *(144)*. A similar finding has been noted in patients with pandemic H1N1 influenza infection *(145)*. Tramontana et al. reported on 17 HSCT patients and 15 oncologic patients with laboratory-confirmed pandemic H1N1 influenza. All HSCT patients <100 days posttransplant or with severe GVHD required ICU admission, and the in-hospital mortality rate was 21.9% *(145)*. Virus was shed up to 28 days during oseltamivir therapy. An H275Y mutation developed in four of seven patients who were PCR positive after 4 days of oseltamivir therapy *(145)*. These studies suggest that HSCT patients should not be removed from Droplet Precautions until it is documented that they are no longer shedding influenza virus *(145)*.

Outbreaks of influenza among hospitalized patients including HSCT patients are commonly reported *(108, 199–203)*. Healthcare workers are often implicated as potential sources of transmission demonstrating the importance that all healthcare personnel who work in HSCT units receive annual influenza vaccination *(201–203)*. Additional interventions in the setting of an outbreak include strict infection prevention and control precautions. These include enforcing barrier precautions, masking universally, minimizing the number of staff entering the unit and patients' rooms, screening of visitors and other personnel, delaying nonessential admissions to the unit, surveying

actively for respiratory virus infection in all patients and unit staff, and using antiviral chemoprophylaxis for HSCT patients regardless of earlier vaccine status for the duration of the outbreak (*108*,143).

Influenza vaccine should be administered to patients prior to transplantation, because response to influenza vaccine is extremely limited for at least 6 months after transplantation *(204)*. Influenza vaccine does not fully protect patients until 2 years following HSCT. All family members and close or household contacts of HSCT recipients should continue to be vaccinated annually as long as the HSCT recipient remains immunosuppressed (143) (see also Chapter 42).

Parainfluenza Parainfluenza viruses are divided into four serotypes (205). Of the four types, parainfluenza 3 is the most common, followed by serotypes 1 and 2 (205). Parainfluenza virus can cause serious lower respiratory tract disease in both adults and children who undergo HSCT *(206)*. Significant risk factors for progression from upper to lower respiratory tract infection have included corticosteroids use and lymphopenia (205,*207,208*). Parainfluenza outbreaks in HSCT recipients have been reported *(109,110,209,210)*. These outbreaks were caused by introduction of parainfluenza 3 virus strains from a community reservoir into the HSCT population with subsequent person-to-person transmission within the unit *(110,211)*. Some studies revealed that, most likely, transmission occurred initially in the outpatient setting *(209–211)*. The mortality rate in HSCT patients infected with parainfluenza has been reported to be 33% to 38.5% *(110,208,210)*. Infection prevention and control measures much like those described for influenza are the most important strategy for preventing parainfluenza infection and transmission among HSCT recipients. Many outbreaks report the need for prolonged enforcement of surveillance, isolation, cohorting, and other infection prevention issues *(210,211)*. The outpatient setting should also be included in these prevention strategies.

Respiratory Syncytial Virus RSV accounts for one-third to one half of community-acquired respiratory viral infections among HSCT recipients *(138,141)*. Healthcare-associated transmission has been well documented among HSCT recipients, and the risk of healthcare-associated infection increases during community outbreaks *(106,107,212)*. Almost 60% (19/33) of the RSV infections in HSCT recipients are complicated by pneumonia, with an associated mortality between 51% and 80%. This infection may be complicated by pneumonia, and the risk of progression to pneumonia is greater in patients who are pre-engraftment, who underwent HSCT <1 month prior to infection, who are lymphopenic, and who have preexisting obstructive airway disease (*103*,143). RSV spreads via large droplets from respiratory secretions or by contamination of hands or surfaces and subsequent contact with the mucous membranes of the eyes and nose. Prevention of this viral infection is the best strategy given the limited therapeutic options and the tremendous morbidity associated with these infections. Comprehensive programs that include surveillance and isolation have been shown to prevent transmission among children *(213)*. A multifaceted infection control strategy is essential in the event of a healthcare-associated RSV outbreak; prompt identification of cases with active screening, cohorting, isolation of infected patients, screening of staff and visitors for upper respiratory tract symptoms, cleaning of equipment, and educating staff have been demonstrated as effective measures in controlling outbreaks on HSCT units *(214)*.

Coronavirus Coronaviruses are a family of single-stranded RNA viruses that cause respiratory disease among humans. Until the 2002 to 2003 respiratory virus season, two coronavirus strains, OC43 and 229E, were known to cause respiratory disease *(215)*. Patients generally present with mild upper respiratory symptoms, although pneumonia has been described *(215,216)*. Limited data are available about the clinical syndromes among HSCT patients. In a case series of two patients who had received autologous transplants, both developed pneumonia characterized by a dry, nonproductive cough and interstitial infiltrates on radiographs *(139)*. Milano et al. *(146)* conducted a prospective surveillance study in allogeneic HSCT recipients and reported that the incidence of coronavirus infection among these patients was 11.1%. Nine of twenty-two patients were asymptomatic and 3/22 patients had prolonged viral shedding *(146)*.

In 2003, severe acute respiratory syndrome was described, which has rejuvenated interest in this virus and the clinical syndromes it causes. Published reports from several cohorts of patients noted a febrile syndrome characterized by cough, myalgias, dyspnea, and occasionally diarrhea with some patients going on to develop respiratory failure *(217–219)*. The spectrum of disease in HSCT patients is not well described.

Human Herpes Viruses Infections

Cytomegalovirus Cytomegalovirus (CMV), a double-stranded DNA herpes virus, is a major cause of morbidity and mortality among HSCT patients. Asymptomatic infection or symptomatic disease can result from either newly acquired infection from CMV-infected bone marrow or blood products or reactivation of previous infection. Risk factors for symptomatic CMV disease in HSCT patients include CMV seropositivity in the HSCT recipient, receipt of CMV seropositive hematopoietic stem cells or blood products by a CMV-seronegative recipient, allogeneic HSCT, use of T-cell–depleted graft, use of a mismatched or unrelated donor, the development of GVHD, prolonged immunosuppression, lymphopenia following transplantation, use of high-dose corticosteroids, alemtuzumab, fludarabine, or 2-chlorodeoxyadenosine, and failure of development of a CMV-specific cellular immune response *(22,91,220–225)*.

Serious CMV disease most frequently results in interstitial pneumonitis (143). Other manifestations include gastroenteritis, hepatitis, and encephalitis; retinitis has also been reported in HSCT recipients *(226,227)*.

Quantitative polymerase chain reaction (PCR) for CMV DNA or RNA is the most sensitive method for detecting CMV and has been used to determine the need for preemptive therapy (143,*225*,*228*). CMV pp65 Ag in leukocytes (antigenemia) can also be used, but the test may be falsely negative in patients with neutropenia (143,*229*,*230*).

Despite treatment with ganciclovir and IVIG, mortality from CMV pneumonia remains as high as 20% to 75% *(231–234)*. Among autologous HCST patients who developed

CMV pneumonia, all were previously CMV seropositive and all except two had underlying hematologic malignancies *(235)*. Most cases (n = 11) occurred <30 days posttransplant, although five cases occurred >100 days posttransplant. Thirty-one percent of patients died. New infection with CMV among CMV-seronegative HSCT patients has dramatically decreased since the use of CMV seronegative or leukocyte-reduced blood products have been implemented. In one study, the rate of exogenous infection was 23% compared to 0% in seronegative patients receiving CMV-seronegative red blood cell and leukocyte-depleted platelets *(236)*. CMV-seronegative blood products are felt to be comparable to filtered leukocyte-reduced blood products with regard to risk of CMV transmission *(236)*.

The overall incidence of developing CMV pneumonia in the first 100 days after transplantation is 7% *(91)*. CMV infection is much less likely to cause serious disease following autologous HSCT *(237)*. The incidence of CMV infection is 38.8% to 61%; however, only 0.8% to 6.9% of patients develop end-organ disease *(230,237,238)*. A review of CMV pneumonia in autologous HSCT recipients at one institution reported that 2% (16/795) of autologous HSCT patients developed CMV pneumonitis *(235)*. However, historically, 45% to 87% of allogeneic HSCT patients develop CMV infection and 21% to 43% develop disease *(237,239)*. The current standard of care in patients who are seropositive or have received seropositive transplants is to receive prophylactic antiviral therapy or preemptive antiviral therapy after detection of CMV reactivation with diagnostic testing. The rates of CMV disease in HSCT patients are now 5% to 18% (143,*222,240*).

Historically, the majority of CMV infections occur between 30 and 100 days following transplantation, with a median day of onset between the 40th and 50th day *(22,237)*. However, the risk of developing CMV disease later after transplantation appears to be increasing as prophylaxis and preemptive strategies are employed early after HSCT. The trend where CMV infection develops in HSCT cases at longer intervals after the transplant may be related to delayed reconstitution of CMV-specific T-cell immunity in the face of ganciclovir prophylaxis. Strategies for preventing late CMV disease in HSCT patients with high risk include use of continued surveillance and preemptive antiviral therapy. No precautions beyond Standard Precautions are recommended.

Herpes Simplex Virus Herpes simplex virus (HSV) infection is an important cause of morbidity in HSCT patients due to the severe mucocutaneous lesions produced by reactivation of latent virus *(136)*. Prior to the routine implementation of prophylaxis, HSV was the most common viral infection seen after HSCT, occurring in up to 80% of seropositive individuals in the first 50 days after HSCT *(136,241)*. Shedding of the virus is most frequent from days 14 through 28 after HSCT *(136)*. In contrast, only 1% of previously seronegative patients excrete the virus. The disease most often involves the oropharynx, but can manifest itself by limited or disseminated cutaneous disease. Less frequently, HSV may produce keratitis, pneumonitis, hepatitis, or encephalitis *(136)*. Importantly, healthcare-associated transmission of HSV from infected patients to healthcare workers and family members is reported *(242,243)*. Several outbreaks suggest that immunocompromised patients with herpes simplex pneumonia are most likely to transmit the virus *(242,243)*. In one of these studies, molecular typing of strains confirmed that the patients', healthcare workers', and family members' strains were genetically identical *(242)*. An emerging concern is the increasing frequency of HSV strains that are resistant to acyclovir *(244–249)*. One study demonstrated that 7% (14/196) of patients undergoing allogeneic HSCT were infected with acyclovir resistant HSV-1; seven cases were also resistant to foscarnet. Standard Precautions are recommended for all patients. In addition, patients with lesions should be placed on Contact Precautions (127). In instances with HSV pneumonia, Droplet Precautions should be considered.

Varicella-Zoster Virus Varicella-zoster virus (VZV) is caused by a DNA virus in the herpes family. It is the cause of varicella (chicken pox), which represents primary infection, and herpes zoster (shingles), which represents reactivation of latent VZV infection *(250)*. Although varicella is generally a mild disease in children, serious morbidity and mortality are common if infection occurs in immunocompromised patients *(251)*. Among patients developing varicella while receiving chemotherapy for malignancy or immunosuppressive therapy following transplantation, severe disease has been reported in 36% and death in 13% *(252,253)*. Encephalitis has also been reported in allogeneic HSCT patients *(254,255)*. In children, 28% not treated with antivirals develop pneumonia *(251)*. The skin lesions may form for up to 2 weeks and crusting may require 3 to 4 weeks *(251)*.

The majority of VZV infections in adults are due to reactivation of latent virus. In contrast to HSV infections that usually develop in the first month after HSCT, VZV-seropositive HSCT recipients develop VZV reactivation during the 3 to 12 months after HSCT (median = 5 months) *(252,256–264)*.

Risk factors for reactivation of VZV include chronic GVHD, a diagnosis of leukemia and other lymphoproliferative disorder, CD4 lymphocyte count of <800 cells/L, HLA mismatch, a myeloablative regimen with total body irradiation, CD34+ cell-selected allogeneic and autologous peripheral blood HSCT, and age >50 years *(252,258,260,265–268)*. Although most patients present with a dermatomal rash, cutaneous dissemination occurs in 6% to 23% of patients, encephalitis occurs in 5% of patients, and visceral involvement is noted in up to 14% of patients *(261,264,268–270)*. Visceral involvement most commonly involves the lungs and liver, and abdominal symptoms such as pain, nausea, and vomiting can precede the development of vesicular rash by several days *(271)*. Although antiviral suppression is standard of care for HSV disease, the role of antiviral suppression for the prevention of VZV has not been established in HSCT patients. While oral acyclovir for 6 months after transplant suppressed VZV reactivation, patients have developed rapid onset of VZV infections after the cessation of therapy *(256,268,272)*. The concerns about development of resistant strains of herpes viruses may outweigh the utility of prophylaxis. Regardless of VZV serologic status, HSCT candidates and recipients should avoid exposure to persons with active VZV infections and to persons who develop a rash after VZV vaccine (143). In hospital such patients should be placed on Airborne and Contact Precautions as immunocompromised hosts with VZV shed virus from the respiratory tract and lesions and transmission

to other patients is documented *(273)*. VZV-seronegative HSCT patients who are exposed to VZV or a vaccinee with a rash and are not immunocompetent should receive VZIG within 96 hours of exposure (143,*274*). A recent study by Hata et al. (*275*) demonstrated that inactivated varicella vaccine given before autologous HSCT and during the first 90 days after significantly reduced the risk of herpes zoster; 33% of unvaccinated patients compared to 13% of vaccinated patients developed zoster.

Varicella is extremely contagious, with secondary attack rates of >90% *(276,277)*. The incubation period of varicella ranges from 8 to 21 days, but most patients develop disease between 14 and 16 days after exposure. Patients with varicella become infectious 24 to 48 hours prior to the onset of rash, and viral shedding is prolonged by 2 days in the immunocompromised host *(251)*. Transmission is thought to be due to direct contact with infectious persons. However, based on several outbreaks where patients and/or healthcare workers with no exposure developed varicella, airborne transmission is presumed *(273,278–280)*. Sawyer et al. *(281)* used PCR technology to determine whether VZV could be transmitted by aerosol spray. VZV DNA was detected in 64 of 78 (82%) air samples from hospital rooms housing patients with varicella infections and 9 of 13 (69%) rooms of patients with herpes zoster *(281)*. VZV was detected from infected patients' beds for 1 to 6 days following the onset of rash, and on some occasions could be detected outside of the patients' rooms. Interestingly, this study contradicts investigators who suggest fomites are not important in the transmission of VZV *(276)*.

Airborne transmission is suspected to be a primary mechanism of transmission of disease among patients with hematologic malignancy and patients undergoing HSCT *(273,278–280)*. Leclair et al. *(279)* described an outbreak of varicella that occurred in a pediatric hospital. Twenty-four of thirty-two patients hospitalized on an infant ward were exposed and susceptible to varicella. Ultimately 15 (62.5%) patients developed chickenpox after an index case requiring mechanical ventilation was hospitalized. Studies of distribution of air documented increased airflow to those rooms where a higher number of cases occurred. These investigators suggest that increased concentrations of virus and droplets were expelled from the exhaust loop of the ventilator. In a similar instance, Gustafson et al. *(280)* demonstrated that the risk of children developing varicella was related to how near they came to the index case's room. Eight (11%) exposed children developed varicella. The attack rate was higher for children exposed to the patient early in his disease (8/28; 28.6%) *(280)*. Based on airflow studies, the pressure in all rooms was positive relative to that of the outside corridor. Moreover, 10% of a tracer gas released in the patient's room was measured in corridor air *(280)*. Furthermore, airborne transmission may occur with herpes zoster that involves more than one dermatome. For instance, an adult patient developed herpes zoster after receiving high-dose steroids, and three nurses developed varicella *(273)*. Two of the three nurses had no contact with the patient. HSCT recipients with primary varicella infection or disseminated herpes zoster should be placed on Airborne and Contact Precautions (127). Patients with localized herpes zoster should also be placed on Airborne Precautions until disseminated infection is ruled out, because most HSCT recipients are in an immunocompromised state (127). The precautions should be maintained until lesions are dry and crusted (127). In HSCT recipients with varicella pneumonia, precautions should be maintained for the duration of the illness (127). Susceptible healthcare personnel should not enter the room if immune caregivers are available (127). For susceptible nonimmunized healthcare personnel who are exposed to a varicella patient, postexposure prophylaxis with vaccine is recommended as soon as possible but within 120 hours; for susceptible exposed personnel for whom vaccine is contraindicated, Varicella Zoster Immunoglobulin (VZIG) should be provided within 96 hours. Use Airborne Precautions for exposed susceptible persons and furlough exposed susceptible healthcare personnel beginning 8 days after the first exposure until 21 days after the last exposure or for 28 days if VZIG was given (127).

Hospital transmission of varicella is well recognized. Healthcare personnel should have evidence of immunity to varicella *(274)*. Institutions should establish protocols and recommendations for screening and vaccinating personnel and for management personnel after exposures in the work place *(274)* (see also Chapter 43).

Epstein–Barr Virus Epstein–Barr virus (EBV) has been associated with various clinical syndromes. It can cause primary infection, reactivation, and chronic active infection in HSCT patients *(264,282)*. Most EBV reactivations are asymptomatic; however, the complications such as encephalitis/myelitis, pneumonia, and hepatitis can occur *(264)*. The role of EBV as a cause of posttransplant lymphoproliferative disorder (PTLD) is well described *(264,282)*. This disorder occurs predominantly in recipients with profound T-cell cytopenia such as a T-cell–depleted graft (143,*283*). Other risk factors include unrelated donor HLA mismatch, use of antithymocyte globulin, and use of anti-CD3 monocloncal antibodies for GVHD prophylaxis *(282–284)*.

HSCT donors and candidates should be tested for the presence of anti-EBV IgG antibody before transplantation to determine the risk for primary EBV after HSCT (143). Standard Precautions are used for this microorganism (127). No additional isolation is needed.

Human Herpes Virus Types 6 and 7 The scope of disease caused by human herpes virus type 6 or 7 (HHV-6 or HHV-7) in HSCT patients has yet to be fully elucidated. Both viruses are frequent causes of febrile infection in children and the etiologic agents of exanthem subitum. Primary infection usually occurs in the first year of life and seroprevalence in adults exceeds 90% *(285)*. Following primary infection, the virus establishes latency in peripheral blood mononuclear cells as well as salivary glands and neural cells *(286)*. Reactivation of latent virus is felt to be the source of infection in the majority of HSCT patients. Although HHV-6 cannot be cultured from the blood of healthy adults, roughly 40% to 50% of HSCT patients develop HHV-6 viremia 2 to 4 weeks after transplantation *(287,288)*. Patients receiving allogeneic HSCT have been reported to be at higher risk for reactivation of HHV-6 *(287)*. Although most HSCT patients with HHV-6 reactivation are asymptomatic, several studies have demonstrated a correlation between reactivation of HHV-6 and both maculopapular rash and fever following HSCT transplantation *(287,289–291)*. Other studies have

shown an association between central nervous system symptoms including encephalitis and detection of HHV-6 in cerebrospinal fluid (CSF) *(288)*. Wang et al. *(292)* examined CSF from 22 allogeneic HSCT patients with central nervous system symptoms and found that 23% (5/22) had detectable HHV-6 DNA and no other potential pathogen identified. In addition, 11 of the 22 patients without detectable HHV-6 had other causes identified that explained central nervous system symptoms *(292)*. Hospital transmission has not been reported to date. Standard Precautions are recommended for these patients.

Limited studies have examined HHV-7 infection in these patients. HHV-7 associated CNS involvement among HSCT recipients has been reported *(293–296)*.

Viral Gastroenteritis

Rotavirus Rotavirus is a common cause of nonbacterial gastroenteritis in children. It has also been a significant cause of diarrhea in HSCT recipients *(297,298)*. The symptoms of rotavirus infection in HSCT patients included diarrhea, vomiting, abdominal pain, and loss of appetite *(298)*.

Several healthcare-associated outbreaks of rotavirus infection have been reported *(299–302)*. One outbreak was reported to be related to shared toys in a playroom on a pediatric oncology floor *(303)*.

Environmental contamination is common despite cleaning since rotavirus is a nonenveloped virus and can survive on nonporous surfaces for a long period of time *(300,301,304–306)*. Disinfectants that can be used for rotavirus include sodium hypochlorite, phenol-based products, and *ortho*-phenylphenol with alcohol *(307)*.

Rotavirus was reported to have asymptomatic shedding, and prolonged shedding may occur in immunocompromised patients (126,*303,308*) (see also Chapter 50).

Norovirus Norovirus is the leading cause of outbreaks of nonbacterial gastroenteritis in the community and can be explosive in healthcare settings (126,*309*). Roddie et al. *(310)* retrospectively reviewed 12 HSCT recipients with norovirus infection. The median time after transplantation to the development of symptoms was 10.5 months (range 0.25–96 months). Patients present with fever, transient nausea, and vomiting. Diarrhea can be prolonged, lasting a median of 3 months (range = 0.5–14 months). Norovirus is highly transmissible by the fecal–oral route and by environmental and fomite contamination *(309)*. Moreover, it can survive in chlorine and varying temperatures (freezing and heating to 60°C). Quaternary ammonium compounds and alcohols are ineffective as disinfectants *(309,311)*. Hand washing with soap and water should be implemented. Routine alcohol-based hand rubs may be ineffective for preventing norovirus transmission (126,*309*). Newer alcohol-based products have been introduced and are effective in inactivating the virus *(312)*.

Patients should be placed on Contact Precautions. The environment should be aggressively cleaned. A hypochlorite-based cleaning agent is recommended for use on hard, nonporous environmental surfaces at a concentration of 1,000 ppm depending on the level of contamination and types of surfaces (126,*313*). Cohorting and symptom screening may be instituted if ongoing transmission occurs. Rapid and aggressive responses are important when this microorganism is suspected because of how explosive it can be in hospitals *(309,314)*.

Other Viruses

Parvovirus B19 Parvovirus B19 is an uncommon pathogen in the HSCT population, occurring in 1.4% of transplant patients at one institution *(315)*. Transmission via transplantation may occur *(316)*. It has been associated with prolonged anemia and viral shedding in the peritransplant period as well as in patients with chronic GVHD *(317–320)*. Parvovirus B19 has also been associated with rash, arthralgia, hepatitis, pneumonitis, and myocarditis *(321)*. Multiorgan failure has also been reported *(322)*. IVIG has been used for treatment in the absence of evidence from a randomized trial *(321)*.

Polyoma Virus Two viruses warrant mention. First, Polyoma BK virus was first reported in renal transplant patients in 1971 *(323)*. The isolation of BK virus in HSCT recipients most often correlates with secondary viral replication due to impaired polyomavirus-specific cellular immunity (143). Hence, viruria occurs in about 60% to 80% of patients after HSCT, usually within 2 months *(324–330)*. Approximately 20% of patients with viruria will develop hemorrhagic cystitis *(324,331,332)*. Factors that may contribute to hemorrhagic cystitis include presence of pretransplant BK virus IgG antibody, type of conditioning regimen, allogeneic HSCT, type of donor, GVHD, and a high peak BK urine viral load *(324,331,333)*. Hemorrhagic cystitis from BK virus typically occurs after engraftment and must be distinguished from hemorrhagic cystitis caused by other pathogens including adenovirus and CMV (143,*324*).

Second, Polyoma JC virus infection has also been reported to cause progressive multifocal leukoencephalopathy (PML) in HSCT recipients *(334,335)*. Standard Precautions are used for patients with either polyoma virus infection.

West Nile Virus West Nile virus (WNV) is a mosquito-borne flavivirus that is indigenous to Africa, Asia, Australia, and southern Europe *(336)*. It was first noted in North America in 1999, and the number of yearly cases in the United States has continued to increase since that time. It is of concern to caregivers of HSCT patients because of convincing evidence that it can be transmitted by blood transfusion and organ transplantation *(337,338)*. Tests to detect viral nucleic acid within blood products are now available and are being used to assess the blood supply for WNV.

In the general population, approximately 20% of persons infected with the virus develop a mild febrile illness and only 1 in 150 develops meningitis or encephalitis *(339)*. However, all of the patients who received organs from a donor who had received blood containing WNV developed clinical WNV; three of the four developed encephalitis and one died, suggesting that the disease is more virulent in immunocompromised hosts *(338)*. The diverse clinical presentations of WNV neurologic disease include meningoencephalitis, meningitis, flaccid paralysis, ataxia, cranial nerve abnormalities, extrapyramidal signs, myelitis, polyradiculitis, optic neuritis, and seizures. The incubation period is 3 to 14 days, and most patients

demonstrate a CSF pleocytosis *(339)*. At least two cases of WNV infection have been reported in patients who underwent HSCT *(340)*. In both cases, the infection was fatal.

This population is considered to be at increased risk of infection if they come from areas where WNV is endemic or because they receive blood products. WNV should be suspected in all HSCT patients who have received blood products or have exposure to mosquitoes and present with fevers and neurologic symptoms *(337,341–343)*.

Prevention strategies include avoiding exposure to mosquitoes and may include screening of the blood supply. Standard Precautions are used in these patients.

Bacterial Infections

Viridans streptococci Bacteremia caused by viridans streptococci is associated with a sepsis-like syndrome among HSCT and neutropenic patients *(62,65)*. One investigator reported that streptococci cause 71% of bloodstream infections in children undergoing HSCT *(344)*. Likewise, Heimdahl et al. *(60)* showed that oral microorganisms, particularly α-hemolytic streptococci, caused 24 of 59 infections that occurred in neutropenic patients early after HSCT. The important predisposing factors for viridans streptococcal bacteremia are severe neutropenia and oral mucositis. Besides mucositis, dental health also has impact on viridans streptococcal bacteremia in HSCT recipients. Graber et al. *(345)* demonstrated that HSCT recipients with streptococcal bacteremia were more likely to have severe intraoral pathology while neutropenic compared to patients without an identified focus of infection (26% vs. 0%) and slightly shorter interval between the last dental procedure and the onset of neutropenia (11 vs. 14 days). Risk factors for viridans streptococcal bacteremia include prophylactic administration of trimethoprim-sulfamethoxazole, beta-lactams, or a fluoroquinolone and chemotherapy-induced gastrointestinal toxicity treated with H2 antagonists or antacids *(67,346)*. Penicillin-, cephalosporin-, and quinolone-resistant strains of viridans streptococci have been reported *(346–350)*. Attributable mortality rate for pre-engraftment viridans streptococcal bacteremia is 6% to 30% *(67)*. Empiric vancomycin therapy is recommended in HSCT patients with viridians streptococcal infection if penicillin resistance is suspected either because of local microbiologic data or host risk factors *(351)*. Vancomycin should be narrowed based on final susceptibilities. The prudent use of vancomycin is needed to minimize vancomycin-resistant microorganisms in this patient group.

Vancomycin-Resistant Enterococcus Enterococci are commensal flora of the human gastrointestinal tract. In normal hosts, they may have limited pathogenicity, but in HSCT recipients VRE are associated with significant morbidity and mortality *(352,353)*. Reported rates of colonization are variable (4.7–40.2%), although rates are increasing in some studies *(352,354–356)*. Kamboj et al. *(357)* noted that 27.5% of allogeneic HSCT had VRE colonization at pretransplant screening between 2008 and 2009. VRE were the most common cause of primary bacteremia (53.5% of all positive blood cultures) in the early posttransplant period (days 4–10 after HSCT), and only 53% of patients with VRE bacteremia had positive surveillance cultures growing at pretransplant screening. The independent risk factors for VRE bacteremia were VRE colonization and allograft with T-cell depletion. The mortality in this study was 4.4% compared to 15% in patients with non-VRE bacteremia *(357)*. The increased incidence of VRE occurred after implementing vancomycin prophylaxis in the peritransplant period to prevent viridans streptococci infection in myeloablative HSCT *(357)*.

Several studies have evaluated risk factors for VRE infection *(132,133,358–360)*. Independent risk factors for developing VRE infection include neutropenia for more than 1 week, the use of oral vancomycin, and mucositis severity *(133,358)*. Zaas et al. *(132)* reported that the risk factors for infection in colonized patients included diabetes mellitus, gastrointestinal procedures, acute renal failure, and use of vancomycin for 7 days in the 60 days before admission. *C. difficile*–associated diarrhea has also been noted as a risk factor for VRE colonization and bacteremia *(132,358)*.

Hospital factors that predict colonization and infection with VRE include location in a high-risk area such as the ICU or oncology unit, length of hospitalization, number of individual contacts with VRE carriers, and overall proportion of patients colonized with VRE on a unit *(361–364)*. VRE can be transmitted by person-to-person spread or from the contaminated environment. Most hospital transmission occurs via the contaminated hands of healthcare workers. VRE survives on hands for at least 60 minutes after inoculation and are recovered on the hands in 10% to 43% of workers caring for VRE-colonized patients *(241,365)*. In addition, case–control studies have shown that exposure to a healthcare worker caring for a VRE-infected or a VRE-colonized patient increases the risk of acquiring VRE *(366)*. VRE can survive for long periods (up to 7 days) on dry surfaces and is recovered in 7% to 30% of environmental surfaces cultured during outbreaks of VRE *(365,367,368)*. Environmental contamination increases twofold when patients have diarrhea or are colonized in multiple body sites *(368,369)*. Not surprisingly, VRE outbreaks have been linked to many fomites including contaminated electronic thermometers and ear oximeters *(370,371)*.

The relationship between antibiotic exposure and colonization and infection with VRE has been extensively studied. The most consistently recognized antimicrobials associated with VRE acquisition are vancomycin, extended-spectrum cephalosporins, and antianaerobic agents *(363,372–375)*. Both the total amount of antimicrobials and the therapy are risk factors for VRE *(364)*. There is a consistent epidemiologic association between previous use of oral vancomycin and subsequent development of VRE colonization, which is likely related to selection pressure in the gastrointestinal tract, leading to the recommendation that oral vancomycin not be used routinely in the therapy of *C. difficile* colitis *(364)*. The relationship between intravenous vancomycin therapy and VRE colonization and infection is more controversial. Although several studies have noted an association between vancomycin and VRE, others have not found an effect *(369,372–374,376–382)*. Although vancomycin therapy likely does not cause VRE to develop or increase the chance that a patient will acquire VRE, it likely exerts selective pressure in the gastrointestinal tract and increases the burden of preexisting VRE to a detectable level *(364)*. Consequently, the prudent use of vancomycin

in patients at high risk for VRE, particularly HSCT patients, is highly recommended.

Extended-spectrum cephalosporins and antianaerobic drugs have also been strongly associated with VRE *(376,381,383)*. Among HSCT patients, Edmond et al. *(363)* reported that patients who received metronidazole or imipenem were 2.5 times more likely to develop a VRE bloodstream infection. One group was able to reduce the VRE acquisition rate on a leukemia unit by substituting piperacillin-tazobactam for ceftazidime as therapy for febrile neutropenia with no change in vancomycin use *(384)*. The theoretical mechanism of this observation is that extended-spectrum penicillins have some activity against enterococci whereas cephalosporins do not, allowing for some reduction of VRE overgrowth in the gastrointestinal tract *(364)*. Some oncology centers have moved toward the use of extended-spectrum penicillins rather than cephalosporins as a means to reduce rates of VRE colonization and infection, but studies to date have not confirmed the benefit of this approach *(385–387)*.

VRE colonization may persist for up to 1 year *(388)*. Among 253 immunocompromised patients, Lai et al. found 70% of patients were persistent fecal carriers for up to 303 days (median = 41) *(389)*. Of the 49 patients whose later stool cultures no longer grew VRE, four patients became recolonized. Beezhold et al. *(390)* found that all patients with VRE bloodstream infections were colonized either in the gastrointestinal tract (100%) or on the skin (86%).

The impact of these infections cannot be underestimated in this population. VRE bacteremia is associated with increased mortality in HSCT patients. In a well-designed historical cohort study of 27 leukemic patients with VRE bacteremia, Edmond et al. *(363)* reported a mortality of 67%, compared to a 30% mortality in closely matched controls without VRE bacteremia. Several studies suggest that VRE infections not only increase hospital length of stay, but also consequently inflate the cost of care to both the hospital and the patient *(363,391)*.

A number of outbreaks of VRE among HSCT units or hematological wards have been reported *(376,392,393)*. Most implicate infection control breaches and antibiotic overuse *(376,392,393)*. Approaches to outbreak control included staff education, weekly surveillance, isolation of colonized patients, hand hygiene, environmental cleaning, and changing antibiotic policies *(376,392,393)* (see also Chapter 33).

Methicillin-Resistant Staphylococcus aureus Resistance to methicillin among *S. aureus* was first noted in 1961, the first year that methicillin was available. Since the late 1980s, rates of MRSA in the hospital setting have continued to increase. Among HSCT patients, *S. aureus* is a significant pathogen, particularly as a cause of catheter-related bloodstream infection *(94)*. Risk factors for the acquisition of MRSA include previous or prolonged hospitalization, advanced age, recent surgery, enteral feedings, and open skin lesions *(394–396)*. The overall frequency of MRSA in a study of HSCT recipients was 5%, and was most commonly seen in unrelated-donor (9%), sibling allogeneic (6%), and autologous (3%) recipients. More than half (21/41) of the events occur 1 month to 6 years after transplantation, 15/41 occurred pretransplant and 5/41 were detected early posttransplant. The mortality rate was highest in the early posttransplant group with most patients presenting with bacteremia *(397,398)*. Mihu et al. *(397)* reported a case fatality rate of 15% with an attributable mortality rate of 8%. Risk factors for late *S. aureus* bacteremia in allogeneic HSCT recipients included skin GVHD and prolonged hospital length of stay *(397)*. MRSA is transmitted primarily on the hands of healthcare workers; thus, hand hygiene coupled with Contact Precautions form the backbone of the prevention of transmission of MRSA. One study suggested that the environment and common items in the environment may play a more important role than previously recognized *(399)*. Many centers perform surveillance cultures of the anterior nares at the time of admission and weekly to facilitate the early identification of patients with MRSA. This strategy facilitates the identification and rapid isolation of patients who could be colonized with the microorganism. Given that many of these patients have been previously hospitalized and exposed to antibiotics, such a strategy may be cost effective in this population. For patients with recurrent MRSA infection, current guidelines suggest that eradication of the carrier state can be attempted by applying a 2% mupirocin calcium ointment to the nares, and by the use of topical antiseptics such as chlorhexidine for bathing (126) (see also Chapter 29).

S. aureus with reduced susceptibility to glycopeptides has been reported in HSCT patients *(400)*. Current guidelines recommend that institutions should conduct routine surveillance for the emergence of *Staphylococcus* species strains with reduced susceptibility to vancomycin (126).

Antibiotic-Resistant Gram-Negative Microorganisms Gram-negative pathogens are described in detail in Chapters 34 and 35 "Enterobacteriaceae" and "Nonfermentative Gram-Negative Bacilli," respectively. These microorganisms are significant causes of bloodstream infection in HSCT patients. Mikulska et al. *(401)* found a significant decrease in the gram-positive bacteria/gram-negative rods ratio from 2.4 to 1 between 2004 and 2007. Fluoroquinolone resistance was common (74%) among gram-negative microorganisms in this study, likely because all patients received fluoroquinolones for prophylaxis. In a prospective multicenter study from Brazil, it was found that bacteremia was caused by gram-negative bacteria in 37% of patients and by gram-positive bacteria in 47% of patients *(402)*. Mixed infections were noted in 16% of patients *(402)*. *P. aeruginosa* (22%), *Klebsiella pneumoniae* (19%), and *E. coli* (17%) accounted for the majority of gram-negative isolates and 37% were resistant to multiple antimicrobials *(402)*.

A number of outbreaks of gram-negative microorganisms have been reported among HSCT patients and on hematologic units (*47*,*403*,404,*405–413*). Most *P. aeruginosa* outbreaks are related to water sources such as shower heads, basins, sinks, bathtubs, faucets, bidets, water closets, and bath toys *(403,405,407–412)*. Some studies have demonstrated microorganisms on healthcare personnel's hands suggesting that poor hand hygiene plays a role in transmitting these microorganisms *(414–416)*. Infected healthcare personnel can also play a role in healthcare-associated *P. aeruginosa* infection. Healthcare personnel with intermittent otitis externa and onychomycosis have

been implicated in outbreaks *(415–418)*. Artificial fingernails have also been associated with a *P. aeruginosa* outbreak *(419)*.

S. maltophilia has been well described in HSCT recipients *(47,420–425)*. This microorganism is typically resistant to extended-spectrum beta-lactam agents and carbapenems *(426)*. Patients commonly present with breakthrough infections while receiving broad-spectrum antibacterial treatment *(427)*. Risk factors for *S. maltophilia* infection included broad-spectrum antibacterial therapy, mechanical ventilation, intravenous catheterization, neutropenia, mucositis, and diarrhea *(47,425,426,428–431)*.

Outbreaks of *S. maltophilia* have been associated with contaminated water faucets, bottled water, and hand moisturizers *(47,422–424)*.

Other gram-negative pathogens are causes of infections and outbreaks in this patient population. An outbreak of multidrug-resistant *Serratia marcescens* infections in an oncology unit involving HSCT patients resulted from inadequate infection control practices and poor hand hygiene *(432)*. No environmental culture was positive for *S. marcescens* except for the control buttons of an intravenous pump, which yielded *S. marcescens (432)*. A few studies also demonstrated the role of healthcare personnels' hands in transmitting *S. marcescens (433–435)*.

In Israel, an outbreak of carbapenem-resistant *K. pneumoniae* among HSCT patients was reported *(436)*. Eight patients had bacteremia, and all were neutropenic or had GVHD *(436)*. Three patients died *(436)*.

Overall, outbreaks of these resistant microorganisms can occur from inadequate infection control measurements including hand hygiene and environmental cleaning and use of broad-spectrum antibacterial agents.

HSCT patients with colonization/infection with multidrug-resistant microorganisms should be placed on Contact Precautions. Institutions should have a written policy to minimize the impact of these resistant microorganisms on quality of patient care.

Clostridium difficile *C. difficile* was first identified as a cause of antibiotic-associated colitis in 1978; it has now become the most common cause of healthcare-associated diarrhea and inflammatory colitis. *C. difficile* disease and diagnosis is discussed in Chapter 37.

Patients who develop *C. difficile*-associated disease (CDAD) have altered intestinal flora related to the use of antibiotics, enemas, and intestinal stimulants *(437–439)*. Up to 30% of patients treated with antibiotics develop diarrhea, and in 20% to 25% of cases of antibiotic-associated diarrhea *C. difficile* is detected in stool *(438,439)*. The risk of acquisition increases as the patients' length of hospital stay increases, and more than 20% of adults are colonized after a week of hospitalization *(437,440)*. Clabots et al. *(441)* found the rate of acquisition proportionate to the length of hospital stay; 13% of patients hospitalized for 1 to 2 weeks were colonized and 50% of those hospitalized for more than 4 weeks were colonized. Patients who have been recently exposed to a healthcare institution are at increased risk of *C. difficile* colonization and diarrhea *(442)*. Importantly, broad-spectrum antibiotics commonly used for empiric therapy for neutropenic fevers and prophylaxis against opportunistic infections are associated with *C. difficile* colonization and infections *(114,437,443,444)*. In addition, antineoplastic chemotherapeutic agents, especially methotrexate, increase the risk of CDAD *(445)*. Gerard et al. recovered *C. difficile* and/or its toxin in 13 of 37 (35%) hospitalized cancer patients on oral antibiotics and in 15/119 (13%) of other patients ($p < .005$) *(443)*.

C. difficile colonization may be a marker for VRE colonization in patients with hematologic malignancies and HSCT *(446)*. Recipients of HSCT are at high risk of developing CDAD. One study suggests that CDAD may be more common among HSCT recipients than previous studies suggest *(443)*. Yuen et al. *(447)* prospectively studied HSCT recipients and found that *C. difficile* was the most common microorganism recovered from diarrheal stools. Among these patients, mortality was no different among patients with and without *C. difficile* isolated from stools. Chopra et al. *(448)* demonstrated that the CDAD rate /10,000 patients days among HSCT recipients was 24 compared to 2.6 in general patients and 16.8 in oncology patients. Most cases of CDAD occurred in the peritransplant period, within 30 days before or after HSCT. The authors addressed that conventional risk factors such as exposure to antibiotics and conditioning regimens likely play a significant role in the pathogenesis of CDAD in this population *(448)*.

Healthcare-associated outbreaks of *C. difficile* have been well documented, including outbreaks in HSCT units *(439,449–458)*. Contaminated environmental surfaces are an important and underrecognized reservoir of *C. difficile* spores, and serve as a source of the microorganism from which it can be transmitted to other patients *(450,459–461)*. These spores can remain viable on surfaces of inanimate objects for months. *C. difficile* is transmitted directly from patient to patient via the hands of healthcare workers or indirectly through contaminated equipment such as bedpans, urinals, call bells, and contaminated environmental surfaces such as bed rails, floors, and toilet seats *(437,449,450,459–461)*.

Prevention and control for endemic and epidemic disease is similar. Patients should be placed on Contact Precautions. Single rooms are preferred. Aggressive cleaning of the environment with bleach or other agents with activity against spores is an important control measure. Finally, antibiotic use should be minimized and tailored to agents that are less likely to aggravate disease (see also Chapter 37). The use of lyophilized *Saccharomyces boulardii* to reduce diarrhea is not recommended because of the risk for development of fungemia with the microorganism (126,*462*).

Legionella species Since the first documented legionellosis outbreak in Philadelphia involving American Legion convention delegates in 1976, numerous epidemic and sporadic cases including those associated with hospitals have been reported in the literature *(463–465)*. Initially, healthcare-associated *Legionella* infections were reported in centers that housed immunocompromised patients *(463)*. Outbreaks pointed to HSCT patients as high-risk patients with significant morbidity and mortality of 40% to 50% *(45,158,463,466)*. Marston et al. *(467)* found that patients with hematologic malignancies and *Legionella* infections were 22.4 times (95% confidence interval [CI], 19.0, 25.9) more likely to die than nonimmunocompromised hosts. These patients are at particular risk of developing

a *Legionella* infection, because they are neutropenic for long periods of time and have defects in cell-mediated immunity *(468)*. The incidence of healthcare-associated Legionella pneumonia among HSCT recipients varies. Several factors contribute to the incidence: (a) the concentration of *Legionella* spp. in the hospital's water supply; (b) the type of exposure to water; (c) the weather and rainfall; (d) the monitoring and treatment strategy for the water supply; and (e) the availability of adequate diagnostic tests (culture, direct fluorescent antigen, and urinary antigen) *(466,469–475)*. Among the 40 *Legionella* species, *Legionella pneumophila* is the most pathogenic, accounting for about 90% of the cases. Furthermore, of more than 14 identified serogroups of *L.pneumophila,* serogroup 1 accounts for more than 80% of the reported cases *(467)*. Other species that have been reported in HSCT patients include *L. micdadei* and *L. feelleii (469,476). L. pneumophila,* its concentration and density in the hospital water distribution system and the number of distal sites in the water distribution system that are culture positive for *Legionella* have been epidemiologically linked to healthcare-associated Legionnaires' disease *(44,463,471,477–481)*.

Legionnaire's disease is acquired by inhalation of water aerosols or aspiration of water contaminated by *Legionella (482–484)*. Aerosols have been generated from cooling towers, air conditioners, humidifiers, evaporative condensers, respiratory therapy equipment, and whirlpool baths *(472,477,485–496)*. Other investigators suggest that nasogastric tubes increase the risk of legionellosis presumably by facilitating microaspiration *(497,498). Legionella* infection should be considered in any HSCT patient with pneumonia, and appropriate testing for the agent should occur in all cases. Methods for detection of *Legionella* include culture, direct fluorescent antibody testing of bronchoalveolar lavage washings, and urine testing for *L. pneumophila* serogroup 1 antigen. Outbreaks of *L. pneumophila* serogroup 3 and nonpneumophila species in HSCT transplant units emphasize the importance of not relying only on urine testing for diagnosis *(499,500)*. Furthermore, isolates from clinical samples are needed to compare to water isolates to establish an epidemiologic link.

Surveillance for cases of healthcare-associated *Legionella* should be performed routinely in HSCT patients (126,501). Cases that occur in patients who have been continuously hospitalized for 10 days before the onset of illness are considered definite healthcare-associated cases, and cases that occur 2 to 9 days after admission are considered possible healthcare-associated cases (126). Appropriate reporting to the healthcare epidemiologist or infection preventionist (IP) and the health department should occur in response to a suspected healthcare-associated case; patients do not need to be isolated. However, healthcare epidemiology will initiate an investigation to determine the potential sources and implement prevention and control measures (as discussed below and in Chapter 36).

Mycobacterium tuberculosis The frequency of occurrence of *M. tuberculosis* infection in HSCT patients ranges from 0.001% to 16% in published studies *(502–504)*. The incidence of tuberculosis in HSCT patients is proportional to the incidence of tuberculosis in the general population and varies in different geographic areas *(505)*. One study showed that the incidence in allogeneic HSCT was higher than in the general population but equally frequent in autologous HSCT patients *(506)*. Patients can present with pulmonary, extrapulmonary, or disseminated disease. Pulmonary tuberculosis is the most common site of infection, but the classical manifestations of tuberculosis such as apical infiltration and cavitation are rare, and nonspecific pulmonary infiltrates are more common *(502,503,505,507)*. The diagnosis of tuberculosis can be challenging, with only a few patients having sputum showing acid-fast bacilli on smear. Nucleic acid amplification techniques have high specificity (98–99%) but low sensitivity (at least 80% in a smear-positive specimen and lower in a smear-negative specimen). Given the diagnostic challenges, therapy should be initiated in suspected cases after an aggressive diagnostic workup to obtain the relevant tissues for culture *(508)*. Clinical disease may be caused by reactivation of latent infection or may be newly acquired infection *(503,507)*. A number of biomarkers are being investigated for predicting reactivation disease *(509)*. The Interferon (IFN)-gamma release assay (IGRA) facilitates the diagnosis of latent tuberculosis with good specificity (99%) but low sensitivity (70–90%) *(510,511)*. Signs and symptoms usually occur late (median 324 days posttransplant in one study), but one quarter of reported cases occur before day 100 *(506,507,512)*. Risk factors for developing tuberculosis included allogeneic transplant, total body irradiation, corticosteroid use, and chronic GVHD *(504,506,512)*. Mortality varies from 0% to 50% in various studies and is higher in allogeneic HSCT and in disseminated disease *(507)*. Guidelines recommend evaluation for latent or active tuberculosis in patients who are candidates for HSCT *(513)*. Assessment should include a history of previous active tuberculosis, previous exposure, and results of previous tuberculin skin tests (TSTs) or IGRAs *(513)*. Concurrent, TST may not be helpful because patients are often already immunosuppressed prior to transplant *(513)*. Results from a meta-analysis demonstrated that IGRAs were more sensitive than TSTs among immunocompromised patients suspected of having tuberculosis *(511)*.

There have been no reports of outbreaks of tuberculosis in HSCT patients, but they have been well described in other settings; some of them involved transmission of multidrug-resistant tuberculosis (MDR-TB) *(514–521)*. Outbreaks are likely not reported, because these patients are cared for in a protective environment, some patients have latent infection, a long incubation period, or there are problems in diagnosis. There is a lack of good molecular techniques for epidemiologic investigations, especially in the countries where tuberculosis is endemic *(514,522)*. Institutions should follow CDC guidelines for preventing the transmission of *Mycobacterium tuberculosis* that are detailed in Chapter 38 "*Mycobacterium tuberculosis*."

Nontuberculous Mycobacteria Unlike tuberculosis, the healthcare-associated environment plays an important role in nontuberculous mycobacterial infections *(523)*. Municipal water supplies and potable water systems are major reservoirs for these microorganisms *(523,524)*. Nontuberculous Mycobacteria (NTM) are relatively resistant to disinfection, elevated temperature, and ultraviolet light compared with other pathogenic bacteria that may colonize potable water systems *(524)*.

A number of outbreaks and pseudo-outbreaks due to NTM have been reported in healthcare facilities *(524)*.

They have also been described in HSCT patients, with the majority being catheter-related, pulmonary, cutaneous, and disseminated infections *(525–529)*. The incidence ranges from 0.4% to 4.9% *(512,526,528, 530–532)*. The median time between HSCT and appearance of infection was 4.6 months *(525)*. The most commonly isolated *Mycobacterium* species are those that grow rapidly, such as *M. avium intracellulare* and *M. haemophilum*. Risk factors for NTM infections include having a matched-unrelated donor or a mismatched HSCT, and bronchiolitis obliterans *(532)*.

An outbreak of bacteremia associated with *M. mucogenicum* in six HSCT patients has been reported *(43)*. The microorganisms were isolated from several water sources in the hospital and DNA analysis demonstrated that one patient's blood isolate and an isolate from shower water were identical. The authors hypothesized that water contaminated the central venous catheters during bathing and concluded that guidelines on prevention of catheter-related infection should be strictly followed *(43)* (see also Chapter 39).

Nocardia species Nocardia species are aerobic actinomycetes that are found in organic matter and soil *(533)*. Commonly, this microorganism produces a focal lung lesion that may cavitate; it frequently disseminates to involve the brain and skin. Disease in this population is commonly associated with a normal white blood cell count *(534)*. Approximately 0.2% (1 of 554) of autologous HSCT patients and 1.6% (5 of 320) of allogeneic HSCT recipients have developed nocardiosis *(534)*. The risk of a patient developing nocardial infection was 9.3 times higher among allogeneic HSCT recipients especially in the setting of acute or chronic GVHD *(534)*. Some patients have had extensive exposure to soil or to organic matter before the nocardial infection developed. Nocardial infection can develop despite receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis. The mortality among these patient populations is high *(535–538)*. Standard Precautions are recommended for patients with this infection.

Fungal Infections

Invasive fungal infections (IFIs) are important causes of morbidity and mortality after HSCT. Infections due to *Candida* and *Aspergillus* species represent the vast majority of IFIs post-HSCT. *Candida* species were the most frequent cause of IFIs in the 1980s, predominately occurring before engraftment associated with conditioning-induced mucositis and central lines *(539,540)*. Prospective randomized placebo-control clinical trials demonstrated that primary antifungal prophylaxis with fluconazole post-HSCT decreases rates of infection due to *Candida* species significantly (541,*542*). One study showed a significant survival benefit as well (541,*542*). The above led to the almost routine use of fluconazole prophylaxis in most transplant centers in the 1990s, which resulted in marked reductions in the rates of candidiasis (541,*543*). With the rates of *Candida* infections post-HSCT decreasing, there were increasing reports of emergence of fluconazole-resistant *Candida* species and invasive mold infections, caused predominately by *Aspergillus* species (*544,545,*546). In addition, IFIs due to other than A*spergillus* molds, including the Zygomycetes, *Fusarium,* and *Scedosporium* species, are emerging *(547,548)*. In a prospective study from the Prospective Antifungal Therapy (PATH) Alliance registry, invasive aspergillosis (IA) was the most common IFI in HSCT patients, followed by candidiasis and zygomycosis (549). Another prospective surveillance study from the transplant-associated infection surveillance network (TRANSNET), which identified 983 IFIs among 875 HSCT recipients, also showed that IA was the most frequently identified infection followed by invasive candidiasis and zygomycosis (546).

Aspergillus species *Aspergillus* species produce conidia that are inhaled and can potentially colonize human airways and—under the right circumstances—cause invasive disease *(550)*. The most common species causing infection in HSCT patients is *A. fumigatus*, although an increase in non-*fumigatus* species of *Aspergillus* (e.g., *A. flavus* and *A. terreus*) has been described over the past several decades (546,*551,552*). Invasive aspergillosis most commonly involves the sinuses and the lungs, but can occasionally disseminate to other organs including the skin and the brain *(553–560)*. The incidence of IA among allogeneic HSCT recipients increased from 5% in the late 1980s to approximately 11% in the early 1990s and has remained high since then (*401*,*551*,*561–566*,567,*568*). Higher rates of IA may, in part, be attributed to higher risk HSCTs practices leading to more immunocompromised hosts, prolonged patient survival, longer periods of susceptibility to *Aspergillus* infections, and the widespread use of fluconazole leading to a lower incidence of infections due to *Candida* species *(561,569)*.

Notably, all HSCT recipients are not equally affected by *Aspergillus* species., as the incidence of IA differs based on the severity and the duration of neutropenia and GVHD, the type of transplant (lower among autologous [0–5.3%] compared to allogeneic HSCT [10%]), HLA match (higher in HLA mismatched and unrelated donors 10.5% vs. matched related 7.3%), and graft manipulation (higher in T-cell–depleted [4–16%] versus unmanipulated grafts [2.2–7%]) *(401,561,565,566,568,570,571)*. Infections due to *Aspergillus* species occur following a bimodal distribution with an early (before) and late (after engraftment) peak that correlate with neutropenia and GVHD and associated therapies, respectively *(572)*.

Mortality rates in HSCT recipients have decreased from older estimates of 75% to 90% (*401*,546,549,*562,572–576*). The risk of death increases when pulmonary function before HSCT is impaired, HLA-mismatched stem cells are received, neutropenia, malnutrition, elevated bilirubin, and creatinine levels are present, corticosteroids at ≥2 mg/kg per day are administered, or disseminated and proven invasive aspergillosis occurring >40days after HSCT is diagnosed (567). Notably, receipt of nonmyeloablative conditioning and peripheral blood stem cells were associated with a decreased risk of all-cause mortality (567). Standard Precautions are used to care for these patients.

The environment clearly has an impact on whether patients develop disease. Construction and/or renovation and suboptimal maintenance, cleaning, and protection of the environment have been the most important causes of *Aspergillus* infection. Multiple outbreaks reported in the literature have illustrated the risks associated with these activities (Table 59-2) (*50,*51,*553,577–600*). Patients housed outside of a HEPA-filtered or laminar airflow environment

TABLE 59-2

Aspergillus Outbreaks Involving Patients with HSCT or Hematologic Malignancy

Study	*Risk Factors*	*Site*	*Cause of Outbreak/Reservoir*	*No. of Cases*	*No. of Deaths*	*Control Measures*	*Microorganisms*
Aisner et al. 1976 *(578)*	Hematologic malignancy, metastatic carcinoma	Pulmonary laryngeal sinus	Fireproofing contaminated during construction	8	At least 3	Copper-8-quinonolate	*A. flavus* *A. fumigatus* *A. niger* *Aspergillus species*
Lentino et al. 1982 *(579)*	Hematologic malignancy, renal transplant recipients	Disseminated	Road construction, Window air conditioners were contaminated with *Aspergillus species*	10	10	Not specified	*A. flavus* *A. fumigatus* *Aspergillus species*
Rotstein et al. 1985 (580)	HSCT recipients	Pulmonary sinus Disseminated	Nebulizer Increased severity of illness	10	10	Not specified	*A. flavus* *A. fumigatus*
Opal et al. 1986 *(581)*	Hematologic malignancy high-dose corticosteroid therapy Carcinoma	Disseminated	Renovation	11	11	Copper-8-quinonolate to decontaminate work area Airtight barriers HEPA filters in patient rooms Negative pressure in construction area Traffic between construction site and patient areas strictly controlled	*A. flavus* *A. fumigatus* *A. niger* *Aspergillus species*
Allo et al. 1987 *(553)*	Hematologic malignancy Aplastic anemia	Primary cutaneous Disseminated	Contaminated ventilation system in operating room	9	2	Cleaned ventilation system	*A. flavus*
Ruutu et al. 1987 *(869)*	Hematologic malignancy HSCT recipients	Pulmonary Disseminated	Dirty ventilation system	8	6	Cleaned ventilation system Cleaned ventilation ducts and space above false ceiling Fittings around HEPA filters resealed Fine filters changed Handles removed from windows Increased speed of ventilation fans	*A. fumigatus*
Perraud et al. 1987 *(582)*	Hematologic malignancy	Disseminated	Construction/ renovation Insulation Blinds	22	18	Not specified	*A. fumigatus*

(*Continued*)

TABLE 59-2

***Aspergillus* Outbreaks Involving Patients with HSCT or Hematologic Malignancy (*Continued*)**

Study	*Risk Factors*	*Site*	*Cause of Outbreak/Reservoir*	*No. of Cases*	*No. of Deaths*	*Control Measures*	*Microorganisms*
Sherertz et al. 1987 *(50)*	HSCT recipients	Pulmonary Disseminated	Not specified	14	Not specified	Laminar airflow HEPA filtration	*A. fumigatus* *A. flavus* *Aspergillus species*
Weems et al. 1987 *(583)*	Advanced age Hematologic malignancy, Renal transplant recipients NICU (colonized cases only)	Disseminated Skin	Major construction with ground site preparation Interior renovation Demolition and contamination of HVAC system Excessive dust from: Demolition and contamination of HVAC system Construction traffic	5	At least 4	Windows in patient rooms permanently sealed	*Aspergillus species* *Mucor species*
Barnes et al. 1989 *(584)*	HSCT recipients	Not specified	Construction	6	6	Laminar airflow	*A. fumigatus*
Hopkins et al 1989 *(585)*	Renal transplantation Hematologic malignancy	Pulmonary Disseminated	Construction in central radiology Unfiltered air in construction areas	6	2	Renovation completed	*A. fumigatus*
Arnow et al. 1991 *(586)*	Hematologic malignancy	Pulmonary Disseminated	Inanimate environment	33	Not specified	Filters removed Cleaned gaps Environmental cleaning Inspections of water damage	*A. fumigatus* *A. flavus*
Flynn et al 1993 *(587)*	HSCT recipients Hematologic malignancy Metastatic carcinoma	Pulmonary Disseminated	Renovations two floors below ICU Rerouting of duct work Removal of false ceilings Entry through stairwell/elevator	4 (2) Infections (2) coloniza-tions	4	Increased monitoring during outbreak to maintain positive pressure in unit	*A. terreus*

Gerson et al. 1994 *(589)*	HSCT recipients Hematologic malignancy	Pulmonary Sinus Disseminated	Carpet	13	1	Antimicrobial carpet shampoo Water extraction employed with shampoo	*A. fumigatus* *A. flavus*
Anderson et al. 1996 *(590)*	Hematologic malignancy HSCT recipients	Pulmonary Disseminated	Defective conduit door for trash Contaminated vacuum cleaner	6	At least 1	Vacuum cleaner replaced Duct sealed Itraconazole prophylaxis	*A. flavus* *A. fumigatus* *A. niger*
Leenders 1996 *(592)*	Hematologic malignancy	Pulmonary	Not known	5	2	Random amplification of polymorphic DNA analysis Close windows New air-handling system maintenance	*A. fumigatus* *A. flavus*
Loo et al. 1996 *(593)*	Hematologic malignancy HSCT recipients	Pulmonary Sinus	Construction	36	17	Portable HEPA filters Copper-8-quinolinolate applied Windows sealed Ceiling tiles replaced Blinds replaced Ventilation system maintained regularly	*A. flavus* *A. fumigatus* *A. niger*
Loudon et al. 1996 *(591)*	HSCT patients	Skin	Contaminated ward kitchen	3	0	Clean ward kitchen	*A. niger*
Gaspar et al. 1999 *(597)*	Hematologic malignancy	Not specified	Construction	11	1	Airtight barriers used to separate construction area from unit Patients moved to another unit	*A. fumigatus*
Lass-Florl et al. 2000 *(596)*	Hematologic malignancy HSCT recipients	Pulmonary Sinus Disseminated	Potted plant on the unit	14	9	Potted plants removed from the unit	*A. terreus*
Thio et al. 2000 (51)	Hematologic malignancy	Disseminated	Construction	29	Not specified	N95 masks worn by patients outside of HEPA-filtered areas Floors wet mopped Traffic patterns altered Blinds replaced Outside bricks sealed Pressure adjusted Unit cleaned	*A. flavus*

(*Continued*)

TABLE 59-2

***Aspergillus* Outbreaks Involving Patients with HSCT or Hematologic Malignancy (*Continued*)**

Study	*Risk Factors*	*Site*	*Cause of Outbreak/Reservoir*	*No. of Cases*	*No. of Deaths*	*Control Measures*	*Microorganisms*
Oren et al. 2001 *(588)*	Hematologic malignancy HSCT recipients	Pulmonary	Construction	31/111	8	HEPA-filtered unit Amphotericin B IV prophylaxis	*Aspergillus species*
Lai et al. 2001 *(595)*	Hematologic malignancy HSCT recipients	Pulmonary Sinus	Construction	3	2	Unit closed for 2 wk Air intake duct cleaned Prefilters, filters, and HEPA-filtration replaced Carpet replaced with vinyl flooring Unit cleaned Airtight barriers used to separate construction area from unit Amphotericin B IV prophylaxis	*A. flavus* *A. niger* *A. versicolor* *Aspergillus species*
Hahn et al. 2002 *(594)*	Hematologic malignancy	Pulmonary Sinus	Contaminated wall insulation Construction	10/55	8	HEPA filters placed at intervals in non-HSCT wing and at the nursing station Wall insulation decontaminated Floor construction site sealed Itraconazole prophylaxis	*A. flavus*
Panackal et al. 2006 *(598)*	HSCT recipients	Pulmonary Skin	Possible construction Contaminated carpet	6	3	Not specified	*A. ustus*
Chang et al. 2008 *(599)*	Hematologic malignancy with neutropenia	Pulmonary	Construction	7	0	Advised patients to avoid construction site and use N95 mask Antifungal prophylaxis (voriconazole or liposomal amphotericin)	*A. fumigatus* *Aspergillus* spp.
Kidd et al. 2009 *(600)*	HSCT recipients Hematologic malignancy	Not specified	Intensive care unit	3	3	ICU closure	*A. fumigatus*

are at a 10-fold higher risk to develop healthcare-associated *Aspergillus* infection *(50)*. The use of HEPA filtration with laminar airflow for HSCT recipients can reduce the magnitude of risk for acquiring healthcare-associated *Aspergillus* infections and is discussed below (see "Prevention and Control Strategies"). Several experts argue that potable water is a source of fungi in this population *(601–603)*.

Candida species The incidence of *Candida* infections ranges from 22% to 25% among HSCT recipients *(604–607)*. *Candida* infections generally occur in the early posttransplant period with a mean time to onset of 2 weeks, coinciding with postconditioning periods of mucositis and neutropenia. *Candida* species may translocate via breaks in the mucosal surfaces associated with mucositis or by colonizing long-term intravascular catheters. Healthcare-associated transmission of *Candida* species may occur via indirect contact between patients by the contaminated hands of healthcare workers *(608–610)*.

The spectrum of candidal disease has changed with the widespread use of fluconazole for prophylaxis, with a shift from *C. albicans* responsible for more than 50% of cases, to non-*Candida albicans Candida* species (*543*,546,*611*). For instance, in a prospective surveillance study of invasive fungal infection in HSCT recipients, Kontoyiannis et al. reported that *C. glabata* is the most common *Candida* sp. followed by *C. albicans* and *C. parapsilosis* (546). Similarly, in a recent study on prospectively collected data from a multicenter registry on HSCT recipients with IFIs between 2004 and 2007, non-*C. albicans Candida* species collectively were the most common cause of invasive candidiasis with *C. glabrata* being the most frequently isolated species (549).

Clinically, *Candida* species cause infections ranging from superficial skin and mucosal involvement to fungemia and dissemination to internal organs, predominately the liver and spleen *(611)*. Hepatosplenic candidiasis is a distinct syndrome in neutropenic patients most commonly observed upon resolution of neutropenia and manifesting with right upper quadrant pain, elevated transaminases, and liver and spleen lesions on imaging tests *(612)*. Risk factors for candidal infection have included advanced age, prolonged neutropenia, delayed engraftment, cytotoxic chemotherapy, the use of broad-spectrum antibiotics or steroids, longer duration of hospitalization, presence of GVHD, concomitant CMV disease, and transplantation for acute leukemia *(608,611,613)*. One study demonstrated that prior use of a tunneled catheter and being colonized at other sites increased the odds of developing candidemia 7- and 10-fold, respectively *(614)*. Prospective studies among patients admitted to a medical intensive care unit and an HSCT unit found that risk factors for *C. glabrata* acquisition increased with prolonged hospitalization and prior antimicrobial use *(615)*. Patients with leukemia and those who had received antifungal prophylaxis were more likely to develop non-*C. albicans* fungemia and the rates of *C. krusei* and *C. glabrata* infections and colonization among HSCT patients receiving fluconazole are increasing *(616)*. In another study, fluconazole prophylaxis was the single most important risk factor accounting for the increase in *C. krusei* (OR = 27.07) and *C. glabrata* (OR = 5.08) *(617)*. Standard Precautions are used for patients with fungal infections. In some settings, infection control personnel may add Contact Precautions if the resistance pattern causes them concern.

Other Fungal Infections Less frequently encountered molds, such as the Zygomycetes, *Fusarium*, and *Scedosporium* species, have emerged as significant pathogens causing IFIs among HSCT recipients *(539,618,619)*. These microorganisms produce spectra of human disease similar to *Aspergillus* species. Zygomycosis can present as rhinocerebral, pulmonary, or disseminated disease and is associated with high mortality rates *(620)*. Recent studies suggest potential breakthrough zycomycosis infections in HSCT patients while on voriconazole *(621–623)*. Outbreaks of zygomycosis associated with construction, renovation, and disruption of the hospital environment have also been reported *(624)*. For example, cases in a pediatric oncology unit were deemed secondary to water damage in a linen storeroom and a patient's shower room *(625)*.

Fusarium infections in the immunocompromised host may disseminate rapidly and occasionally present with characteristic skin lesions with central necrosis and an erythematous base *(626,627)*. A recent epidemiologic study showed that *Fusarium* species isolated from the water and from aerosolized water within a hospital were genetically related to isolates from patients infected with *Fusarium (628). Scedosporium* species have also been increasingly reported as pathogens in the HSCT setting *(552)*. Common clinical manifestations may vary from localized cutaneous infection to disseminated disease with CNS, pulmonary, and skin involvement *(629,630)*. They can also present as fungemia *(630,631). Trichosporon capitatum* may cause bloodstream infections in HSCT patients; in one report, it was isolated from the stool of three leukemic patients, and all three patients were treated with an azole antifungal compound *(632)*. Mortality can be as high as 64% *(633)*. Standard Precautions are used for these patients.

Pneumocystis jiroveci *Pneumocystis jiroveci* is a fungus that remains an important pathogen among HSCT recipients. Prior to the routine use of antimicrobial prophylaxis, *P. jiroveci* pneumonia (PCP) complicated 6.8% to 16% of HSCT and occurred between 40 and 80 days after transplantation *(136,634)*. Since the implementation of prophylaxis, PCP occurs in approximately 2% to 13% of HSCT patients with most cases occurring more than 6 months post-HSCT when prophylaxis is stopped or terminated due to toxicity *(635–637)*. Risk factors for PCP include corticosteroid and other immunosuppressant use, relapse, and chronic GVHD, and patients with these risk factors should have prophylaxis continued beyond the standard 6 months. Mortality varies among studies, with rates up to 89% in some reports *(638)*.

Person-to-person transmission of *P. jiroveci* has been proposed based on studies in animal models, geographically and temporally linked clusters of PCP among immunocompromised patients, and increases in *of P. jiroveci* antibody titers among persons in contact with patients who have PCP. Outbreaks of *P. jiroveci* infections have been reported including patients with hematologic malignancy and renal transplant patients *(639–649)*. Some studies had evidence from molecular typing to confirm person-to-person transmission *(644–646,648,649). P. jiroveci* was found on environmental

surveys, but environmental cleaning did not terminate the outbreak *(648)*. No outbreaks have been reported in HSCT units. This may be due to the efficacy of prophylactic regimens and possibly due to the protective environment. Standard Precautions are recommended for patients with PCP; however, if evidence of person-to-person spread is suspected or confirmed within HSCT units, it seems prudent to implement Contact and Airborne Precautions for the patients (127).

Toxoplasma gondii *Toxoplasma gondii* is a protozoan that commonly causes asymptomatic infection in immunocompetent individuals. However, the microorganism can cause life-threatening infection in immunocompromised patients including those undergoing HSCT *(650)*. In these hosts, infection can occur as a new primary infection, but 95% of cases represents reactivation of old disease *(513)*. Toxoplasmosis most commonly involves the central nervous system, presenting as focal lesions, encephalitis, or rarely, chorioretinitis *(651,652)*. In areas of low endemicity, toxoplasmosis occurs in approximately 0.3% of transplants, with higher rates of 6% seen in Europe *(650,651,653,654)*. Disease most often occurs within the first 6 months after transplant, with a median time to symptom onset of 50 to 64 days *(651,652)*. Risk factors for toxoplasmosis included seropositive allogeneic HSCT who have received cord blood, an unrelated donor, T-cell–depleted transplants, previous alemtuzumab, acute and chronic GVHD, and inability to take trimethoprim/sulfamethaxoazole *(653)*.

Guidelines recommend that candidates for allogeneic HSCT be tested for toxoplasmosis IgG antibody to determine whether they are at risk for disease reactivation after HSCT *(513)*. To facilitate the early diagnosis of reactivated infection, PCR screening of peripheral blood specimen and preemptive therapy can be considered in patients at high risk *(513,653)*.

PREVENTION AND CONTROL STRATEGIES

The source of infections in HSCT recipients may come from an exogenous source, such as person-to-person contact or the environment, or from an endogenous source by reactivation of previous infections. Standard infection prevention and control approaches and vaccination are used to prevent infections form exogenous sources and antimicrobial prophylaxis and preemptive therapy are used to prevent some endogenous infections.

Additional prevention and control strategies are based on summary evidence in some cases, expert opinion based on epidemiology, or results of an outbreak investigation. In this patient population and with movements of patients from the inpatient to the outpatient settings, careful attention must be paid to the role played by the environment, foods, pets, and daily activities in the pathogenesis of opportunistic infections. Given that the immunosuppression from HSCT lasts much longer than the patient's stay in hospital and as HSCTs are increasingly being performed in the outpatient setting, many practices should be incorporated into the outpatient setting, the home environment, and the hospital setting. Because of the high mortality associated with infections in these patients, diagnostic challenges, and limited therapeutic agents, attention to control and prevention of infections is critical in this high-risk population.

Guidelines for preventing opportunistic infections among HCST recipients have been published as have guidelines regarding environmental infection control (501,*655*). These documents and additional scientific evidence that can be extrapolated from studies in other patient populations can be used to develop a plan for infection control in HSCT patients. In addition, the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC), the Society for Healthcare Epidemiology of America (SHEA), and the Infectious Diseases Society of America (IDSA) have developed several other relevant sets of compendiums and guidelines, including ones regarding:

1. Prevention of transmission of infectious disease in healthcare settings (127)
2. Hand hygiene methods *(656)*
3. Prevention of central line–associated BSI, and urinary tract infections *(97,657,658)*
4. Prevention of *C. difficile* infection, and MRSA *(659–661)*
5. Prevention and control of multidrug-resistant microorganisms in healthcare setting *(662)*
6. Prevention of healthcare-associated pneumonia and ventilator-associated pneumonia including policies and procedures on HSCT units or on their patients *(663,664)*

Beyond the guidelines, several caveats should be further considered in these patients. First, prevention and control of infection in these patients can involve their caregivers and family members, and their environment. Healthcare-associated infection may be acquired from infected patients, staff, visitors, or contaminated items in the patients' environment. Although this tenet is true with many patient groups, it particularly applies to HSCT recipients and the units where they are housed. Second, for many diseases, the infection control procedures are multifaceted. For example, healthcare-associated outbreaks or transmission of RSV, influenza, *C. difficile*, and VRE require integrated programs with strict attention to isolation procedures, hand hygiene, and environmental cleaning procedures to control and prevent transmission. Third, because data are not always available for this setting, common sense is critical in developing prevention and control plans. Recent studies have shown that these measures may be cost-effective; by decreasing the number of infections in a hospital with a high prevalence of VRE, authors in two studies projected over $100,000 in annual savings *(665,666)*. Karanfil et al. *(213)* also projected a savings of $88,000 annually with a comprehensive program to control RSV. Garcia et al. *(214)* reduced the incidence of RSV infections from 4.4 per 1,000 patient days before the interventions were applied to 1.0 per 1,000 patient days after introducing such a program in an HCST unit.

We discuss the specific elements of programs that can be developed to prevent transmission of epidemiologically important diseases below. Healthcare workers should be educated; feedback should be provided to physicians, providers, and nurses about infection rates and compliance with policies and procedures (process measures); infection control practices (isolation precautions) must be complied with; the environment must be carefully cleaned; and antibiotics must be used judiciously. Furthermore, management always includes strict hand hygiene, limiting exposure to infected persons during the respiratory virus season, screening of patients and healthcare workers, restricting visitors who could be incubating communicable diseases,

using appropriate barrier precautions, and furloughing ill healthcare workers. This section reviews infection data so that programs can be tailored to the epidemiologic issues in a given hospital and applied to HSCT units.

Hand Hygiene

General guidelines from HICPAC and WHO on hand hygiene and antisepsis should be followed and have recently been revised *(656,667)*. Because microorganisms are transmitted by contaminated hands, appropriate hand hygiene is the cornerstone for controlling the spread of many infectious agents (see also Chapter 91).

Isolation and Barrier Precautions

Isolation and the use of barrier precautions are implemented to prevent patients or healthcare workers from acquiring or transmitting communicable diseases or pathogenic microorganisms.

CDC/HICPAC isolation guidelines for hospitalized patients should be similarly applied to HSCT patients (127). The guidelines are formulated using two levels of protection: one is standard and applied to all patients, and the other is based on the potential of disease or microorganism transmission. Contact, Droplet, and Airborne Precautions are the most common forms of isolation that are implemented in addition to Standard Precautions. Personal protective equipment such as gowns, gloves, or masks should be donned before entering a patient's room and discarded before leaving the patient's environment (127,*668*).

HSCT units should implement Airborne Precautions for HSCT recipients with airborne infections such as pulmonary or laryngeal tuberculosis, varicella-zoster, and measles. Optimally, this would include placing patients in a protective environment with anteroom and providing N95 or higher-level respirators or masks for healthcare personnel (127). An anteroom is used to further support the appropriate air-balance relative to the corridor and the protective environment (127). Alternatively, place the patient in an Airborne Infection Isolation Room (AIIR) and use portable, industrial-grade HEPA filters in the room to enhance filtration of spores (127). A patient with varicella infection also needs Contact Precautions (see also Chapter 84).

Examples of infectious diseases that require Contact Precautions include VRE, multidrug-resistant gram-negative bacilli, MRSA, *C. difficile*, rotavirus, norovirus, RSV, parainfluenza, and adenovirus (126,127). Adenovirus, influenza, parvovirus, and pertussis require Droplet Precautions for prevention (See the HICPAC "2007 Guideline for isolation precautions" for other infectious diseases [127]). Precautions should be maintained for at least the duration of illness and longer if there is evidence of persistent shedding of the microorganism *(147,669–672)*.

In centers in which many patients are transferred from other institutions, consideration can be given to preemptive isolation while awaiting results of surveillance cultures. Colonization with VRE, MRSA, or MDR gram-negative microorganisms may remain for long periods extending beyond the hospitalization. The duration of Contact Precautions remains an unresolved issue for many infections in this population. Some microorganisms may demonstrate clearance after decolonization therapy but subsequently return *(662)*. One recommended approach is to discontinue Contact Precautions when three or more surveillance cultures are repeatedly negative over the course of a week or two in a patient who has not received antimicrobial therapy for several weeks, especially in the absence of a draining wound, profuse respiratory secretions, or evidence implicating the specific patient in ongoing transmission within the facility *(662)*. In patients with known colonization, Contact Precautions should be continued during hospital readmissions (126). The institutions should have policies about isolation in patients with multidrug-resistant microorganisms.

Blood Product Screening and Prevention of Infection from Extraneous Contamination

As blood products are an important source of several viruses and parasites, screening for agents that cause hepatitis, HIV, and other agents is standard practice in North America. Still, CMV transmission via residual buffy coat cells remains a significant issue in these patients. Among 97 HSCT recipients who were CMV seronegative before transplantation, one of 32 patients who received seronegative products and eight of 25 who received standard blood products developed CMV infection ($p < .007$) *(673)*. In the absence of seronegative products, blood should be depleted of cellular elements. This can be accomplished by several techniques including irradiation or use of specialized filters. Hematopoietic cells for either allogeneic or autologous transplantation are collected from a donor and stored. Infections can occur among recipients of contaminated marrow or blood products *(674)*. Rarely, an infected donor can transmit microorganisms to a patient. More commonly, the patient receives contaminated blood products or marrow that was contaminated during processing and storage. Transfusion-associated infection caused by several microorganisms have been reported: HIV, HTLV I and II, human herpesviruses including CMV, EBV, HHV-6, and HHV-8; Hepatitis viruses that are hepatitis A, B, C, D, E, G, SEN virus and transfusion transmitted virus (TTV); WNV; Parvovirus, dengue virus, bacteria, *Rickettsia*, protozoa (*Toxoplasma gondii*, *Leishmania* species,*Trypanosoma cruzi*, *Babesia* species, *Plasmodium* species) and prion disease (vCJD) *(338,340,341,650,675–724)*. To prevent transmission to HSCT recipients, programs now obtain a history and perform a physical examination on the donor *(725,726)*. Donors are asked about high-risk behaviors, previous travel, and signs and symptoms of infection prior to harvesting the marrow, and serum is screened for serologic evidence of disease *(674,725,727)*. Some infections, such as HBV, can be prevented by vaccination. HBV-naïve HSCT candidates should not receive transplants from hepatitis B-infected donors, if another equally suitable donor is available but it is not absolutely contraindicated (143). Antiviral treatment plays an important role in this situation (143).

Bone marrow can be contaminated during harvesting and during the *ex vivo* processing. The amount of contamination that occurs during *in vitro* processing of bone marrow varies between 2.6% and 17% *(728–732)*. In one study, cultured bone marrow from both allogeneic and autologous donors did not grow microorganisms at the time of harvest; however, 12/153 (8%) samples grew microorganisms when the marrow was thawed prior to infusion (729). Gram-negative microorganisms were most commonly isolated

including *Pseudomonas* species in 5/12 samples. One patient developed *R. picketti* sepsis following infusion of bone marrow cells. Rowley et al. showed that the risk of contamination of marrow increased as it was manipulated *(728)*. Schepers et al. demonstrated a significant decrease in contamination from 5% to 2.6% when appropriate procedures were introduced *(730)*. Contamination has been traced to heparin and contaminated ficoll separation medium *(730,733)*. Finally, Kassis et al. describe an outbreak due to a *Mycobacterium mucogenicum*-related pathogen that contaminated peripheral hematopoietic stem cell products *(734)*. The source of the outbreak was traced to ice cubes used in processing the peripheral blood stem cell products *(734)*.

Environmental Management

Room Ventilation and Protective Environment Ventilation systems are a critical infrastructure in hospitals and must have certain capacities to protect high-risk patients (501). HSCT patients should be placed in protective environment (PE) rooms with positive airflow relative to the corridor and have >12 air exchanges per hour (126). Airflow should be directed and enter one side of the room and be exhausted from the opposite side (501). Air pressure in patient rooms should be maintained at 2.5 Pa higher than any adjoining corridors, anterooms, or bathrooms. Minimal leakage of air is required; therefore, rooms should be well sealed around windows, electrical outlets, and other sources of air (126). Based on a large amount of data showing that filtered air decreases the risk of invasive fungal disease, the evidence-based guidelines for preventing opportunistic infections among HSCT recipients recommend several air filtration strategies, such as air filtration with point-of-use HEPA filtration that removes 99.97% of particles >0.3 μm in size (126). Some institutions have built laminar airflow (LAF) rooms, which are more efficient than HEPA filtration alone but are more expensive and produce more noise. Studies have found that laminar air flow, HEPA filtration, and portable HEPA filters improve ventilation overall and in the setting of hospital renovation and construction *(584,735)*. Many investigators have found a significant decrease in particles and in *Aspergillus* spores in air samples. For example, one of these investigators reported 32% (6/19) of the children undergoing HSCT died of invasive pulmonary aspergillosis during an *Aspergillus* outbreak associated with construction *(736)*. With use of LAF rooms, no more cases of invasive pulmonary aspergillosis occurred *(736)* (Table 59-3). More importantly, a group of allogeneic HSCT patients placed in conventional protective isolation (single patient room and any combination of hand washing, gloves, mask, and gown) were compared to a group placed in HEPA-filtered LAF rooms *(737)*. The 1-year overall risk of transplant-related mortality in the first 100 days post-transplantation was significantly lower in the group treated in HEPA-filtered LAF units compared to those treated by conventional protective isolation. Other investigators have examined the importance of other interventions in the setting of HEPA filtration or LAF rooms. At least two studies have shown that LAF rooms and gastrointestinal decontamination decrease infection rates and decrease adverse outcomes *(738,739)*. Buckner et al. *(738)* found that patients in LAF rooms with gastrointestinal tract decontamination had less illness severity and required fewer granulocyte transfusions (5/46 vs. 22/44; $p < .0001$). Several other investigators advocate use of LAF rooms and sterile diet, gastrointestinal decontamination, and skin cleansing to prevent infections in granulocytopenic patients *(737,740,741)*. To reiterate, HSCT patients, especially allogeneic transplants, should be placed in private rooms with HEPA filtration of air (point of use) with at least 12 air exchanges per hour (126). These rooms should be under positive pressure with respect to the corridors. Although this technology is expensive, the data support improved patient outcomes.

The efficacy of portable machines with HEPA filters has been evaluated and showed benefit in some studies *(593,742)*. Guidelines recommended their use only for lower-risk neutropenic patients in the setting of a shortage of protective environment rooms, because they have never been compared with central HEPA filters in preventing infection.

To reiterate, HSCT patients, especially allogeneic transplants, should be placed in private rooms with HEPA filtration of air (point of use) with at least 12 air exchanges per hour (126). These rooms should be under positive pressure with respect to the corridors. Although this technology is expensive, the data support improved patient outcomes.

Anterooms are helpful in case of HSCT recipients requiring Airborne Precautions, but they are optional according to guidelines (126,501). Anterooms should be used to ensure appropriate air balance relative to the protective environment and the hallway; an independent exhaust of contaminated air to the outside should be provided, or a HEPA filter should be placed in the exhaust duct if return air is to be recirculated (126,501). If a protective environment room with an anteroom is not available, the patient should be placed in a standard airborne infection isolation room and a portable, industrial-grade HEPA filter should be used to enhance the removal of spores in the room (126).

The pressure in the room should be continuously monitored using a system that alarms when the pressure differential between any patients' room and hallway or anteroom falls to below 2.5 Pa *(743)*.

If an outbreak of healthcare-associated pneumonia caused by *Aspergillus* is identified, air should be sampled while a source is investigated *(663)*. Air samples should be taken using a high-volume air sampler. Sample volumes of at least 1,000 L is recommended (51). Low-volume air samplers are not effective for detection of the low numbers of microorganisms that can be of concern among these patients (51) (see also Chapter 84).

Room Decoration and Furnishings Floor surfaces should be smooth and nonporous that makes them easy to clean to diminish dust in the rooms (126). Carpeting should not be placed in any part of a unit since it is associated with healthcare-associated aspergillosis *(589)*. Furniture should be scrubable, nonporous, and easily disinfected (126). Gerson et al. *(589)* reported an outbreak related to carpet tile that was contaminated after a fire. Hence, when damage occurs in a unit due to fire or water, infection control personnel need to inspect the area and consider air and environmental sampling as described below.

Construction and Renovation Construction and renovation projects are common in many hospitals as they strive

TABLE 59-3

General Recommendations for Prevention and Outbreak Management of Healthcare-Associated Aspergillosis and Other Invasive Fungal Infections among HSCT Recipients

Category	*Specific Element*
Education	- HSCT recipients and their caregivers should be educated regarding strategies to avoid environmental exposure to *Aspergillus* and other fungal infections
Ventilation	- Protective environment that consists of ◦ HEPA filtration with 99.97% efficiency ◦ Maintain ≥12 air changes per hour ◦ Well-sealed rooms - Direct airflow - Continuous pressure monitoring with alarm system
Environment	- Eliminate carpet and other sources of dust - Clean rooms (all surfaces) at least daily for dust control - Avoid dust generating activities (use wet mopping, HEPA vacuuming) - Eliminate flowers, potted ornamental plants - Eliminate areas where water or condensation can collect - Clean area after any renovation or construction
Personal hygiene	- Have patients wear masks (N-95) when out of protected environment - Avoid unprocessed food; certain beans and raw fruits - Consider other protective environment (mobile tents)
Construction	- Develop policy for construction and renovation with risk levels - Seal off construction areas and place under negative pressure; use rigid dust proof barriers; seal door, etc. - During outdoor construction seal intake air - Clean area daily if within the hospital or buildings - Treat fireproofing with fungicide (copper-8-quinolinolate) - Assure filters properly sealed in new buildings - Minimize patient exposure to high-risk activities - Minimize the traffic through construction area - Exhaust construction dust
Cleaning rooms	- Use thorough cleaning procedures to ensure daily decontamination and cleanliness of the room - Using approved solution, remove fingerprints and smudges from light switches, door flames, walls, window sills, and glass; spray the solution on the cleaning cloth or carefully on the wall surface to prevent exposure - Terminally clean room on patient discharge or every 3 week
Cleaning bathrooms	- Using an approved solution, wipe down surfaces, lower ledges, and pipes of sink; for more aggressive sink cleaning, use a scouring cleanser to remove soil or stain buildup; clean the mirror with glass cleaner and wipe dry with paper towels; thoroughly clean all ceiling vents, shelves, cabinets, and waste baskets, with germicide - Pay special attention to corners, soap and dish, and drain in showers and sinks; sanitize the shower with germicide and a cleaning cloth; wipe the ceramic tile to prevent a soap buildup; check the shower curtain for possible replacement; clean inside toilet bowl with an approved cleanser and clean the outside bowl with approved germicidal solution, sanitize the inside of the toilet and urinal using a bowl mop saturated with germicide solution; the bowl mop should be worked around, making sure to get into the upper and the lower ledges; accidental spills can be cleaned up by flushing with water and wiping
Waste removal	- Put on gloves, grasp the liner twist, and tie closed - Remove the liner from the basket and replace with a new liner - Place the waste in a trash cart approved by infection control; wash hands thoroughly again and put on new gloves
Restock supplies and inspect room	- Wash hands thoroughly again and put on new gloves; replace soap and paper products in restroom and at the sink; if a discharge, make the patient bed according to discharge procedures; area cleaner inspects room to see that all steps have been covered and the room meets approval - Notify nursing manager or responsible administrator and maintenance of leaks, wet dry wall, or water damage.

(*Continued*)

TABLE 59-3

General Recommendations for Prevention and Outbreak Management of Healthcare-Associated Aspergillosis and Other Invasive Fungal Infections among HSCT Recipients (*Continued*)

Category	*Specific Element*
Surveillance	- Define disease and find cases of healthcare-associated infection - Use large-volume (>1,000 L) air samplers to detect *Aspergillus* or fungal spores
Intervention if healthcare-associated case occurs (501)	- Review pressure-differential monitoring documentation to verify the pressure differentials in the PE rooms and outside - Conduct a prospective search for additional cases and intensify retrospective epidemiologic review of the hospital's medical and laboratory records - Conduct an environmental assessment to find and eliminate the source - Collect environmental samples from potential sources - If either an environmental source of airborne fungi or an engineering problem with filtration or pressure differentials is identified, promptly perform corrective measures to eliminate the source and route of entry - Use an EPA-registered antifungal biocide (e.g., copper-8-quinolinolate) for decontaminating structural materials - If an environmental source of airborne fungi is not identified, review infection-control measures, including engineering controls, to identify potential areas for correction or improvement - If possible, perform molecular subtyping of *Aspergillus* spp. isolated from patients and the environment to compare their strain identities - If they receive antifungal prophylaxis without activity against *Aspergillus* (e.g., fluconazole), consideration could be given to using voriconazole or posaconazole

to update facilities. Construction, renovation, and maintenance, whether minor or major, pose special problems for patients undergoing HSCT. Because of their immunosuppression, patients are at risk for developing infections from microorganisms (e.g., *Aspergillus* or *Legionella* spp.) released from construction sites, or from destruction of existing structures and renovation, or from the water supply. This association with construction has been based on outbreak investigations and endemic assessment of cases with geographic proximity, temporal relationships, the finding of *Aspergillus* in the environment and supporting molecular typing data, and the control of these infections with appropriate interventions. Despite the lack of direct proof, few dispute the relationship. Hence, any construction or renovation project requires a multidisciplinary team to review the plans for demolition and construction, placement of barriers, and egress and entry to areas (126). All institutions should have a policy for construction and renovation that allows hospital staff to assess the risks any project could pose to patients. Such construction policies should be part of contracts if outside contractors are used for institutionally based projects. Contractors should have back up equipment available and onsite. The numbers of *Aspergillus* spores in unfiltered ambient air have been measured in several locales and vary from 0.1 to 15 CFU/m^3. The numbers vary with wind, weather conditions, and season *(744)*. Streifel et al. *(745)* showed that the numbers and concentrations of thermotolerant fungi, especially *A. fumigatus*, increase significantly after demolition of a hospital building. The concentration of thermotolerant fungi and *A. fumigatus* increased by 1.8 log 10—10^2 to 10^5 and 3.3 log10—10 to 10^4, respectively, after the building's demolition *(745)*. Because of these data, construction standards are required for any unit housing HSCT patients. These include many elements such as placing appropriate barriers, sealing the barriers, moving high-risk patients away from construction, using negative pressure and HEPA filtration, and assuring that the air-handling system is functioning properly, and exhausting construction dust appropriately. Because of the risk of transmission of *Aspergillus* or other microorganisms in the air-handling systems, construction personnel must work with the institution's engineers to isolate heating and ventilation systems. In addition, airtight barriers have been found to significantly reduce the number of *Aspergillus* spores from 4.2 ± 0.4 spores/m^3 inside the barrier to 1.0 ± 0.3 spores/m^3 outside the barrier *(581)*. Spore counts were also obtained from adjacent hospital units and found to be highest on the floor directly below construction (2.3 ± 1.3 spores/m^3 below the construction site and 1.1 ± 0.6 spores/m^3 in adjacent wards). Implosions require concurrent monitoring to determine whether the air-handling system will require manipulation *(746)*. Srinivasan et al. *(746)* did serial measurements in adjacent buildings and city blocks when a building was imploded near a cancer center. They found that engineers could adjust hospital air-handling systems to the movement of the debris cloud produced by the implosion *(746)*. These systems could accommodate the modest increase in *Aspergillus*, other fungi, and particles generated by the implosion. In addition, air samples containing *Aspergillus* species were paralleled by particle counts, suggesting these can be used to guide any interventions.

Fireproofing can harbor microorganisms including *Aspergillus*. Copper-8-quinolinolate, a fungicide, can be used to decontaminate environmental surfaces. This compound

is highly active against clinically important fungi including *Aspergillus* species and has been used to abort several outbreaks *(578)*. It also has the advantage of having persistent antifungal activity and will theoretically prevent fungi or molds from growing if subsequent water damage occurs *(578)*. Opal et al. *(581)* cultured a mean of 4.9 ± 1.5 *Aspergillus* spores/m^3 from environmental surfaces in a hospital unit before they were treated with copper-8-quinolinolate. After treating surfaces with this fungicide, a mean of 0.1 ± 0.1 *Aspergillus* spores/m^3 were cultured *(581)*. Construction traffic patterns should be directed to allow for efficient waste disposal through garbage chutes. If not feasible, construction waste should be removed in covered bins. Floors should be cleaned (wet mopped) following the removal of construction waste. Construction personnel should avoid traversing areas where high-risk patients are located. Protective clothing may be appropriate to prevent dissemination of microorganisms into the air. Traffic should be directed away from construction. Cooper et al. *(747)* demonstrated that the construction measures described above were effective in controlling the amount of ambient *Aspergillus* and *Aspergillus* disease. The amounts of viable pathogenic fungi were similar between areas under construction and those that were not. There was no difference in the incidence of invasive aspergillosis between 2000 and 2001 (incidence density ratio = 1.2; 95% CI = 0.3–4.1).

HSCT recipients should avoid construction areas. Wearing N95 respirators is recommended while traveling outside protective environment rooms (51). Raad et al. *(748)* demonstrated the effectiveness of wearing high-efficiency masks when the high-risk neutropenic patients left their rooms in construction periods. The rate of healthcare-associated aspergillosis decreased from 0.73 cases per 1,000 hospital patient days to 0.24 per 1,000 hospital patient days during the two study periods *(748)*.

During construction periods, environmental surveillance should be considered; however, monitoring for cases of aspergillosis should also be performed (126). If an outbreak is suspected, microbiological air sampling may be performed (126).

After construction, one must ensure new filters are properly seated. We recommend visual inspections to determine whether or not water damage has occurred. Based on the experience of Rhame we further recommend obtaining air samples prior to opening such areas to patients *(749)* (see Chapter 83).

Water and Water Management Water treatment beyond that provided by municipal water systems is primarily aimed at preventing healthcare-associated *Legionella* infections. Prevention strategies vary by institution and depend on the immunologic status of the patients, the design and construction of the facility, the available resources, and state and local health department regulations *(483)*. Strategies for prevention and control of healthcare-associated legionellosis may include decontamination followed by a maintenance phase. Several caveats must be considered in any plan to treat water and to prevent *Legionella* infections. First, in the initial phase, the effectiveness of a water treatment plan in a hospital water distribution system should be assessed long-term, over 3 to 5 years. Second, most strategies to treat hospital water distribution systems have not been compared to each other. Hence, one is forced to look at the characteristics of the water system in the institution and choose the best engineering and most cost-effective option.

Surveillance for healthcare-associated *Legionella* in the water is the ultimate test of the efficacy of any water treatment plan. If this approach is taken, a comprehensive plan will provide the most useful information (501). Appropriate diagnostic tests must be used to evaluate patients with healthcare-associated pneumonia and to diagnose *Legionella* infections (126). Targeting high-risk patients such as those who have undergone transplantation has been proposed and has the advantage of being cost efficient *(483,750)*. Goetz and Yu *(750)* suggest that culturing the water supply and targeting high-risk patients for specialized *Legionella* laboratory tests may help clinicians discover *Legionella* cases in the absence of an outbreak. One strategy requires periodic culturing of the potable water system if more than 30% of cultures of distal outlets (faucets) yield *Legionella* species, or if the system has been decontaminated *(751)*. Current guidelines recommend performing periodic culture surveillance for *Legionella* species in potable water for HSCT units (126,501). Documentation of environmental sources of *Legionella* or a case of healthcare-associated infection should prompt active surveillance, looking for clinical cases and a source of *Legionella*. The approach is based on the theory that in the absence of *Legionella* in water cultures, no cases of healthcare-associated legionellosis can occur *(483)*. In this case, the potable water system, potable water outlets in the patient's room, and cooling towers should be cultured by a laboratory with expertise in processing environmental samples. In addition, other potential sources including humidifiers, portable airconditioners, nebulizers, fountains, irrigation equipment, whirlpools, and ice machines should be investigated. If such environmental surveillance cultures yield *Legionella*, the water supply should be decontaminated; HSCT patients should be restricted from bathing or showering in *Legionella*-contaminated water; water from faucets should not be used in the HSCT area, and bottled water should be used by patients for drinking, brushing teeth, or flushing nasogastric tubes (126).

A decorative fountain was reported to be the source of a healthcare-associated *Legionella* outbreak in one study *(105)*. Hence, fountains should not be installed in HSCT units or in other areas where these patients spend time (126).

For additional information, see Chapter 36.

Besides *Legionella*, the hospital water system can be a source of an outbreak or pseudo-outbreak involving other microorganisms such as NTM, fungi, and nonfermenter gram-negative microorganisms (*Pseudomonas* spp., *Burkholderia* spp., *Stenotrophomonas* spp., *Acinetobacter* spp., *Ralstonia* spp., *Sphingomonas* spp., *Afipia felis*) *(523,524,752)*. Whenever outbreaks of these microorganisms occur, the link to a water reservoir should be on the priority list to investigate.

Equipment Supplies and equipment should be monitored for dust or potential mold contamination, particularly materials that are used on patients' skin. An outbreak of mucormycosis has been linked to contaminated elastic bandages;

therefore, dressing supplies should be examined regularly. Materials that are out of date, damaged, or contaminated should be discarded (126,*753*). An outbreak of primary cutaneous aspergillosis has been associated with the use of an intravenous arm board *(754)*. For this reason, when arm boards are used, they should be changed frequently (126).

Plants and Fresh Flowers Plants, fresh flowers, and vases have been shown to harbor bacteria and other microorganisms that are pathogenic for immunocompromised patients. Within 3 days of fresh flowers being placed in water, the water contains up to 1×10^{13} CFU of bacteria per milliliter of water *(39)*. When cultured, *P. aeruginosa*, *Burkholderia cepacia*, *P. alcaligenes*, *A. hydrophila*, *Acinetobacter* spp., *Flavobacterium* spp., *E. coli*, *Klebsiella* spp., and *Proteus mirabilis* may be recovered *(39)*. Other authors have found that water cultured from flower vases in hospitals may contain pathogenic fungi as well *(40)*. The microorganism counts increased logarithmically and significantly ($p < .0005$) over time and were not different if distilled or sterile water was substituted for tap water *(39)*. Several investigators found that water obtained from flower vases contains microorganisms that are highly resistant to antimicrobial agents *(39,40)*. Because of these data, most HSCT units do not allow fresh flowers or live plants to be brought in to patients. Although there is no strong evidence that fresh flowers and plants cause invasive mold infections among HSCT recipients, current guidelines suggest that they not be allowed in HSCT recipients' rooms and that exposure to soil-based materials should be avoided (126).

Toys Toys have been associated with outbreaks on pediatric oncology units *(303,409)*. For example, outbreaks of rotavirus in pediatric oncology units related to communal toys in the playroom and an outbreak of multidrug-resistant *P. aeruginosa* related to water-retaining bath toys in a pediatric oncology ward have been reported *(303,409)*. If toys are used in HSCT units, they should be cleaned and disinfected appropriately. Toys that cannot be washed or disinfected should not be used (126).

Environmental Cleaning The overall cleanliness of the unit is important and recent data highlight the role of the environment in contribution to healthcare-associated infections and outbreaks *(755–761)*: Bootsma et al. (*761*) used mathematical modeling and estimated that the prevalence of gram-negatives on environmental surfaces in ICUs was between 15% and 26%. They then estimated that between 21% and 28% of gram-negative colonizations were acquired from exogenous sources *(761)*. Carling et al. *(762)* showed that only 47% of targeted objects and surfaces had been cleaned. With education, sustained cleaning of over 85% of objects was achieved *(762)*. Thorough cleaning has been integrated into protocols to decrease environmental contamination and infection and hence is required after patients are discharged from a hospital room, or after a patient is seen in the outpatient clinic (501,*757*,*763–766*). If a dedicated clinic room is provided, cleaning at the end of the day may suffice. Many microorganisms can contaminate the environment through contaminated secretions or through transmission on contaminated hands. Environmental cleaning is an important method to reduce transmission of multidrug-resistant microorganisms *(767)*. Because these microorganisms survive in harsh conditions, thorough cleaning is indicated with the appropriate disinfectant. Isopropyl alcohol and most disinfectants (sodium hypochlorite, phenolic, and quaternary ammonium compounds) are effective against VRE *(768)*. To prevent transmission of *C. difficile*, chlorine-containing cleaning products with at least 1,000 ppm available chlorine are recommended for decontamination of inanimate objects and environmental surfaces *(661)*. Chlorine bleach solution (1,000–5,000 ppm) is also recommended to prevent norovirus transmission *(755)*. However, novel methods that evaluate the effectiveness of cleaning illustrate that attention to compliance with standard cleaning techniques and the use of appropriate products is important *(762)*.

Accumulation of dust should be prevented. Furthermore, cleaning activities should not generate dust (Table 59-3) (126). Thus, surfaces should be wiped with wet cloths and mops. Special HEPA vacuums should be used in HSCT units (126). Thio et al. (*51*) demonstrated that wet mopping could disperse 30,000 particles/m^3 into the air as compared to 800,000 particles/m^3 after dry mopping. Anderson et al. *(590)* noted that airborne *A. fumigatus* rose from 24 CFU/m^3 before vacuuming to 62 CFU/m^3 while the vacuum was being used.

Personal Hygiene

Damage to the oral cavity caused by cytotoxic, infectious, and hemorrhagic complications of GVHD is reflected by the severity of the mucositis. The oral cavity is a reservoir for microorganisms. The microorganisms accounting for most oral infections are HSV and *C. albicans (57)*. By reducing the number of oral microorganisms through optimal care, the risk of developing a life-threatening systemic infection from an oral source may be reduced. Aggressive dental and oral hygiene interventions can ameliorate oral complications prior to transplantation, as elimination of oral infection is paramount for the success of HSCT (126). Preferably, all HSCT candidates should undergo a dental evaluation and complete invasive oral procedures 10–14 days before starting conditioning therapy (126,*769*). Daily showers and good perineal care are recommended to optimize skin care (126). Mucositis should be managed following established guidelines *(770)*.

Food Preparation and Handling

Careful food preparation is required in all patients but particularly important in patients undergoing transplantation. Guidelines recommend a low-microbial diet for HSCT recipients, although the evidence to support this practice is limited (126,*771*,*772*). Gardner et al. *(773)* investigated the value of a neutropenic diet in 153 patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. The patients were randomized to receive only a cooked diet or a diet containing fresh fruit and fresh vegetables (raw diet). All patients were in a protective environment and received antimicrobial prophylaxis. The outcome revealed 29% of patients in the cooked group and 35% of patients in the raw group developed a major infection, which was not statistically different *(773)*. Fever of unknown origin in the group receiving cooked food was higher than in the group eating raw food (51% vs. 36%), but the probability of death was not different *(773)*. However, attention to the types

of foods and appropriate storage and handling is needed for all HSCT recipients to prevent food-borne diseases (774). Non-neutropenic HSCT recipients still have immunosuppression for a period of time after transplantation; therefore, food safety is an important issue for these patients. Formal recommendations have been published that include recommendations for adequately cooking certain foods, although restricting exposure to certain fruits and vegetables and dairy products is advised *(775)*. HSCT recipients should not consume raw or undercooked eggs or foods that might have them in the ingredients (774). Several microorganisms that cause foodborne illnesses could also infect these hosts and cause severe illness. One example is nontyphoidal salmonellosis (NTS), which is an emerging problem that can lead to bacteremia in HSCT recipients *(118,776)*. Hence, food should be appropriately stored and well cooked. HSCT recipients and their caregivers should be educated regarding diet; they should be advised about which foods to avoid including those which may contain yeast or molds (774).

Visitors

Visitors and family members, although critical to the care of the HSCT patients, can be a source of infectious diseases that can lead to infection in patients. Visitors must clean their hands and follow isolation and barrier precautions. They should be vaccinated including vaccination for influenza to prevent transmission of diseases to HSCT patients. Visitors who are ill with potentially infectious diseases should not be allowed into the institution and should be screened for diarrhea, vomiting, fever, conjunctivitis, undiagnosed rash, upper respiratory symptoms, recent exposure to people with symptoms consistent with an acute infectious illness, or recently vaccinated with live vaccine (e.g., polio, MMR, or varicella vaccines). In addition, visitors should be screened for respiratory illness and not allowed to visit an HSCT unit while symptomatic or infectious. Allowing children to visit is very controversial, as they are exposed to many infectious and communicable diseases in school, at play, or in day-care settings. The risks and benefits should be weighed, but additional precautions may be necessary if children are allowed on units. Certainly, more restrictive policies are needed if community or unit-based outbreaks of a communicable disease are in progress. Such strategies have been effectively used to prevent further transmission of influenza, pertussis, SARS, and RSV.

Healthcare Personnel

All healthcare workers should have immunizations required by the institution including measles, mumps, rubella, and evidence of immunity to varicella or of receipt of the varicella vaccine (see Chapters 43, 51, and 75). Varicella vaccine can be administered to susceptible healthcare workers working on HSCT units *(274)*. If a local, vesicular reaction after the vaccine occurs, the healthcare worker should avoid contact with HSCT recipients until all lesions resolve or no new lesions appear within a 24-hour period *(274)*. Vaccine-associated infections can be spread among household contacts, but no data are available on spread among healthcare workers *(777)*.

All healthcare workers should be vaccinated against influenza annually. Early detection of influenza in healthcare institutions is crucial for preventing healthcare-associated transmission. Influenza vaccine in healthy, young healthcare workers is 88% efficacious for influenza A and 89% for influenza B *(778)*. In addition, Potter et al. demonstrated that vaccinating healthcare workers for influenza reduced influenza-like illness and decreased mortality 47% *(779)*. Current guidelines strongly recommend influenza vaccine in healthcare workers *(182)*.

Healthcare workers with transmissible infectious diseases should follow the recommendations regarding work restrictions *(780)*. Institutions should provide a written policy about immunizations and work restrictions for healthcare workers who work in HSCT units.

ANTIMICROBIAL PROPHYLAXIS

Antiviral Chemoprophylaxis

Cytomegalovirus CMV disease causes significant morbidity and mortality among patients undergoing HSCT, even in the face of antiviral therapy. As such, much effort has been directed toward prevention of CMV disease. Two basic strategies for CMV prevention have been employed: use of antiviral agents in all patients (prophylactic therapy), and screening of at-risk populations for evidence of CMV shedding with early treatment of those patients (preemptive therapy). All patients undergoing HSCT should undergo serum testing for anti-CMV antibodies before transplantation (143). In addition, the guidelines strongly recommend that all at-risk allogenic HSCT recipients (CMV-seropositive HSCT recipients and CMV-seronegative recipients with a CMV-seropositive donor) should receive either prophylactic or preemptive treatment with ganciclovir, with preemptive therapy being preferred (143). Further discussion of this subject is beyond the scope of this chapter. The high incidence of granulocytopenia associated with these therapies potentially exposes a large number of patients who do not have CMV disease to the risk of neutropenic bacterial infections. Furthermore, prophylaxis does not prevent reactivation of CMV later in the patient's course after ganciclovir has been discontinued.

Newer antiviral agents have also been tested and have been shown to be effective in preventing CMV infection including valacyclovir.

The preemptive treatment strategy relies on active surveillance for CMV shedding and initiation of treatment prior to the development of clinical CMV disease. A number of techniques have been employed to detect CMV shedding including shell-vial cultures, detection of pp65 antigen, and detection of CMV-DNA PCR. Shell-vial cultures can take up to 2 days to give a positive result and are therefore less useful in prompt detection of shedding. Detection of CMV pp65 antigen from peripheral white blood cells is currently the most common technique to detect viremia; however, false-negative tests can occur if the patient is neutropenic. The highest levels of serum antigen are seen among patients with pneumonitis, gastroenteritis, and viremia. Overall, the positive predictive value for CMV disease in HSCT patients is 53% and the negative predictive value 91%, and the antigen test was positive a median of 10 days before cultures were positive in all pneumonitis patients *(229)*.

Valganciclovir, an oral prodrug of ganciclovir, has been used in preemptive therapy (143). The results from uncontrolled studies suggest that the efficacy and safety of

valganciclovir, when used as preemptive therapy, are comparable with intravenous ganciclovir *(225,781–788)*.

Foscarnet has been studied for preemptive therapy in allogeneic HSCT patients with CMV antigenemia and the result was comparable to ganciclovir *(789)*. The guideline places it as alternative therapy, because it requires prehydration and electrolyte monitoring (143). However, patients who cannot tolerate ganciclovir should be treated with foscarnet (143).

Cidofovir has also been evaluated in a number of nonrandomized studies with acceptable results *(790–792)*. Because of nephrotoxicity, its use in HSCT may be limited *(225)*. The current guideline recommends cidofovir as second-line preemptive therapy (143). Cross-resistance between ganciclovir and cidofovir can occur *(793)*.

Currently, there is no benefit to routinely administering ganciclovir to HSCT patients who are greater than 100 days posttransplant (143). However, antiviral therapy should be continued after 100 days in HSCT patients in whom virus can be detected.

Prophylaxis for HSV and VZV Acyclovir should be offered prophylactically to all HSCT patients who are HSV seropositive (143). This strategy prevents reactivation of disease. Prophylaxis should be initiated with the conditioning regimen and continued until engraftment occurs or mucositis resolves. Several studies have shown that oral acyclovir prevents the reactivation of oral HSV infections *(794–797)*. Eighty percent of seropositive patients excrete HSV during the first 50 days after transplantation *(136)*. In contrast, fewer than 1% of seronegative patients excrete virus. Wade et al. *(796)* gave acyclovir or placebo to 49 HSCT patients for 5 weeks beginning 1 week before transplantation. Five of twenty-four patients receiving acyclovir developed HSV infection during prophylaxis, compared to 17 of 25 patients receiving placebo ($p < .01$) *(796)*. Among patients taking a minimum of 40% of their prescribed drug, acyclovir was 96% virologically effective and 100% clinically effective during the period of administration.

Valaciclovir, famciclovir, and ganciclovir are active against HSV (143,*264*,*798*). Although less studied, valaciclovir and famciclovir can be used for HSV prevention (143,*264*,*799,800*). Use of ganciclovir prophylaxis for CMV is adequate for HSV prevention (143).

Two prospective studies suggest that acyclovir prevents varicella infection in HSCT recipients *(801,802)*. In these studies, acyclovir was continued for 1 year, and was demonstrated to be highly effective in reducing the risk of VZV disease during the year while receiving the medication *(801,802)*. Post study, VZV occurred in patients who needed to continue immunosuppressive therapy *(801,802)*. Continued use of acyclovir may be recommended in HSCT recipients with chronic GVHD or patients with immunosuppressive therapy *(279)*.

Valacyclovir may be used for VZV prophylaxis based on a nonrandomized study in allogeneic HSCT recipients *(803)*.

Ganciclovir also has activity against VZV. One nonrandomized study demonstrated that it is effective for VZV prophylaxis in HSCT *(268)*.

Optimal duration of VZV prophylaxis in HSCT recipients with chronic GVHD or patients with immunosuppressive therapy is unknown. The current guideline suggests that acyclovir may continue until 6 months after discontinuing all systemic immunosuppressive agents (143).

Antibacterial Prophylaxis

Because of the high mortality associated with bacterial infections, particularly during the pre-engraftment phase, research has been directed toward the prevention of these infections using antimicrobial agents. Importantly, guidelines for the use of antimicrobial agents in neutropenic patients have been developed that include a risk assessment, a systematic evaluation of the patient, and a stepwise approach to use of these agents *(351)*. These guidelines provide a measured and thoughtful approach to the use of vancomycin that will help limit resistance *(253)*. The rationale for prophylactic administration of antibiotics is based on data that show that the majority of bacterial infections arise during the neutropenic phase from the patient's endogenous flora. Prophylactic antibiotics, therefore, have been used to selectively decontaminate certain body sites. As the gut is the primary reservoir of potentially pathogenic bacteria, attempts at decontamination have focused on this site. The downside of eliminating the resident flora is the potential for selection of other, potentially more resistant, microorganisms. In addition, the benefits of these agents must be balanced against the deleterious effects including toxicity, resistance, fungal overgrowth, and superinfections *(804–807)*. Although many regimens have been used in the past, this discussion focuses on agents currently in use and on studies focusing on HSCT patients *(351,808–810)*.

Two meta-analyses in the 1990s performed by Cruciani et al. *(810)* and Engels et al. *(809)* revealed that fluoroquinolone prophylaxis compared to placebo or trimethoprim-sulfamethoxazole in neutropenic patients could reduce the rate of infectious complications, but it had no effect on infection-related mortality. Gafter-Gvili et al *(811)*. performed another meta-analysis and showed that fluoroquinolone prophylaxis reduced the risk for all-cause mortality when compared to placebo (relative risk = 0.52). However, fluoroquinolone prophylaxis increased the risk for harboring bacilli resistant to this class of agents *(811)*.

Bucaneve et al. *(808)* performed a prospective, multicenter, double-blinded, randomized study to investigate the effect of prophylactic use of 500 mg of levofloxacin in patients with cancer and neutropenia. Patients were assigned to receive 500 mg of levofloxacin orally or placebo everyday until neutropenia had resolved. Patients who received levofloxacin had a lower rate of microbiologically confirmed infections than the placebo group, but the mortality rates were similar *(808)*. Current guidelines recommend levofloxacin for prevention of bacterial infections in adult HSCT recipients with predicted neutropenia for 7 days or more (812). No data are available in children, although some experts also use levofloxacin for pediatric HSCT (812). Prophylaxis should start at the time of stem cell infusion and should be continued until recovery from neutropenia or the start of empiric treatment for febrile neutropenia (812). Local epidemiological data should be determined before utilizing fluoroquinolone in prophylactic regimens for HSCT patients because of increasing rates of fluoroquinolone resistance worldwide (812,*813*). For example, a study from Taiwan reported by Chen et al. *(814)*

demonstrates that only 50% of *E. coli* and 44% of *P. aeruginosa* isolated from patients admitted to hemato-oncology wards were susceptible to ciprofloxacin. Gram-negative microorganisms caused 60% of the cases of bacteremia in neutropenic patients in this institution *(814)*.

The expected consequences of antibacterial prophylaxis that impact infection control groups are the emergence of resistant microorganisms and infections and superinfections caused by fungi *(805,806)*.

TMP-SMX has been used to prevent PCP for years, and retrospective data provide information about its utility in preventing bacterial infections *(815)*. In most studies, patients receiving TMP-SMX have lower infection rates than patients receiving placebo *(351,815)*. In one large study of adult and pediatric patients who were randomized to placebo or 160/800 mg of TMP-SMX until the neutropenia resolved, those who received TMP-SMX developed fewer infections (26% vs. 39%; $p < .02$) *(816)*. There have been no studies examining the use of TMP-SMX specifically in HSCT recipients, but its use is attractive, as these patients require TMP-SMX for PCP prophylaxis. TMP-SMX also provides some protection against toxoplasma, nocardia, and some enteric pathogens *(513)*. Unfortunately, drug side effects associated with higher doses, primarily skin manifestations, occur in approximately 20% of patients *(817)*.

The spectrum of infecting microorganisms in HSCT patients has shifted with the use of both TMP-SMX and quinolones; gram-positive infections have increased *(818)*. A particularly marked increase in alpha-hemolytic streptococcal infections has been noted in patients receiving ciprofloxacin, which has poor activity against streptococci *(54,60,344)*. The mortality associated with gram-positive infections is lower than that seen with gram-negative sepsis, and the overall burden of bacterial infections is decreased with prophylaxis *(136)*. Prophylactic strategies to decrease the morbidity associated with these infections have yet to be defined in randomized trials. Some centers currently include penicillin V, a first-generation cephalosporin, or vancomycin in their regimen, at least while the patient has mucositis *(344,819–821)*. Of note, there is no good evidence to confirm the benefit of adding an anti–gram-positive agent to the prophylaxis regimen. One meta-analysis demonstrated no difference between patients who received a fluoroquinolone alone and patients who received a fluoroquinolone in combination with gram-positive prophylaxis in terms of occurrence of clinically documented infections, unexplained fever, or infections-related mortality *(822)*.

Current guidelines only recommend that prolonged antibiotic prophylaxis for preventing infection with *S. pneumoniae* among allogeneic recipients with chronic GVHD for as long as active chronic GVHD treatment is administered. Antibiotic selection should be guided by local antibiotic resistance patterns (812).

Vancomycin flushes, injections, and dwells and insertion prophylaxis have been used to prevent catheter-related bloodstream infections *(823–828)*. Prophylaxis to prevent infections related to insertion has not been shown efficacious, and centers should follow the recommendations for skin preparation and catheter care described in the national guidelines *(97,826,828)*. Studies examining the impact of vancomycin prophylaxis to prevent line-associated infections report mixed results *(823–828)*. Controversy arises as other components tested including heparin may have impacted the results, and antimicrobial resistance likely develops in this setting.

In summary, prophylaxis is recommended for bacterial infection prevention in patients with neutropenia and for prevention of PCP (812). The routine use of vancomycin (or other antimicrobial agents) to prevent central-line infections is not recommended (*351*,812,*829*).

Antifungal Prophylaxis

Invasive fungal infections cause significant morbidity and mortality among HSCT recipients (549,*830*,*831*). As their presentation may be insidious, diagnosis and treatment challenging, and clinical outcomes dismal, primary antifungal prophylaxis has become an attractive strategy. The advent of potent and well-tolerated antifungal agents, namely the azoles, has made primary antifungal prophylaxis achievable. Two large randomized, placebo-controlled trials validated the use of fluconazole for primary antifungal prophylaxis among HSCT recipients (541,*832*). Goodman et al. conducted a double-blinded randomized clinical trial in which patients were randomized to receive 400 mg of fluconazole or placebo (541). Autologous and allogeneic HSCT recipients received fluconazole or placebo upon initiation of the conditioning regimen, which was discontinued when the ANC was over 1,000/mm^3 for 7 consecutive days. (541). Fluconazole was associated with significantly fewer IFIs (2.8% for fluconazole vs. 15.8% for placebo; $p < .001$), predominately *Candida* infections, and lower mortality attributable to IFIs compared to placebo (1 of 179 for patients taking fluconazole vs. 10 of 177 for patients taking placebo; $p < .001$) (541). Another study involving 300 allogeneic HSCT recipients showed that fluconazole again lowered rates of IFIs (no *C. albicans* infections in fluconazole group compared with 18 in the placebo group, $p < .001$) *(832)*. A significant survival benefit was also found in this study, with 20% mortality in the fluconazole arm versus 35% in the placebo; *p*-value .004 *(832)*. In a subsequent analysis of this study, administration of fluconazole was associated with persistent survival benefit in terms of candidiasis-related death, even after discontinuation of fluconazole at day 75 post-HSCT *(542)*. There were 17.5% more patients in the fluconazole arm surviving compared to the placebo group by 8 years after HSCT *(542)*. In addition, fluconazole administration appeared to be associated with a decreased incidence of severe gut GVHD *(542)*. Moreover, the patients who were treated with fluconazole for 75 days had significantly fewer systemic candidal infections "late" (more than 110 days) after HSCT, and more patients who received placebo died with candidiasis during this late period *(542)*.

The higher rates of IA prompted investigators to study antifungal agents with activity against *Aspergillus* species as primary antifungal prophylaxis in the HSCT setting. Itraconazole is a broad-spectrum triazole with activity against—among others—*Aspergillus* and *Candida* species. A randomized, placebo-controlled, double-blind, multicenter trial among 405 neutropenic patients with hematologic malignancies showed that proven or suspected deep fungal infection occurred in 24% (48/201) and 33% (67/204) of patients in the itraconazole and placebo arms,

respectively ($p = .035$) *(833)*. Candidemia was significantly lower among patients receiving itraconazole as compared to placebo ($p = .01$), and a marginal survival benefit ($p = .06$) was found in the itraconazole arm. In another randomized, placebo-controlled trial involving over 200 HSCT patients, those patients receiving placebo developed fungal infections (superficial or systemic) more frequently than those receiving itraconazole (15% vs. 6%; $p = .03$) *(834)*. Among patients with profound and prolonged neutropenia, those receiving placebo used more empirical amphotericin B (61% vs. 22%; $p = .0001$) and developed more systemic fungal infections (19% vs. 6%; $p = .04$). Additional prospective randomized studies examined the impact of fluconazole or itraconazole for 180 days posttransplant or until 4 weeks after discontinuation of GVHD) therapy *(835)*. Significantly fewer patients developed an IFI in the itraconazole (7%) compared to the fluconazole arm (15%; $p = .03$) *(835)*. Rates of invasive candidiasis were similar in both arms ($p = .67$), while invasive mold infections were significantly lower in the itraconazole group (5%) compared to the fluconazole arm (12%; $p = .03$) *(835)*. More patients in the itraconazole arm had to discontinue their prophylaxis, because of toxicities or gastrointestinal intolerance (36% vs. 16%, $p < .001$) *(835)*. Due to poor tolerability, absorption issues, drug–drug interactions, and toxicities, the utility of itraconazole as a primary universal antifungal prophylaxis agent is limited (*833*,*836*,*837*,838).

Low-dose amphotericin B prophylaxis to avoid the toxicity of conventional doses has been considered for antifungal prophylaxis. A number of studies have examined the use of different low-dose protocols in different populations at potential risk with varying results. Rousey et al. *(839)* demonstrated that low-dose amphotericin B starting during the conditioning regimen significantly decreased the overall and *Aspergillus*-specific mortality *(839)*. In fact, when used among patients receiving corticosteroids for acute GVHD, low-dose amphotericin B reduced the risk for fungal infection from 30% to 9%; *p*-value .01 *(840)*. Other formulations of amphotericin B have also been studied and similar results found, including an aerosolized form and a liposomal preparation *(841–844)*. However, at least one investigator did not replicate these findings among autologous HSCT patients *(845)*. Aerosolized liposomal amphotericin B (L-AmB) was evaluated as prophylaxis during neutropenia in a randomized, placebo-controlled trial among 271 patients. The patients were randomized to receive 2.5 mL of L-AmB. Nebulization was performed for 30 minute per day on 2 consecutive days per week. The weekly regimen was repeated until neutrophil recovery, with a maximum of 12 inhalations per neutropenic episodes. The outcomes showed that 4% of 139 patients treated with liposomal amphotericin B had developed invasive pulmonary aspergillosis (IPA), while 14% of 132 patients receiving placebo developed IPA with significantly more adverse effect (most frequently coughing but not renal toxicity) in the L-AmB group; *p* .002 *(846)*.

More recently voriconazole, a newer agent, has been studied. Fluconazole 400 mg per day was compared to voriconazole 400 mg per day in 600 allogeneic HSCT recipients *(847)*. Antifungal agents were given for 100 days after transplant and up to 180 days in case of higher-risk patients. The primary end point was fungal-free survival at 180 days. There were trends to fewer IFIs, A*spergillus* infections, and less frequent empiric antifungal therapy in the voriconazole arm. There was no survival benefit, and safety was similar in both arms.

Posaconazole, a newer broad-spectrum oral triazole with activity against the Zygomycetes, was compared with oral fluconazole for prophylaxis against IFIs in allogeneic HSCT recipients with GVHD who were receiving immunosuppressive therapy *(848)*. Posaconazole was found to be as effective as fluconazole in preventing all IFIs (5.3% and 9.0%, respectively; odds ratio, 0.56; 95 percent confidence interval [CI], 0.30 to 1.07; $p = 0.07$) and was superior to fluconazole in preventing proven or probable IA (1% in posaconazole group vs. 7% in fluconazole group; $p < .001$); however, overall mortality was similar in the two groups *(848)*. Based on the above, the Infectious Diseases Society of America's clinical practice guidelines for the treatment of aspergillosis recommends the use of posaconazole in HSCT recipients with GVHD who are at high risk for IA *(849)*.

Micafungin, an echinocandin antifungal agent, was evaluated for prophylaxis against IFIs during neutropenia in patients undergoing HSCT *(850)*. A prospective, randomized, double-blind study in adult and pediatric patients compared micafungin and fluconazole *(851)*. Micafungin treatment decreased proven, probable, or suspected systemic fungal infections more often than among patients in the fluconazole group (80% in the micafungin group vs. 73.5% in the fluconazole group were free of IFIs; $p = .03$) *(851)*. However, use of micafungin as a prophylactic agent is limited due to cost and lack of an oral formulation (838).

Ultimately, the selection of an appropriate prophylaxis protocol depends on the epidemiology at a given institution. Daily fluconazole prophylaxis is still recommended (838,*852*). However, institutions with high-risk HSCT patients, high rates of fluconazole-resistant *Candida* infections or *Aspergillus* infections may consider using other alternatives, including voriconazole or posaconazole. Moreover, ongoing surveillance efforts are necessary to adjust prophylaxis strategies to an evolving microbiologic flora.

Prophylaxis for *Pneumocystis jiroveci* Pneumonia

Prophylaxis with TMP-SMX has been shown to prevent PCP in immunocompromised patients *(351,638,853)*. (TMP-SMX has already been mentioned in antibacterial prophylaxis.)

Oral dapsone is recommended as alternative regimens for PCP prophylaxis *(655)*. For HIV-positive patients, it has been considered to be the best alternative regimen after TMP-SMX, but there are limited data for HSCT patients *(854)*. Souza et al. *(855)* performed a study that compared the effectiveness between dapsone and TMP-SMZ in preventing PCP among allogeneic HSCT recipients and demonstrated that the incidence of PCP among patients receiving dapsone was 7.2%, whereas the incidence of PCP among patients receiving TMP-SMX was 0.37% and 6.8% in historical controls who received no prophylaxis *(855)*. However, the dose regimen used in this study was lower than the current recommendation in the guideline, and this study was not a randomized study. Dapsone was recommended

only for patients who had TMP-SMZ allergy and failed to have desensitization *(855)*. Adverse effects of dapsone include hypersensitivity, methemoglobinemia, hepatitis, and hemolysis *(655)*.

Atovaquone and aerosolized pentamidine have limited data in HSCT recipients.

Prophylaxis should be administered from engraftment until at least 6 months after HSCT in all allogeneic HSCT recipients and autologous HSCT recipients with underlying hematologic malignancies, those receiving intense conditioning regimens or graft manipulation, or those who have recently received purine analogs *(638,655)*. Some experts recommend an additional 1- to 2-week course of PCP prophylaxis before transplantation *(655)* (see Table 59-4).

Postexposure Prophylaxis for Communicable Diseases

Infection control personnel should evaluate HSCT patients who are exposed to communicable diseases based on hospital policy. Personnel need to assess the type of exposure, the duration of exposure, how infectious the microorganism is, how it is transmitted, and in some instances consider how immunocompromised the patient is. In several situations, additional interventions may be needed. For example, HSCT patients who are not immunocompetent and who are susceptible to varicella and exposed should receive varicella-zoster immunoglobulin (VZIG), if available within 72 to 96 hours of exposure, ideally within 48 hours (143,*274*). Exposure is defined as sharing a room with an infected patient or prolonged face-to-face contact with an infectious person *(276)*. Adults should receive 125 U/10 kg or a maximum of 625 U (143). The prophylaxis should be given to HSCT recipients <24 months after HSCT or >24 months and on immunosuppressive therapy or with chronic GVHD. Since VZIG efficacy was not impressive, 25% to 45% of patients receiving VZIG developed clinical varicella infection (856,*857*,*858*). For this reason, many centers offer acyclovir or valciclovir in addition to VZIG as a postexposure regimen, although data to support this practice are limited, and it has not been studied in HSCT recipients (859). The medications should continue until 22 days after exposure or 28 days in patients receiving VZIG (143,859). The other issue that remains controversial is postexposure prophylaxis among VZV-seropositive HSCT recipients (859). At least 57 possible reinfections in immunocompromised patients have been described (856). Moreover, false-positive VZV antibody results can occur in patients who received immunoglobulin or blood products (859). Experts recommend consideration of postexposure prophylaxis for VZV in seropositive-HSCT recipients as an optional therapy (*264*,859). Weinstock et al. *(859)* suggest that postexposure prophylaxis for VZV in seropositive-HSCT recipients should be offered routinely in autologous HSCT recipients <6 months, allogeneic HSCT recipients <12 months, patients receiving immunosuppressive therapy, and patients with active GVHD or other immunosuppressive states. The single exception is seropositive patients who have previously experienced and episode of VZV disease after HSCT who appear to be at no risk (859). The varicella vaccine is contraindicated in HSCT patients until 24 months after HSCT (860).

Antiviral agents with activity against influenza, such as amantadine, rimantadine, or the newer neuraminidase inhibitors (oseltamivir, zanamivir), are indicated for preemptive therapy (or prophylaxis) during outbreaks and may be administered during influenza season, while influenza-like illness is present in the community. These agents have been used in the setting of influenza in HSCT patients, although little information is available about the efficacy in these patients. Drug resistance patterns of the virus should be used for guiding the choice of antiviral agents (143).

Prophylaxis should be administered to patients exposed to *Neisseria meningitidis* infections. Pneumonia may present a special case and guidelines for prophylaxis of patients exposed to *N. meningitidis* pneumonia should be individualized. One outbreak in the literature describes five oncology patients hospitalized on the same hospital unit, but not in adjacent rooms, who developed *N. meningitidis* colonization or infection *(861)*. The index patient had *N. meningitidis* pneumonia. Based on the extensive transmission associated with this cluster, we believe more liberal standards for prophylaxis are indicated in HSCT patients exposed to patients with *N. meningitidis* pneumonia.

Immunization of HSCT Recipients

Vaccines for influenza and hepatitis B, pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* conjugate vaccine, inactivated polio, MMR, and TDaP should be administered to patients optimally prior to undergoing HSCT (860). These vaccinations are important in preventing infections that occur late after HSCT. HSCT recipients should be routinely revaccinated after transplantation because antibody titers decline during the 1 to 10 years after HSCT (860). The American College of Physicians recommends annual influenza vaccination of immunocompromised individuals and their family members before the winter season. HSCT patients who do not receive pretransplant vaccination may demonstrate an immune response with PCV and inactivated influenza vaccine as soon as 4 to 6 months after HSCT (860). Vaccination with TDaP, *H. influenzae* conjugate vaccine, inactivated polio, and recombinant hepatitis B can be given 6 to 12 months after HSCT (860). Vaccination with MMR should occur 24 months after HSCT (860). These vaccines have been shown to be efficacious in healthy individuals but may not stimulate an adequate antibody response in individuals receiving chemotherapy.

Antimicrobial Stewardship

Because of prolonged hospitalization, an immunosuppressed state, and often extensive exposure to antimicrobials, the HSCT population is uniquely at risk for developing infections with resistant microorganisms. Antimicrobial stewardship is important in this population to lower the risk of such infections and to ensure that antimicrobials are given at the correct dose and for only as long as they are needed to maximize patient safety. Although the topic of Antimicrobial Stewardship is covered in Chapter 87, specific areas that may be of use to address in the HSCT population include indications for initial and prolonged vancomycin use and tailoring antimicrobial use based on microbiology data.

TABLE 59-4

Common Antimicrobial Prophylaxis Use in HSCT Patients

Infection	*Host*	*Pre-engraftment*	*Postengraftment*
Bacteria (all)	Neutropenic patients	Fluoroquinolone with antipseudomonal activity First line: Levofloxacin 500 mg once daily or ciprofloxacin 500 mg twice daily [a]Depend on local susceptibility data	
S. pneumoniae	cGVHD		Late phase: Penicillin, in areas in which the incidence of penicillin-resistant *Streptococcus pneumoniae* is not high 250–500 mg orally twice daily or 500–1,000 mg once daily Alternatives: macrolides or fluoroquinolones or second-generation cephalosporins
PCP	All allogeneic HSCT recipients; or autologous HSCT recipients with underlying hematological malignancies, those receiving intense conditioning regimens or graft manipulation, or those who have recently received purine analogs (BIII)		First choice: Trimethoprim-sulfamethoxazole 1 double-strength (160/800 mg) tablet orally daily or 1 double-strength tablet orally thrice per week administered per BMT unit protocol, preferably postengraftment Alternatives: Dapsone, Atovaquone, Nebulized pentamidine Until at least 6 mo
CMV	All CMV-sero-positive and CMV-sero-negative with a CMV-sero-positive donor		Preemptive or prophylactic treatment First line: ganciclovir 5 mg/kg/dose iv Induction: twice daily for 7–14 d Maintenance: daily Alternatives: Foscarnet, valganciclovir, cidofovir
HSV	HSV-seropositive allogeneic recipients	Acyclovir Adult: 400–800 mg orally twice daily Pediatrics: (<40 kg) 250 mg/m^2/dose iv every 8 h; Maximum dose: 80 mg/kg/d (or until mucositis resolved) Alternatives: Valacyclovir	
VZV	VZV- sero-positive		Acyclovir 800 mg orally twice daily for 1 y Alternative: Valacyclovir May continue beyond 1 y in GVHD
Fungus:	Allogeneic HSCT recipients; or autologous HSCT recipients who have or will have prolonged neutropenia and mucosal damage from intense conditioning regimens, graft manipulation or who have recently received purine analogs	First choice: Fluconazole 400 mg daily	
Candida spp.		Alternative: Itraconazole, micafungin Fluconazole resistant *Candida* spp.: Micafungin Posaconazole	
Fungus: *Aspergillus* spp.	Allogeneic HSCT recipients with GVHD		Posaconazole or voriconazole

[a]Depend on local susceptibility. In some parts of the world, the incidence of quinolone resistance organisms is high *(350,402,813)*.

Surveillance Activities

Surveillance activities should target disease processes and microorganisms that are most problematic in the HSCT population at an individual institution. Helpful guidelines for appropriate surveillance activities are emerging for institutions that maintain HSCT services (126). They advocate strongly for the development of three types of surveillance: an environmentally, a microbiologically, and a clinically based program to support surveillance functions for epidemiologically important microorganisms and communicable diseases. A fourth type, syndromic has been used in the settings of pandemic influenza and may be used in specific settings. However, discussion of this later strategy is beyond the scope of this chapter

For environmental surveillance, periodic routine culturing for *Legionella* species in water samples from the potable water supply should be included (126). Infection control programs must have the expertise and resources to respond quickly to outbreaks, clusters, or a case of healthcare-associated *Legionella* infection (501,*862*). We have noted many of these recommendations throughout this chapter.

In the setting of construction, monitoring for clinical cases of aspergillosis and other invasive mold infections should be performed (126). Microbiological air sampling may be performed in patient care areas when an outbreak is suspected (126).

In the era of multidrug-resistant microorganisms, laboratories must have the capability of identifying resistant enterococci, methicillin- and vancomycin-resistant *S. aureus,* and microorganisms that produce extended-spectrum beta-lactamases (ESBL), and other important resistant mechanisms in gram-negative pathogens (126). Institutions should conduct routine surveillance for the emergence of *Staphylococcus* species strains with reduced susceptibility to vancomycin (126). Patients not known to be colonized with VRE or MRSA should have weekly perirectal and nares swabs, respectively. Guidelines for management of multidrug-resistant microorganisms in healthcare settings should be followed (126,*662*). Data on antibiotic susceptibility of viridans streptococci should be collected in these patients to guide antibiotic selection in neutropenic patients.

Because bloodstream infections cause significant morbidity and mortality in these patients, we recommend that, at a minimum, surveillance for healthcare-associated bloodstream infections be done with a focus on those related to catheters *(88,89,863–865)*. However, there are some challenging issues about definitions for surveillance especially for catheter-related bloodstream infection. Because almost all of these patients had indwelling catheters during treatment, including while they had bacteremia, which might occur primarily from mucositis or infection somewhere else that cannot be detected because of the absence of a leukocyte response line-associated bacteremia may be difficult to identify with confidence *(866)*. CDC definitions may not be appropriate in these settings and may produce data that does not reflect just those microorganisms related to catheters. Hence, some studies use modified CDC definitions among neutropenic patients *(77,867,868)* (Table 59-5).

TABLE 59-5

Recommendation for Infection Control Surveillance in HSCT Recipients

Surveillance	*Descriptions*
Environmental	*Legionella*: Periodic routine culturing of potable water supply Aspergillus/Other molds:consider in the setting of construction/renovation
Microbiological	Bacteria: - Active surveillance for vancomycin-resistance enterococci Surveillance for clinical cultures for - Viridans-*Streptococci* and their susceptibility to penicillin and cephalosporin - *S. aureus* species with reduced susceptibility to vancomycin - Multidrug-resistance gram-negative bacilli - Fluoroquinolone resistance (to consider antimicrobial prophylaxis during neutropenia) - *C. difficile* infection Virus: Consider monitoring for respiratory viruses Monitoring influenza activity and oseltamivir resistance in influenza viruses
Clinical	Consider surveillance for - Bacteremia/catheter-related bloodstream infection and their susceptibility pattern

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SECTION VIII

Epidemiology and Prevention of Healthcare-Associated Infections Related to Diagnostic and Therapeutic Procedures

CHAPTER 60

Healthcare-Associated Infections in Anesthesia

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INTRODUCTION

Modern anesthesiology originated in the 1800s *(1)*. William Clark was reportedly the first person to use ether as an anesthetic, administering it initially during a tooth extraction *(1,2)*. Soon thereafter, other healthcare providers followed suit, including William T. G. Morton, a dentist, and John Collins Warren, a professor of surgery at Harvard, who both utilized ether for anesthetic purposes *(1)*. From the very beginning, anesthesiology attracted physicians with a broad range of clinical interests and skill sets. It is, therefore, not surprising that Dr. John Snow, an early British anesthesiologist who calculated dosages for chloroform and ether, conducted epidemiologic studies that elucidated the source of the cholera epidemic in Soho, London, in 1854. His data convinced the local council to remove the handle of the Broad Street pump *(3–5)*. Thus, both modern anesthesiology and epidemiology have similar roots.

Snow further developed his epidemiological expertise over time, but he did not address the potential relationship between the practice of general anesthesia and healthcare-associated infections (HAIs). This question was first raised in 1873 by Skinner, a physician interested in the infection control and prevention practices of anesthesiologists *(6)*. Since then, numerous anesthesia personnel have investigated whether anesthesia equipment and medications transmit infections to patients, and numerous groups have published infection prevention and control guidelines and practice advisories specifically for anesthesia practice (*7*,*8*,9,*10–13*,14–17,*18–27*). In addition, the Centers for Disease Control and Prevention (CDC) has published guidelines that are relevant to anesthesia practice (28,*29–33*).

However, despite these guidelines and despite advances in anesthetic practices, surgical techniques, sterilization, and disinfection, HAIs continue to complicate healthcare, including procedures done by anesthesia providers. Some of the anesthetic and surgical advancements have increased the complexity of patient care, thereby providing more reservoirs for pathogens and more opportunities for these pathogens to cause infections. Moreover, multidrug-resistant bacteria cause many HAIs, further complicating care *(30)*. Given the human and monetary costs of these infections, numerous governments have created programs that encourage healthcare providers to adopt best practices and implement other preventive measures. In the United States, for example, the Centers for Medicaid and Medicare Services (CMS) will no longer reimburse healthcare facilities for the excess costs associated with some HAIs *(34)*. Thus, healthcare facilities and healthcare providers have additional incentives to study transmission of pathogenic microorganisms, risk factors for HAIs, and preventive measures in *all healthcare settings*, including those in which anesthesia providers work (e.g., operating rooms, preanesthesia and postanesthesia rooms, and pain clinics).

This chapter summarizes the available literature pertaining to the potential role of anesthetic practice and

equipment in intraoperative transmission of pathogens and subsequent HAIs. We review the pathogenesis and epidemiology of infections potentially related to the administration of anesthesia (general, neuraxial, and intravenous), describe and critique reports of outbreaks in which anesthesia personnel may have been the reservoirs of infection, and discuss various anesthetic practices that put either anesthesia providers or patients at risk for exposure to potential pathogens. In addition, we summarize recent studies that have assessed measures for preventing intraoperative bacterial transmission, subsequent HAIs, and occupationally acquired infections.

The Pathogenesis of HAIs Hospital-Wide

Many HAIs are acquired because pathogenic microorganisms are transmitted within the healthcare setting by healthcare workers who do not follow basic precautions that prevent spread, such as those described by the CDC *(30,31)*. For example, healthcare workers may be more likely to follow Standard Precautions and practice good hand hygiene if the patient has an obvious infection than they are if the patient does not have an apparent infection. Consequently, healthcare workers may not do hand hygiene or may not use other precautions that could prevent spread of pathogenic microorganisms from a patient's normal flora (e.g., *Escherichia coli* in the gastrointestinal tract) or from an occult infection. In fact, contaminated hands are the major vector for transmission in the healthcare setting *(31,35–39)*. Hayden et al. *(35)* demonstrated how easy it is for healthcare workers to contaminate their hands. Of 103 healthcare workers (HCWs) whose hand cultures were negative when they entered the room of a patient colonized with vancomycin-resistant enterococci (VRE), 52% contaminated their hands or gloves after touching the environment and 70% contaminated their hands or gloves after touching the patient and the environment. HCWs who wore gloves were significantly less likely to contaminate their hands (5%) despite touching more sites than HCWs who did not wear gloves (37%). Thus, noncompliance with simple preventative measures, such as hand hygiene and Contact Precautions, increases the likelihood that HCWs will transmit pathogenic microorganisms to the next patients they care for or to the environment, which can then serve as a reservoir, particularly for microorganisms such as VRE that survive on environmental surfaces for prolonged periods *(35)*. We must, therefore, study work patterns and practices in various hospital settings, including the operating room and other places where anesthesia providers work, to identify those patterns and practices that enhance transmission of pathogens from patient to patient or from patients to the environment. We must also identify interventions that prevent transmission within specific work environments, such as operating rooms.

Epidemiology of Postoperative HAIs Occurring after General Anesthesia

General Comments General anesthesia, itself, may increase the risk of HAIs. Drugs used routinely during general anesthesia can impair the function of the ciliated epithelium. Opiates directly depress ciliary activity *(40)*, atropine impairs mucociliary clearance by decreasing bronchial secretions and drying the mucous membranes *(41,42)*, and dry anesthetic gases damage the ciliated cells and slow mucus flow *(43–45)*. In addition, high concentrations of oxygen cause an inflammatory response in the ciliated epithelium that leads to tissue sloughing *(46)*.

The patients' intrinsic risk of HAIs and the risk associated with surgical procedures may be increasing. For example, patients undergoing operations at this time are often older and have more underlying diseases than patients undergoing the same procedures a decade ago and, thus, may be at high risk of HAIs *(47)*. In addition, new, more complex procedures have been introduced that may increase patients' risk of infections more than older, less complex procedures. Moreover, surgical procedures and general anesthesia compromise the patient's immune system by (a) breaching the skin and mucus membranes, the first lines of defense against infection; (b) impairing the patients' immune response by exposure to general anesthetics; and (c) inducing a postsurgical inflammatory state *(48)*. Furthermore, the anesthesia environment can become contaminated and some anesthesia equipment can create aerosols of infectious particles that contaminate equipment in the anesthesia work area, which subsequently can be a source of infectious agents for these vulnerable patients *(49–53)*.

Data Suggesting that the Practice of General Anesthesiology and Anesthesia Equipment Are not Source of Infection

Some investigators maintain that anesthesia machines, even when contaminated, do not transmit significant numbers of bacteria because (a) microorganisms are unlikely to survive in the hostile environment of the anesthesia machine due to desiccation by the flow of cold, dry anesthetic gases *(54)* and (b) the rubber and metal parts of the machine and the highly alkaline condensate at the bottom of the CO_2 absorber inhibit growth of bacteria *(55,56)*. The literature discussed below provides evidence in support of these hypotheses.

Colonized or Infected Patients Are not Likely to Contaminate the Anesthesia Machine Several studies suggest that patients colonized or infected with bacterial pathogens rarely contaminate the anesthesia machine *(55,57,58)*. For example, Du Moulin and Saubermann *(55)* studied 15 patients anesthetized with sterile machines. Two throat and sputum cultures were obtained from each patient before general anesthesia was administered; 40% of the patients had cultures yielding more than 10 colony-forming units (CFU) of gram-negative bacteria and 60% had cultures that did not yield gram-negative bacteria. The investigators isolated 1 to 9 CFU per segment of the breathing circuit. However, all cultures from machines used on colonized patients were negative and only three cultures from machines used on patients without gram-negative colonization were positive. Similarly, Stemmermann and Stern *(57)* asked 14 patients with cavitary tuberculosis to breathe into a basal metabolic rate machine (which is similar to an anesthesia breathing circuit) for 10 minutes and then cough. The investigators did not identify *Mycobacterium tuberculosis* in smears or cultures of the saline used to wash the masks and tubing and, thus, concluded that the anesthesia circuit was unlikely to contribute significantly to bacterial

crosscontamination. These data suggest that colonized or infected patients rarely transmit bacterial pathogens via the breathing circuit to the anesthesia machine.

Contaminated Anesthesia Machines Are Unlikely to Transmit Bacterial Microorganisms to Patients Several investigators have used simulations to show that contaminated anesthesia machines are unlikely to transmit bacterial pathogens *(55,59–62)*. For example, Adriani and Rovenstine *(59)* were unable to grow microorganisms from air blown through soda lime canisters contaminated with large numbers of *E. coli* or *M. tuberculosis*. Ziegler and Jacoby *(60)* used a contaminated machine to ventilate a sterile reservoir bag for 30 minutes; cultures of the reservoir bag remained negative. After inoculating the expiratory port of a sterile circle system with 10^8 to 10^9 CFU of either *Enterobacter cloacae* or *Flavobacterium* species, du Moulin and Saubermann *(55)* blew 3 L of nitrous oxide and oxygen per minute through the valve for 3 hours. Every 30 minutes, they obtained samples from the valve and found progressively fewer bacteria in the cultures. They did not recover the indicator microorganisms from other parts of the machine. Ibrahim and Perceval *(62)* seeded cleaned circuits with viridans streptococci or staphylococcal bacteriophages, attached these circuits to machines, and blew air through them. Air sampling cultures obtained from the distal ends of the tubes were all negative.

Anesthesia circuits are not a major source of infections for surgical patients and bacterial filters are not an important preventive measure.

Two prospective clinical trials have been cited as evidence that anesthesia circuits are not a major source of infections for surgical patients. Garibaldi et al. *(63)* randomly assigned 257 patients to be anesthetized with disposable corrugated plastic circuits containing bacterial filters (0.22 μm) and 263 patients to be anesthetized with disposable corrugated plastic circuits without filters. The postoperative pneumonia rates for the two groups did not differ significantly, but the study was powered to detect a 50% difference in rates, which would be difficult to achieve with most interventions. Feeley et al. *(64)* found no difference in postoperative pneumonia rates between 138 patients anesthetized with sterile disposable circuits and 155 patients anesthetized using clean reusable circuits. However, the study had a power of only 17% to detect a 50% difference in rates.

Van Hassel et al. *(65)* reviewed 9 years of surveillance data and found lower respiratory tract infections in 5 of 2,300 (0.2%) patients undergoing operations under regional anesthesia and 31 of 23,500 (0.1%) patients undergoing general anesthesia with tubing that was cleaned only once a day (i.e., was shared by three to seven patients). They changed the soda lime every 3 days and they placed filters at the T pieces only when patients had suspected or overt respiratory tract infections, *M. tuberculosis*, or human immunodeficiency virus (HIV) infection. They concluded that "in our setting, patient factors are most important in the development of postoperative lower respiratory infections and that the role of bacterial filters as a preventive measure is negligible" *(65)*.

In summary, the studies reviewed in this section suggest the following: (a) colonized or infected patients are not likely to contaminate the anesthesia machine; (b) the anesthesia machine does not serve as a significant reservoir for bacterial microorganisms; (c) anesthesia circuits are not a major source of infections for surgical patients and bacterial filters are not an important preventive measure.

Data Suggesting that the Practice of General Anesthesia, Anesthesia Equipment, the Operating Room Environment, Anesthetic Medications, and Anesthesia Personnel Are Associated with HAIs

Endotracheal Tube Studies in experimental animals indicate that endotracheal tubes disrupt the ciliated tracheal epithelium, cause an inflammatory response, and impair mucociliary clearance, increasing the risk of subsequent infections *(66–71)*. In addition, the endotracheal tube can serve as a route by which bacterial pathogens from the patient's oropharynx, healthcare providers' hands, and the surrounding environment can be transmitted into a patient's trachea *(72,73)*. Indeed, several studies have shown that gram-negative bacteria or other potential bacterial pathogens that were not identified by preoperative cultures of the nasopharynx, pharynx, or larynx subsequently contaminated endotracheal tubes in the postoperative period *(72–74)*. In addition, nasal-tracheal intubation has been shown to cause transient bacteremia *(75,76)*. Thus, placement of endotracheal tubes can increase the risk of transmitting bacterial pathogens to patients and can contaminate a patient's lungs with his or her own flora, thereby increasing the risk of HAIs.

Anesthesia machine and circuit (Ambu bag, breathing circuit tubing, Y connector, inspiratory and expiratory valves, CO_2 absorber): Numerous authors cite an outbreak of follicular tonsillitis *(77)* and two outbreaks caused by *Pseudomonas aeruginosa (78,79)* as evidence that contaminated anesthesia machines transmit microorganisms. These reports provide some evidence that anesthesia equipment (anesthesia machine, Ambu bag, and circuit) could be reservoirs for bacterial pathogens and may play a role in bacterial transmission. However, the results of these investigations should be interpreted with caution, because the authors did not conclusively identify the source of the infecting microorganisms. Furthermore, the typing methods evaluated phenotypic, not genotypic, characteristics that do not discriminate between strains and modern molecular typing methods.

Albrecht and Dryden *(80)* also evaluated whether sterilizing the breathing circuits and using a disposable absorber affected the rate of postoperative pneumonia. They retrospectively reviewed the medical records of 220 randomly selected patients who underwent major abdominal operations requiring general anesthesia and who were not infected at the time of the operation. Twenty percent (10/50) of patients who underwent operations before the anesthesia equipment was sterilized, 26% (13/50) of patients who underwent operations when breathing circuits were sterilized but the absorbers were reused, and 6% (7/120) of patients who underwent operations after sterile breathing circuits and disposable absorbers were used acquired postoperative pneumonia. The investigators concluded that contaminated anesthesia machines transmitted bacteria to patients and they should, therefore, be

sterilized between cases. However, the results of this study should be interpreted with caution, because it was an unblinded, uncontrolled retrospective study and because the investigators did not specify their definition of postoperative pneumonia.

Other investigators have evaluated the ability of microorganisms to survive on anesthesia equipment. Investigators either obtained cultures from anesthesia equipment after routine use or conducted *in vitro* studies. In general, such experiments identified a wide variety of bacteria (saprophytic micrococci and bacilli, *Staphylococcus aureus*, coagulase-negative staphylococci, *E. coli*, *P. aeruginosa*, viridans streptococci, *Bacillus* species) contaminating all parts of used anesthesia machines (breathing circuits, rebreathing bags, inspiratory and expiratory valves) with the parts of the machine closest to the patient most heavily contaminated *(78,81–84)*. For example, Meeks et al. *(84)* obtained cultures from anesthesia equipment after use. They grew *Staphylococcus epidermidis* from 73% of face masks, 12% of Y connectors, 6% of breathing circuits, and 6% of rebreathing bags; *S. aureus* from 10% of face masks and 1% of rebreathing tubes; and *Pseudomonas* species from 36% of face masks, 67% of Y connectors, 42% of breathing circuits, and 79% of rebreathing bags. In the study by Livingstone et al. *(85)*, 33% (13/39) of the rubber masks used to anesthetize patients with tuberculosis yielded *M. tuberculosis*. Likewise, several investigators who obtained cultures from face masks used to administer nitrous oxide for dental procedures demonstrated that bacteria from a patient's nose and mouth contaminated the apparatus *(86–88)*.

Investigators have also investigated the potential filtering and bactericidal roles of soda lime canisters and found that they do *not* filter bacterial microorganisms effectively *(83,89,90)*. For example, Murphy et al. *(89)* aerosolized eight different bacterial species into a soda lime canister and found that up to 40% of the microorganisms were not retained in the canister. Investigators have also demonstrated that the soda lime in the canister is *not* uniformly bactericidal. Murphy et al. *(89)* found that, at room temperature, 1 gram of soda lime killed *Klebsiella pneumoniae, Candida albicans, S. aureus, P. aeruginosa, Serratia marcescens, E. coli,* and *S. pneumoniae* within 10 minutes, but 1% of the *Bacillus subtilis* CFU survived at 30 minutes. Dryden *(83)* demonstrated that 4% sodium hydroxide, Sodasorb extract, and Baralyme extract killed *P. aeruginosa* and *Proteus mirabilis* within 15 minutes, but *M. tuberculosis* survived for at least 3 hours in each of the solutions.

Investigators have also used laboratory models to simulate the patient–anesthesia machine interaction and concluded that air could move bacterial pathogens through the breathing circuit *(83,90,91)*. For example, Nielsen et al. *(91)* measured the bacterial content of anesthetic gases before and after passing them through clean and previously used breathing systems to determine whether anesthetic gases could become contaminated when blown through contaminated circuits. Gases passed through clean circuits contained 1.2 to 50.2 (median 4.2) CFU of bacteria per 100 L, compared with 3.3 to 129.8 (median 38.5) CFU of bacteria per 100 L for gas passed through used circuits (Mann–Whitney $p < .01$). The authors concluded that anesthetic gases can transfer microorganisms.

Investigators have also attempted to assess the origin of breathing circuit contamination. Rathgeber et al. *(92)* obtained cultures of breathing circuits used with filters and from those used without filters to assess the origin of microbiologic contamination. When a filter was used, the microorganisms isolated from the breathing circuits were different than the microorganisms detected in the patients' tracheal aspirates. When filters were not used, the same microorganisms were isolated from the patients' tracheal aspirates and from the tubing in 13% of the cases. Thus, the study results demonstrated that patients' bacterial microorganisms can contaminate the breathing circuits and that filters can prevent circuit contamination. However, the investigators were unable to show that filter use changed patient outcomes, because patients were not followed prospectively to determine whether they acquired postoperative pneumonia.

Investigators from the New South Wales (NSW) Health Department studied the potential role of anesthetic equipment in intraoperative viral transmission when they evaluated a cluster of patients who acquired hepatitis C virus (HCV) infection after having operative procedures at a private hospital in Sydney *(93)*. After two persons who had operations on the same day presented to the hospital with acute hepatitis C, NSW health officials tested all patients who had operative procedures during the same session. Three more patients were found to be anti-HCV positive. Surgical personnel were tested and were anti-HCV negative. Patient-to-patient transmission was likely, because all five patients were infected with hepatitis C of the same genotype. The common denominator between patients seemed to be the anesthesia equipment; the same anesthesia circuit was used without a filter and without decontamination for all 11 patients who had procedures during the implicated session. On the basis of these data, the investigators concluded that the HCV was transmitted through a contaminated anesthesia circuit. They hypothesized that the index case's respiratory secretions containing HCV were introduced into the anesthesia circuit and that the virus was transmitted in droplets through minor breaks in the oropharyngeal mucosa of subsequent patients. In response, NSW health officials recommended enforcing existing guidelines that a filter be used in the anesthesia circuit to prevent cross-transmission *(18,19,94)*.

A number of other agencies, including the AANA *(8)*, the Blood-borne Viruses Advisory Panel of the Association of Anaesthetists of Great Britain and Ireland *(22)*, the Department of Health of the Netherlands Committee on Infection Prevention *(23)*, and the Societé Francaise d'Anesthesie et Reanimation *(24)*, have recommended that an appropriate filter be placed between the patient and the breathing system and that either a new filter or a new breathing circuit should be used for each patient. At present, there is no consensus on whether hydrophobic pleated membrane filters are necessary or whether electrostatic filters are adequate. Most studies of filtration efficiency have indicated that the hydrophobic filters are more efficient *(95–97)*. However, a study of patients undergoing general anesthesia found no difference between hydrophobic filters and electrostatic filters *(98)*. Both filter types significantly decreased the incidence of bacterial contamination in the breathing circuits compared with the level of contamination in endotracheal tubes.

Laryngoscopes Inadequate disinfection of laryngoscope blades and handles has been associated with clusters of infection *(99,100)*. These clusters are discussed further in the section "Current Infection Prevention and Control Guidelines and Current Anesthesia Practice."

Equipment in the Anesthesia Work Area Loftus et al. (101,102) and Koff et al. (103) have documented that various pieces of equipment in the anesthesia work area are contaminated with bacterial pathogens. Other investigators have found extensive blood contamination in the anesthesia work area *(104)*. These findings are discussed further in the section "Exposure of Anesthesia Personnel to Patients' Blood and Body Fluids."

Air Air in operating rooms can become contaminated with bacteria. For example, Edmiston et al. *(105)* obtained air samples from a single operating room during 70 different vascular procedures. *S. aureus* and various coagulase-negative staphylococcal species were recovered from 64% and 86% of all samples, respectively. Gram-negative bacteria were recovered less frequently (33%). The magnitude of contamination increased with proximity to the surgical field. Some of the microorganisms were identical to those recovered from HCWs' nares, suggesting that the surgical masks were inefficient *(105)*.

Medications In addition to impairing host defenses, anesthetic medications can become contaminated with viral or bacterial pathogens, which can then be injected directly into the patient's intravascular space *(106–110)*. This has occurred when syringes become contaminated during use, when anesthesia personnel contaminate anesthetic medications either by contaminating multidose vials or by handling medications, such as propofol, improperly *(106–111)*. The role of contaminated medications is discussed further in the sections "Infections Associated with Intravenous Anesthesia and Outbreaks Associated with Anesthesia Personnel."

Anesthesia Providers Anesthesia providers can be colonized or infected with pathogens that can be transmitted to patients *(112–119)*. In addition, anesthesia providers' hands are often contaminated with pathogenic bacteria during all phases of anesthesia: induction, maintenance, and emergence (*120*,121). The role of microorganisms colonizing or infecting anesthesia providers and microorganisms carried on anesthesia providers' hands is discussed further in the sections "Infections Associated with Intravenous Anesthesia and Outbreaks Associated with Anesthesia Personnel."

In summary, the studies reviewed in this section suggest that (a) Bacteria can contaminate all parts of anesthesia circuits, but the highest numbers of bacteria contaminate the parts closest to the patient; (b) Anesthetic gases may carry bacteria from the machine to the patient or vice versa; (c) The soda lime removes bacteria imperfectly and, although it kills many bacterial pathogens, *M. tuberculosis* and *Bacillus* species survive prolonged exposure; (d) Filters decrease contamination of breathing circuits; (e) Anesthesia equipment such as endotracheal tubes, the anesthesia machine, laryngoscope handles/blades, syringes, and medications can serve as reservoirs for bacterial pathogens and may facilitate transmission to patients.

Thus, there are several ways that anesthesia practice could facilitate transmission of bacteria to patients during surgical procedures *(49–53)*. Given that surgical patients often have multiple comorbidities *(47)* and that numerous host defenses are breached or impaired by the surgical incision and by general anesthesia, patients may be particularly susceptible to microorganisms transmitted in the operating room *(48)*. This hypothesis is supported by the results of a prospective, observational study by Hajjar and Girard *(122)*. They found an incidence of 3.4 HAIs per 1,000 patients during the first 72 hours after the operations, suggesting that the source of the infections may have been in the operating room *(122)*. However, the investigators could not directly link the practice of anesthesia or anesthesia equipment to intraoperative transmission of bacterial pathogens to patients. Consequently, many anesthesia providers do not believe that anesthetic practice or the anesthesia work area is associated with HAIs *(123)*. In fact, the studies reviewed thus far provide little objective evidence linking either the practice of anesthesia or anesthesia equipment with direct transmission of bacterial microorganisms to patients.

Recently, Loftus et al. (101) developed and validated a method for assessing intraoperative bacterial transmission to the anesthesia work area and to the stopcocks on the patients' intravenous catheters. These investigators randomly selected 61 operating rooms and decontaminated the adjustable pressure-limiting (APL) valve complex and the agent dial (AD) before the first case of the day. After the case, they cultured the APL valves, the ADs, and the stopcock sets. The number of CFU per surface area sampled (CPSS) on the APL valves and the ADs increased significantly, and 32% (95% confidence interval [95% CI] 20.6–44.9%) of the stopcock sets became contaminated. Most of the contaminating bacteria were skin microorganisms, but these microorganisms can cause bloodstream infections. In addition, methicillin-resistant *S. aureus* (MRSA) was transferred to the APL valves for two patients; the stopcock set became contaminated with *E. cloacae* for one of these patients. VRE was transmitted to all three sites for one patient and pulsed-field gel electrophoresis documented that all three sites were contaminated by the same strain. Moreover, the probability that the stopcock set would become contaminated increased as the CPSS increased, even after adjusting for the CPSS at baseline and for covariates (odds ratio [OR] 1.67; 95% CI 1.10–2.53; $p = .02$).

Subsequently, these investigators extended their observations by assessing transmission of bacteria in 82 pairs of patients (i.e., the first and second cases done in 82 randomly selected operating rooms during the study days) (102). The investigators also cultured the dominant hands of the anesthesia providers before they touched the patients. The investigators used biotyping to determine whether microorganisms cultured from the anesthesia work area (i.e., APL valves and ADs) and from the anesthesia providers' hands were the same. Loftus et al. found that 11.5% of the stopcocks became contaminated, of which 47% were contaminated with isolates found on the anesthesia providers' hands. They identified intraoperative transmission to the anesthesia work area in 89% of the cases and 12% of these work areas were contaminated with isolates from the providers' hands. In one instance, they found

the same microorganism on the hands of the anesthesia provider before the start of the first case, on the stopcock at the end of the first case, on the anesthesia machine at the start of the second case, and on the stopcock and the machine at the end of the second case, suggesting that the anesthesia provider did not perform adequate hand hygiene and that the machine was not cleaned adequately between cases. Most transmission events involved coagulase-negative staphylococci ($n = 8$), or *Micrococcus* spp. ($n = 5$), but a *Streptococcus* spp. ($n = 1$), methicillin-susceptible *S. aureus* ($n = 1$), MRSA ($n = 1$), and *Pseudomonas* spp. ($n = 2$) were also transmitted. Given their methodology, the investigators felt that these percentages were minimal estimates of the actual transmission rates from the anesthesia providers' hands. Furthermore, they found that the number of rooms that attending anesthesiologists supervised simultaneously was an independent predictor of transmission events that could not be linked to providers, suggesting that the attending physicians may have transmitted microorganisms from one patient to another. The investigators also found that patients discharged from the operating room to an intensive care unit (ICU) had a higher incidence of transmission events that could not be linked to providers, suggesting that anesthesia providers may have omitted hand hygiene, because they thought they needed to expedite care for more seriously ill patients. Again, given the limitations of their methods, the investigators felt that their results represented a minimum estimate of the transmission events.

Koff et al. (103) extended this model further when they did an intervention to see whether increasing hand hygiene decreased environmental contamination. They significantly increased (27-fold; $p < .002$) hand hygiene adherence over the baseline rate by giving anesthesia providers dispensers for alcohol-based hand rub that could be attached to their clothing. In addition, they noted that contamination of the anesthesia work area and stopcocks decreased from 32.8% to 7.5% (OR 0.17; 95% CI 0.06–0.51; $p < .01$) and that the incidence of HAIs decreased from 17.2% to 3.8% (OR 0.19; 95% CI 0.00–0.81; $p = .02$).

Conclusions Regarding the Role of the Practice of General Anesthesiology and Anesthesia Equipment as Potential Sources of Infection Until recently, the clinical importance of microorganisms isolated from anesthesia machines and their role in postoperative infections had not been clearly defined. In fact, Hogarth *(124)* concluded following a thorough review of the available literature that there was little evidence to implicate anesthesia machines and breathing systems as either a source of pathogenic bacteria or a vector for transmitting these microorganisms to patients undergoing general anesthesia for surgical procedures. Even the outbreaks reported by Joseph *(77),* Tinne et al. *(78)*, and Olds et al. *(79)*, and the report by Chant et al. *(93)* provide little evidence for transmission of pathogens by anesthesia machines or equipment, because these studies did not use sensitive methods for identifying specific strains and because they did not address whether anesthesia providers complied with critical infection prevention and control practices, such as performing hand hygiene, changing gloves between procedures on the same patient, changing gloves between patients, and cleaning and disinfecting the anesthesia cart and equipment between cases *(125)*. Furthermore, most investigators assessing the role of the anesthetic equipment and staff in the transmission of microorganisms used simulations and did not assess real-life anesthetic procedures in operating rooms. Thus, prior studies do not allow us to determine whether the providers, the patients, or the anesthesia equipment was the source of the infecting microorganisms.

The studies by Loftus et al. (101,102) and Koff et al. (103) were the first to demonstrate that anesthesia environment *and* anesthesia providers *do* transmit bacteria to patients and to document that increasing hand hygiene decreases transmission of bacteria to the anesthesia work area and to stopcocks on patients' intravenous catheters. In addition, their work suggests that transmission of microorganisms in the operating room may not be benign in that the mortality rate was higher for patients whose stopcocks became contaminated (101) and HAI rates were higher in the preintervention period when hand hygiene was poor and environmental contamination was high (102). While their studies did not prove the direct link between poor hand hygiene in the operating room and poor patient outcomes, these studies describe a method that other investigators can use to further this work and they provide a rationale for implementing interventions. Moreover, anesthesia providers can incorporate these interventions easily into their work flow to improve hand hygiene.

Preventing Infections Associated with General Anesthesia Procedures Current recommendations for measures for preventing intraoperative transmission of pathogenic microorganisms are relatively sparse (Table 60-1). We support changing and/or disinfecting breathing circuits and masks between operative cases *(7,8)*. Because in-line circuit filters effectively prevent transfer of bacteria from the patient to the anesthesia machine and from the machine to the patient *(126–128),* we think filters should also be used routinely, particularly for patients with active pulmonary tuberculosis receiving general anesthesia *(29)*. Hand hygiene, cleaning, disinfection, and sterilization of equipment, and environmental cleaning are also important preventive measures. Further studies are needed to identify additional sources of pathogens in the operating room and additional risk factors for intraoperative transmission. Such studies could provide the evidence base for implementing intraoperative preventive measures.

INFECTIONS ASSOCIATED WITH INTRAVENOUS ANESTHESIA

Pathogenesis

Syringes Bacteria from the hands of healthcare workers can contaminate syringes and their contents. Blogg et al. *(111)* noted that 3 of 50 syringes (6%) used repeatedly in an operating room and 4 of 50 syringes (8%) used repeatedly in an ICU were contaminated with bacteria, including *S. aureus* (two syringes), *E. coli* (two syringes), *S. epidermidis*

TABLE 60-1

Recommendations/Guidelines for Infection Control in Anesthesia Equipment

Item	*ASA (7)*	*AANA (8)*	*ANZCA (18)*	*AORN (10–13)*	*CDC (28)*	*Other*
Critical: Items that enter or contact an area that is normally sterile. Examples include, but are not limited to vascular needles, catheters and tubing; syringes; stopcocks; regional block needles and catheters; and urinary catheters.	Use sterile equipment to enter or contact any body area that is normally sterile. Clean reusable items thoroughly and sterilize before reuse. Ensure sterility at the time of use. Follow aseptic techniques when handling and using sterile equipment.	Use sterile items to enter sterile body area or vascular system.		Use sterile items to enter sterile tissue or the vascular system. Clean items thoroughly before disinfection.	Sterilize medical devices or patient-care equipment before use. Clean all items thoroughly before sterilizing or disinfecting.	
Semicritical: Items that come in contact with mucous membranes. Examples include but are not limited to laryngoscope blades, Magill forceps, endotracheal tube stylets, temperature probes, masks, breathing circuits and connectors, nasal and oral airways, self-inflating resuscitation bags, and esophageal stethoscopes.	Rinse items as soon as possible after use, decontaminate by cleaning and sterilize or treat with high-level disinfection. Keep endotracheal and endobronchial tubes free from contamination until they are used.	Sterilize items or treat with high-level disinfection.	Endotracheal tubes, nasal, and pharyngeal airways should be kept sterile until they are used. Reusable face masks must be thoroughly decontaminated and then disinfected before they are reused. Items placed in the upper airway that may cause bleeding, such as laryngoscope blades and temperature probes, must be disinfected before use. The breathing circuit should be sterilized or decontaminated and disinfected or	Reusable anesthesia equipment that comes in contact with mucous membranes, blood, or body fluid is considered semicritical and should be cleaned and then processed by high-level disinfection, pasteurization, or sterilization between each patient use.	Sterilize or at minimum treat items with high-level disinfection.	Separate used laryngoscopes and nondisposable items that are overtly contaminated from clean equipment *(374)*. The part of the breathing circuit between the patient and the filter must either be discarded or cleaned and disinfected after each patient. If a carbon dioxide absorber is also used, the part of the breathing circuit between the absorber and the filter must either be discarded or cleaned and disinfected at the end of each procedure list. If carbon dioxide absorbers are not used, the breathing circuit

(*Continued*)

TABLE 60-1

Recommendations/Guidelines for Infection Control in Anesthesia Equipment (*Continued*)

Item	*ASA (7)*	*AANA (8)*	*ANZCA (18)*	*AORN (10–13)*	*CDC (28)*	*Other*
			protected by a new filter. When a filter is used the disposable items between the patient and the filter should be disposed of between each case and the reusable devices should be decontaminated and disinfected before they are reused. Ventilator circuits should be cleaned and disinfected regularly.			tubing that conducts the gas to and from the filter must either be discarded or cleaned and disinfected at the end of each procedure or operation list. If a filter is not used, the breathing circuit must either be discarded or cleaned and disinfected after each patient. All anesthetic apparatus that comes in contact with a patient or becomes contaminated with blood or body substances for example airways, endotracheal tubes, laryngoscopes, suckers, forceps, temperature probes, esophageal echo probes and face masks must be either discarded or cleaned and disinfected after each patient *(21)*. A new filter should be placed between the patient and the breathing system OR a new breathing system should be used for each patient. Expired gas sampling should be done on The breathing system side of the filter. Filters should not be used for pediatric anesthesia; new breathing systems should be used *(22)*.

Noncritical: Items that touch intact skin or do not make contact with the patient.						
Items that touch the patient. Examples include, but are not limited to blood pressure cuffs, electrocardiograph cables and electrodes, pulse oximeter and skin temperature sensors, stethoscopes, and headstraps.	Clean equipment with a disinfectant at the end of the day and whenever visibly contaminated.	Process equipment with intermediate or low-level disinfection.	Laryngoscope handles should be decontaminated between uses.	Clean and decontaminate items when contaminated or visibly soiled and at the end of the day.	Wash items with detergent or disinfectant, rinse, and dry.	
Items that do not touch the patient. Examples include, but are not limited to exterior surfaces of anesthesia machines, carts, monitors, and tables.	Clean horizontal surfaces of anesthesia machines and carts after each patient.	Clean environmental surfaces with warm water and detergent or with a low low- to intermediate-level disinfectant after each patient procedure; terminally disinfect at the end of the day or when contaminated with blood or body fluids.		Clean and decontaminate items when contaminated or visibly soiled and at the end of the day.		
Single-use items	Reuse is not recommended because there are insufficient data on the safety of this practice for anesthesia equipment. Reuse of single-use items shifts the responsibility/liability	Do not reuse, clean, repackage, or resterilize disposable equipment designed for one-time use and labeled as "single-use" items. Hospitals that reprocess	Items of airway equipment to be placed in direct contact with the respiratory tract and airways labeled by the manufacturer as disposable or for single use only should not be reused.	Single-use items (e.g., suction catheters, breathing circuits, endotracheal tubes, stylets) should be used once and discarded. (*a*) If a device cannot be cleaned, it cannot be reprocessed and reused;	Do not reprocess items or devices that cannot be cleaned and sterilized or disinfected without altering their physical integrity and function.	FDA compliance policy guide: "… the institution or practitioner who reuses a disposable medical device should be able to demonstrate: (a) that the device can be adequately cleaned

(*Continued*)

TABLE 60-1

Recommendations/Guidelines for Infection Control in Anesthesia Equipment (*Continued*)

Item	*ASA (7)*	*AANA (8)*	*ANZCA (18)*	*AORN (10–13)*	*CDC (28)*	*Other*
	from the manufacturer to the user. If single-use items are reprocessed, the users must develop a quality assessment program to ensure disinfection/sterilization is adequate and that the function and integrity are not compromised.	and reuse such products, not the manufacturer, are responsible for their safety and effectiveness. Refer to Food and Drug Administration (FDA) guideline. Disposable products that have been opened but not used or manipulated may be resterilized if the manufacturer approves the process.		(*b*) if sterility of a postprocessed device cannot be demonstrated, the device cannot be reprocessed and reused; (*c*) if the integrity and functionality of a reprocessed device cannot be demonstrated and documented to be as safe for patient care and/or equal to the original device specifications, the device cannot be reprocessed and reused. For further details the reader is referred to the AORN Guidance Statement: Reuse of Single-Use Devices *(11)*		and sterilized, (b) that the physical characteristics or quality of the device will not be adversely affected, and (c) that the device remains safe and effective for its intended use. [A]ny institution or practitioner who resterilizes and/or reuses a disposable medical device must bear full responsibility for the performance, its safety and effectiveness" *(375)*. Medical and Surgical Products Liaison Group and the Association of British Health-Care Industries advise against re-use unless specifically permitted by manufacturers *(376)* The New South Wales Health Department recommends that medical devices marked "single use only" should not be reused unless (*a*) testing documents that the devices are not physically or microbiologically less safe than new items;

					(*b*) reprocessing is controlled and in accordance with Good Manufacturing Processes defined by the Commonwealth Therapeutic Goods Administration; (*c*) reprocessing must be in accordance with the manufacturer's instructions; (d)standard information is needed for informed patient consent *(21)*.
Valves and CO_2 absorber	Clean and disinfect unidirectional valves and CO_2 absorber chambers periodically.	Disassemble, clean, and sterilize CO_2 valves prior to reuse. When a patient has a respiratory infection, use disposable devices (e.g., circle system and absorber with bacterial filter, laryngoscope, and airway products) whenever possible.	When a filter is used in the circuit, sterilization of the carbon dioxide absorber before every case is not necessary. The device including the unidirectional valve should be disinfected regularly.	Absorbers and valves should be cleaned when the soda lime is changed according to the manufacturer's written instructions. Particular attention should be paid to the valves. Routine sterilization or high-level disinfection of the internal components of anesthesia machines is considered unnecessary.	
Bellows	Clean and disinfect tubing and bellows at regular intervals, not after each use. Routine sterilization/ disinfection of the interior of anesthesia machines is not necessary or feasible.	Sterilize the anesthesia bellows and the bellows base or head after every case unless bacterial filters are used to protect the inspiratory, expiratory, and ventilator limbs of the circuit.	Clean and disinfect regularly.	Bellows should be cleaned regularly according to the manufacturer's written instructions. Bellows are thought to represent a low risk for transmission of infection and do not require cleaning and disinfection after each use.	

(*Continued*)

TABLE 60-1

Recommendations/Guidelines for Infection Control in Anesthesia Equipment (*Continued*)

Item	*ASA (7)*	*AANA (8)*	*ANZCA (18)*	*AORN (10–13)*	*CDC (28)*	*Other*
		When using disposable breathing circuits without bacterial filters, replace the ventilator bellows each time the circuit is replaced and the bellows base or head cleaned and sterilized.				
Filters for breathing circuits	There are insufficient outcome data to support routine use of bacterial filters. Use a filter for patients known or suspected to have active tuberculosis.	Use breathing circuits with bacterial filters for all cases.		.	Data do not support using bacterial filters to prevent nosocomial pulmonary infections *(32)*. Use filter if patient has suspected or confirmed active tuberculosis *(29)*.	If used, filters must be discarded after each patient *(26)*. At the current state of knowledge, a new bacterial/viral filter should be used for each case. The filter should be placed so as to protect the breathing circuit from possible contamination by the patient *(23)*.
Heated humidifiers		Clean and sterilize humidifiers after each use. Use sterile water.			Sterilize reusable humidifiers or subject them to high-level disinfection after each use *(32)*.	

ASA, American Society of Anesthesiologists; AANA, American Association of Nurse Anesthetists; ANZCA, Australia and New Zealand College of Anaesthetists; AORN, Association of PeriOperative Registered Nurses; CDC, Centers for Disease Control and Prevention

(three syringes), and viridans streptococci (one syringe). Lessard et al. *(51)* also obtained cultures from syringes used in their operating rooms and found 4 contaminated syringes among 100 that were refilled an average of 3.58 times compared with 3 contaminated syringes among 100 filled only once. Blogg et al. *(111)* also tested whether bacteria (25×10^6 CFU of *S. marcescens*) on the hands could contaminate syringes when they were refilled. All 15 plastic syringes and 35 of 65 (54%) glass syringes were contaminated after they were refilled twice.

To simulate the common syringe technique, several investigators injected liquid from tuberculin syringes through 26-gauge needles into suspensions of *E. coli (129–131)*, *S. aureus (131)*, poliovirus *(132)*, or ^{3}H-thymide *(131)*. After removing the needles, they examined the syringe contents and found that most were contaminated. Plott et al. *(133)* took this line of research one step further. They placed 10 mL of sterile water containing 10^6 plaque-forming units of vesicular stomatitis virus into a multidose vial. They then injected 1 mL of sterile water into the vial, withdrew the syringe, changed the needle, drew 1 mL of air into the syringe, injected the air into a second vial, and withdrew 1 mL of water. All of the second vials were contaminated with vesicular stomatitis virus.

Syringes can become contaminated with a patient's blood or with blood-borne pathogens after just one injection into a patient or into an intravenous line. Fleming and Ogilvie *(134)* found blood in 5 of 50 syringes (10%) used to inject a vaccine subcutaneously, and Hughes *(135)* identified red blood cells in 17 of 39 syringes (44%) used to inject saline intramuscularly. Hughes demonstrated that fluid was aspirated from the needle into the syringe when the needle was removed from the syringe. He hypothesized that the syringe used to administer penicillin was contaminated in this manner and subsequently transmitted serum hepatitis to 26 patients. Other investigators confirmed Hughes's hypothesis *(129,136)*. For example, Lutz et al. *(129)* calculated that 2×10^{-5} mL of fluid were aspirated into the syringe when they removed the needle. Although minuscule, this volume of blood is 200 to 2,000 times greater than the amount required to transmit hepatitis B virus to chimpanzees *(137)*.

Syringe contents may be contaminated with blood when the syringes are used to administer fluids into intravenous lines. Hein et al. *(138)* detected visible blood in 6 and occult blood in 8 of 100 injection ports for intravenous tubing. Similarly, Trepanier et al. *(139)* used Ames Multistix read by a Clinitek 200 module (sensitive to a 1:32,000 dilution) to detect blood in intravenous fluids withdrawn through injection ports. They detected blood in 3.33% (95% CI 2.26–4.73%) of samples withdrawn from the first port and in 0.3% (95% CI 0.01–1.84%) of those withdrawn from the third port. When they injected fluids into intravenous tubing through which blood was infusing, 34% (95% CI 24.8–44.1%) of the syringes were contaminated. Using 10-mL syringes, Parlow *(140)* injected 2-mL aliquots of normal saline into injection ports of intravenous lines used for patients undergoing general anesthesia. After injecting four aliquots per syringe, the investigator removed the needle, filtered the remaining 2 mL of saline, and stained the filter with Papanicolaou's stain. Three of 26 samples (11.5%) contained red blood cells.

Multidose Vials Many drugs used by anesthesia personnel are packaged in multidose vials. Ninety-eight percent of anesthesia personnel surveyed by Kempen used multidose vials opened by unknown persons, and 75% refilled common syringes from multidose vials and did not subsequently discard the vial *(141,142)*. Moreover, a study by Zacher et al. *(143)* suggests that bacteria contaminating the outside of a multidose vial can be injected into the vial if the vial is not disinfected.

Corley et al. *(144)* injected at least one billion *S. aureus* or *E. coli* microorganisms into vials containing succinylcholine chloride, chloroprocaine, tubocurarine, water for injection, and sodium chloride for injection. After 7 days, 99.6% to 100% of the microorganisms were killed. Of the three anesthetic agents tested, only succinylcholine chloride did not kill all of the bacteria. Highsmith et al. *(145)* evaluated whether 12 different pathogens persisted in eight drugs commonly packaged in multidose vials. Cultures of procainamide and methohexital were negative at 24 hours. Succinylcholine chloride, regular insulin, potassium chloride, and thiopental killed slowly or allowed limited survival of several microorganisms. If the bacteria were washed in 0.25% peptone broth (i.e., carried some nutrients with them when injected), all 12 microorganisms survived or proliferated in lidocaine. However, if the bacteria were washed in saline, lidocaine supported growth of only *Pseudomonas cepacia*. Bawden et al. *(146)* inoculated 1 to 100 CFU of *E. coli* or *P. aeruginosa* into 30-mL multidose vials of bacteriostatic water with 0.9% benzyl alcohol, 0.9% sodium chloride with 0.9% benzyl alcohol, and 1% lidocaine hydrochloride with 1 mg/ml of methylparaben. All cultures were positive at 1 hour, and *E. coli* was recovered from the lidocaine at 16 hours. Longfield et al. *(147)* inoculated 11 commonly used medications with suspensions of 10 bacterial species. When stored at 22°C, atropine and D-tubocurarine were sterile at 4 hours, but lidocaine and heparin still contained viable bacteria at 24 hours. At 4°C, bacteria persisted longer in all medications tested. Plott et al. *(133)* injected 10^6 plaque-forming units of vesicular stomatitis virus into sterile water, 1% lidocaine, and 1% lidocaine with 1:100,000 epinephrine. All cultures were positive at 1 hour and cultures of the sterile water and the lidocaine were positive at 1 day. None of the vials contained viable virus at 1 week.

The results of multiple culture surveys indicate that the proportion of multidose vials contaminated by bacteria has ranged from 0% to 27% *(144,146,148–155)*. In their review of 12 studies published between 1958 and 1983, Longfield et al. *(152)* noted that the studies reporting high rates were done before 1973. On the basis of four studies done after 1973, they estimated that 0.6% of used multidose vials were contaminated with bacteria. Longfield et al. suggested that the differences between the results of earlier and more recent studies might be explained by changes in both the types of drugs packaged in multidose vials and the chemicals used as preservatives. After reviewing 15 papers published between 1958 and 1986, Thompson et al. *(156)* estimated that 0.5% of used multidose vials become contaminated with bacteria.

Of the studies we evaluated, only one tested used multidose vials for viral contamination. Petty et al. *(148)* tested 121 used multidose vials for viruses, none of which were

positive. Only two studies evaluated used multidose vials for red blood cells. Melnyk et al. *(151)* evaluated 69 multidose vials; none of the vials were contaminated with bacteria, but one (1.4%) contained red blood cells. Arrington et al. *(157)* noted that many anesthesia staff members withdrew contents from a medication vial, injected the drug into intravenous tubing, and then used the same needle and syringe to withdraw medication for the next patient. Because they were concerned that this practice could contaminate medication vials, the authors tested vials at the end of the day for the presence of occult blood. The first group consisted of vials reused by staff members who used a single needle and syringe as described above. The second group consisted of vials used by the investigators who placed a new needle on the used syringe to withdraw medication from vials. Eleven of 492 (2.2%) vials in the first group and 1 of 369 (0.3%) in the second group contained occult blood. The authors concluded that their study supported the AANA *(8)* and CDC *(30)* guidelines that mandate use of a new needle and a new syringe for each patient and each time a vial is entered.

Epidemiology

A number of outbreaks have been caused by contaminated solutions or anesthetic agents (*106–110*,*158–171*,172,173,*174*). Of the 21 reports reviewed in Table 60-2, 20 were caused by drugs that were contaminated at the healthcare facility and only one was caused by a drug contaminated by the manufacturer. Nine outbreaks were caused by contaminated propofol *(106,108–110,162,163,167,174)*. Bennett et al. *(171)* investigated outbreaks associated with propofol at seven hospitals and found numerous breaks in aseptic technique. For example, anesthesia personnel did not clean vials before opening them and did not wear gloves. They also drew up the drug before the case, transferred syringes containing unused drugs between operating rooms and facilities, and reused syringes. In one hospital, the same strain of *S. aureus* was isolated from the patients and from a lesion on the scalp of the anesthesiologist who prepared the medication *(108)*. A case–control study implicated exposure to propofol as the risk factor, suggesting that the anesthesiologist contaminated the propofol solution. Kuehnert et al. *(108)* noted similar faulty technique. Anesthesia personnel often did not wash their hands before preparing the medications, drew up all the propofol doses required for an entire day at one time, and kept the syringes at room temperature throughout the day. In addition, they often used multidose vials that contained large volumes of propofol, and stored the unused doses in the open vial at room temperature.

Most anesthetic drugs are weak bases dissolved in acidic solutions that inhibit growth of bacteria and fungi *(175–177)*, and most contain a bacteriostatic agent. However, propofol is suspended in a lipid solution that supports bacterial and fungal growth *(176–184)*, and it does not contain a preservative. If anesthesia personnel do not follow aseptic technique when they remove propofol from the glass vial, they can contaminate the solution. The contaminating microorganisms can multiply in propofol while it is infused slowly or while prefilled syringes sit at room temperature. To avoid such problems, the manufacturer recommends that propofol "be drawn into a sterile syringe immediately after the ampoule is opened and administration should commence promptly. Each unit of [propofol] is intended for use in a single patient and the syringe and any unused portion of [propofol] must be discarded at the end of the surgical procedure" *(184,185)*.

Seeberger et al. *(186)* administer propofol using the following protocol. The anesthesiologist must (a) use only 20-mL ampoules of propofol; (b) use an alcohol-based hand rub before starting the procedure; (c) prepare the syringes, lines, and stopcocks just before the procedure; and (d) discard all unused propofol, and never use propofol from the same ampoule for more than one patient. In addition, an infection preventionist conducts continuing education, teaching anesthesia staff members about good infection prevention practice and monitoring their adherence. These investigators reported that between January 1, 1995, and June 30, 1996, they performed 1,407 anesthetic procedures using propofol and 5,026 using thiopentone. Subsequent follow-up revealed that the incidence of catheter-related sepsis of unknown origin was 0.2% for both groups and the incidence of superficial thrombophlebitis and of fever >38°C of unknown origin was <0.1% for both groups. On the basis of these data, they concluded that their precautions were adequate to prevent infections in patients undergoing intravenous anesthesia with propofol.

Other outbreaks reviewed in Table 60-2 illustrate how various breaks in aseptic technique, including narcotic pilfering *(164)* use of the same syringe for more than one patient (*165*,173), and assembling equipment in advance of the procedure *(108,166)*, have led to infections. Although outbreaks associated with contaminated solutions or drugs occur rarely, large numbers of patients can be infected. Most of the reported outbreaks have been related directly to poor aseptic technique, including the unacceptable practices of administering the same solution to more than one patient and entering a single use *(174)* or a multidose vial (173) with a used syringe and needle. Of note, outbreaks of viral hepatitis (seven hepatitis C, four hepatitis B) still occur related to unacceptable practices—reuse of needles or syringes (either for more than one patient or for the same patient by entering a vial with used equipment and administering the remaining medication to other patients) *(165*,*168*,172,173,*174*) and misuse of multidose vials (*107*,*109*,*169*,*170*,173). Rather than saving money, these unacceptable practices actually increase the costs of medical care (due to the costs of investigating outbreaks and treating patients who become infected), harm patients, and destroy careers.

Preventing Infections Related to Intravenous Anesthesia

Table 60-3 summarizes the guidelines that anesthesia societies, government agencies, and others have developed regarding practices that will limit the risk of infection related to intravenous anesthesia. Given the information in the preceding section, we believe that very few infections would occur in association with intravenous anesthesia if anesthesia providers knew the guidelines and followed them.

TABLE 60-2

Outbreaks Related to Intravenous Anesthesia

Author (Reference)	*Year*	*Contaminated Product*	*Infection*	*Number of Patients*	*Microorganism*	*Comments*
Sack *(158)*	1970	Intravenous solution used for numerous patients	Bacteremia	5	*K. pneumoniae, A. cloacae*	Multiple-dose solution used by same anesthesiologist.
Siboni *(159)* Borghans *(160)*	1979	Fentanyl	Bacteremia	16	*P. cepacia*	Intrinsic contamination despite methyl- and propyl-p-hydroxybenzoates included as preservatives.
Maldonado *(161)*	1989	Lidocaine multidose vial	Hepatitis	5	Hepatitis B	Vial used for numerous patients by one anesthesiologist.
CDC *(162)* Daily *(106)*	1990	Propofol infused per pump	Fungemia, end-ophthalmitis	4	*C. albicans*	Breaks in aseptic technique noted in anesthesia practice.
CDC *(162)*	1990	Propofol infused per pump	Fever, hypertension	2	*M. osloensis*	Same infusion, syringe, and pump used for both patients.
CDC *(162)* Villarino *(163)*	1990	Propofol infused per pump	Bacteremia, surgical site infections	13	*S. aureus*	Same phage type isolated from the patients and the hands of the nurse anesthetist, same infusion used for numerous patients.
CDC *(162)*	1990	Propofol infused per pump	Fever, surgical site infections	8	*S. aureus*	Same phage type isolated from the patients and from the anesthesiologist's throat.
Maki *(164)*	1991	Fentanyl in predrawn syringes	Bacteremia	3	*P. pickettii*	Narcotic tampering in pharmacy contaminated the medication.
Froggatt *(165)*	1991	Common syringe used on numerous patients	Hepatitis	6	Hepatitis B	Medication syringes contaminated by blood from a Hepatitis B carrier and used on subsequent patients.
Rudnick *(166)*	1991	Preassembled pressure-monitoring equipment	Bacteremia	9	*P. aeruginosa, E. cloacae, K. pneumoniae*	Pressure-monitoring equipment contaminated with floor-washing solution.
Veber *(110)*	1994	Propofol injections	Bacteremia	4	*K. pneumoniae*	Contents of one vial used for four patients over 18 h.
Kuehnert *(108)*	1997	Propofol injections	Bloodstream infection	5	*S. aureus*	Contents of one vial used on successive patients.
Kidd-Ljunggren *(107)*	1999	Local anesthetic injections	Hepatitis	2	Hepatitis B	A permanent aspiration needle was left in the bottle of local anesthetic. The desired amount was drawn into a syringe. If the patient needed more pain relief, the same syringe was used to obtain the agent. The multidose vial was NOT discarded between patients.
Henry *(167)*	2001	Propofol injections	Bloodstream infection (5) Surgical site infection (2)	7	*S. marcescens*	One anesthesiologist was associated with all cases but only 14% of the controls. All cases received propofol compared with 24% of controls. No cultures of the environment or the anesthesiologist were positive for the etiologic agent.
Massari *(109)*	2001	Propofol	Hepatitis	4	Hepatitis C	Risk factors for infection included being operated on during the same morning session on the same day as the probable source patient. All five patients were infected with genotype 1b. A multidose vial of propofol was the shared by all five patients.

(*Continued*)

TABLE 60-2

Outbreaks Related to Intravenous Anesthesia (*Continued*)

Author (Reference)	*Year*	*Contaminated Product*	*Infection*	*Number of Patients*	*Microorganism*	*Comments*
Meier *(168)*	2002	Sedative injections	Hepatitis	>50	Hepatitis C	Nurse anesthetist in a pain clinic used the same needle and syringe to give sedative injections into ports of intravenous lines.
Anonymous *(169)*	2002	Sedative injections	Hepatitis	28	Hepatitis C	Anesthesiologist in an endoscopy clinic obtained sedative from a multidose vial and gave several injections to the same patient with a single needle and syringe. The multidose vial was used for more than one patient. A patient with chronic hepatitis C, genotype 2C, underwent endoscopy at the beginning of the epidemic period.
Carbonne *(170)*	2003	Fentanyl injections	Hepatitis	2	Hepatitis C	A patient had chronic hepatitis C, subtype 1b. Repeat doses of fentanyl were obtained from a multidose vial with a used syringe and needle. Two patients whose operations followed this patient's operation acquired hepatitis C of the same genotype.
Comstock (173)	2004	Three different sedation medications	Hepatitis	102	Hepatitis C	A nurse prepared one syringe and needle for each of three sedation medications for a single pain clinic session. She injected drugs through heparin locks and she believed these devices were sterile.
Germain (172)	2005	Fentanyl	Hepatitis	3	Hepatitis B and C	Same syringe and needle probably were used to give the source patient fentanyl from two different vials. Fentanyl vial 2 was used for the index case and for cases 2 and 3, but not for a patient who did not become infected. The fentanyl was injected directly into peripheral intravenous catheters without antireflux valves.
CDC *(174)*	2008	Propofol	Hepatitis	≥6; 40,000 involved in the recall	Hepatitis C	A clean needle and syringe were used to draw medication from a single-use vial of propofol, which was injected directly through an intravenous catheter. If a patient required more sedation, the needle was removed from the syringe and replaced with a new needle. The new needle and the used syringe were used to draw more propofol. Backflow from the patient's intravenous catheter or when the needle was removed might have contaminated the syringe with HCV and subsequently contaminated the vial. Propofol remaining in the vial was used to sedate the next patient.

Note: Reference *(171)* describes a case–control study done at seven hospitals that had outbreaks related to misuse of propofol. Thus, references *(106,162,163)* share cases with reference *(171)*.

TABLE 60-3

Recommendations and Guidelines Regarding Medication Use in Anesthesia

Item	*ASA (8)*	*AANA (9)*	*ANZCA (19)*	*CDC (30)*	*Other*
Preservative-free medications	Use as single-patient, single-dose item. Open at the time of use; discard immediately after use. Swab rubber septum or neck with alcohol before entering. Use sterile needles and syringes to aspirate contents.	Clean the ampule before opening. Use a filtered needle to draw up the medication. Cleanse rubber stoppers before each use.			
Medications drawn up into a syringe	Do not give medications from a syringe to more than one patient. Discard medication drawn into a syringe within 24 h.			Do not administer medications from a syringe to multiple patients, even if the needle or the cannula on the syringe is changed.	
Multidose vials	Use aseptic technique. Cleanse rubber stopper. Use sterile needle and syringe each time vial is entered.	Restrict use of multiple-dose vials to one patient only unless strict aseptic technique is used. A new sterile syringe and needle should be used each time the vial is penetrated.	Because of the potential for crossinfection, the use of the contents of multiple-dose vials and ampoules for more than one patient is not recommended except in a dispensing situation where different doses are drawn up before the administration of the first dose to a patient. Likewise it is recommended that the contents of a single dose ampoule are to be used for one patient only.	If multidose vials must be used, both the needle or cannula and syringe used to access the multidose vial must be sterile. Do not keep multidose vials in the immediate patient treatment area and store in accordance with the manufacturer's recommendations; discard if sterility is compromised or questionable.	Single-use ampoules or vials of medication must be used for all injections unless alternative systems are set in place to prevent crossinfection(19). A medication may be taken from a multidose vial or ampoule only if the medication or solution is not readily available in another form. If any medication is taken from a multidose vial or ampoule, a sterile needle and syringe must be used to withdraw the contents. The needle and syringe must be discarded once they have been used. Precautions must be taken to ensure that contaminated materials or fluids are not injected into a multidose vial or ampoule *(21)*.

(*Continued*)

TABLE 60-3

Recommendations and Guidelines Regarding Medication Use in Anesthesia (*Continued*)

Item	*ASA (8)*	*AANA (9)*	*ANZCA (19)*	*CDC (30)*	*Other*
Single-dose vials and ampules				Use single-dose vials for parenteral medications whenever possible. Do not administer medications from single-dose vials or ampules to multiple patients or combine leftover contents for later use.	
Intravenous fluids, tubing, connectors, and disposable pressure transducers	Single use only.	Single use only.		Do not use bags or bottles of intravenous solution as a common source of supply for multiple patients. Use fluid infusion and administration sets (i.e., intravenous bags, tubing and connectors) for one patient only and dispose appropriately after use. Consider a syringe or needle/cannula contaminated once it has been used to enter or connect to a patient's intravenous infusion bag or administration set.	

Stopcocks, injection ports, and other portals of access to sterile fluids	Maintain with sterile technique. Keep free of blood and cover with a sterile cap or a syringe when not in use. Clean injection ports with appropriate disinfectant before entry.	Use sterile technique for all access ports.	
Use of syringes for more than one patient	Syringes are single-patient use items. Do not give medications from a syringe to more than one patient. Consider the syringe contaminated after entry into an intravascular line.	Consider syringes and needles as single-use disposable items. Do not reuse needles and syringes. Dispose of all needles and syringes after every use. Once used they are contaminated.	Needles, cannulae, and syringes are sterile, single-use items; they should not be reused for another patient or to access a medication or solution that might be used for a subsequent patient.
Noninjectable drugs and ointments and sprays	Discard multidose containers if contaminated or if contamination is suspected. Use unit dose packages whenever possible.	Acknowledge the risk of cross-contamination but do not specify practice.	
Other			Use aseptic technique to avoid contamination of sterile injection equipment.

ASA, American Society of Anesthesiologists; AANA, American Association of Nurse Anesthetists; ANZCA, Australia and New Zealand College of Anaesthetists.

INFECTIONS ASSOCIATED WITH NEURAXIAL BLOCKADE

Pathogenesis of Infections Associated with Central Neuraxial Blockade

Microorganisms from exogenous or endogenous sources can enter the subarachnoid and/or epidural space. Epidural catheters used for short-term postoperative analgesia have been found to be contaminated shortly after insertion; the most common microorganism is coagulase-negative staphylococci. Similar to central-venous catheters, bacterial migration from the insertion site along the epidural catheter track is the most common way epidural catheters become colonized *(187)*. Microorganisms may also reach the central nervous system by direct inoculation when the catheter is inserted or by hematogenous spread from a distal site.

North and Brophy *(188)* described a case in which microorganisms from the healthcare provider were most likely inoculated directly when the catheter was inserted. In this case, *S. aureus* of the same phage type was isolated from both the epidural abscess and the nose of the anesthesiologist; *S. aureus* with a different phage type was isolated from the patient's nose *(188)*. Several other groups have reported similar cases. Trautmann et al. *(189)* identified a case of meningitis caused by a *S. aureus* strain that was identical by pulsed-field gel electrophoresis to the *S. aureus* isolate in the anesthesiologist's nose. Schneeberger et al. *(190)* reported a cluster of meningitis cases caused by several streptococcal species after subarachnoid neural blockade administered by one anesthesiologist. The anesthesiologist routinely talked to his patients and did not wear a mask during the procedures. The anesthesiologist complained of recurrent pharyngitis and tonsillitis at the time the first two cases occurred. The investigators concluded that respiratory droplets may have transmitted mouth flora from the anesthesiologist to the patients and, thus, they suggested that all anesthesia personnel wear face masks when performing subarachnoid neural blockade. Assuming that the respiratory tract of anesthesia personnel could be a source of infection, Philips et al. *(191)* conducted a simulation to assess the efficacy of masks. They seated anesthesia staff in a room with controlled ventilation and asked the volunteers to speak directly at blood agar plates placed 30 cm away. The number of bacteria on the plates was significantly lower when masks were worn *(191)*.

Microorganisms can also enter the epidural space by hematogenous spread from other body sites, most often skin infections *(192)*, or by migrating along the catheter tract (*187*,*193–195*). A study by Wulf and Striepling *(196)* suggested that hematogenous spread can occur from infected sites to the epidural space. They performed autopsies on 10 patients who had continuous epidural neural blockade for 2 to 21 days after operative procedures. At postmortem examination, seven of nine patients, who had both infections at other sites and an epidural neural blockade, had evidence of epidural infection. The investigators did not find evidence of epidural infection in the nine control patients who had similar underlying infections but did not have an epidural neural blockade. Pinczower and Gyorke *(197)* reported a case of L1 osteomyelitis caused by *P. aeruginosa* in a 76-year-old man who had a lower respiratory tract infection caused by the same microorganism. Bengtsson et al. *(198)* reported three cases of spinal space infection in 4 years. The three cases occurred in different hospitals, and three different anesthesiologists did the epidural neural blockades. All three patients had coexisting lower-extremity contaminated wounds, and two of the three spinal infections were caused by microorganisms that infected the patients' own wounds. The investigators concluded that infected lower-extremity wounds were a contraindication for epidural anesthesia. On the other hand, Newman *(199)* did not find any epidural catheter-related infections among over 3,000 patients who had epidural neural blockades for postoperative or posttraumatic analgesia, yet some of these patients had lower-extremity infections. Thus, Newman concluded that lower-extremity infections were not a contraindication to epidural anesthesia.

Several investigators have done studies to determine the likelihood that microorganisms infecting a distal site could enter the central nervous system. For example, Carp and Bailey *(200)* did cisternal punctures on rats with *E. coli* bacteremia and 24 hours later the investigators examined the spinal fluid to determine whether the animals' central nervous systems were infected. Control rats (nonbacteremic rats, bacteremic rats that did not have cisternal punctures, and bacteremic rats treated with a single dose of gentamicin before the cisternal puncture) all had sterile spinal fluid. Twelve (30%) of 40 bacteremic rats that were not treated with gentamicin and that underwent cisternal punctures acquired *E. coli* meningitis. The authors acknowledged that their study had several limitations: *E. coli* rarely causes meningitis after neuraxial blockade; the "relative size of the dural tear produced by a 26-gauge needle… is clearly greater in rats compared to that in humans;" the cisternal site is rarely used in clinical anesthesia; and the agents used for neuraxial blockade have a bacteriostatic effect *(200)*. The investigators did not feel that giving a dose of gentamicin before the puncture was a limitation, because febrile obstetric and surgical patients are often treated with antimicrobial agents before they undergo neuraxial blockade. However, unlike researchers, clinicians often do not know the susceptibility patterns of microorganisms infecting their patients before they undergo invasive procedures.

Studies by Goodman et al. *(201)*, Teele et al. *(202)*, and Jakobsen et al. *(203)* are also relevant to the question of whether patients who have infections at other sites or who are bacteremic at the time of a neuraxial blockade are at increased risk of infection. Goodman et al. *(201)* evaluated 531 women, who received either epidural or subarachnoid anesthesia before delivery and who had pathologic evidence of chorioamnionitis. Of these patients, 4 (80%) of 5 women with documented bacteremia, 11 (24%) of 45 women who were febrile, and 174 (76%) of 229 women who had leukocytosis did not receive antimicrobial agents before their blocks, but none of them acquired neurological infections even though many of them were not treated with antimicrobial agents. The investigators concluded that neuraxial blockade "may be safe in parturients with chorioamnionitis without prior antibiotic therapy" *(201)*.

In contrast, Teele et al. *(202)* found a significant association between lumbar puncture performed during

bacteremia and a subsequent diagnosis of bacterial meningitis in children <1 year of age. The investigators retrospectively reviewed the medical records of 271 children who had 277 episodes of bacteremia with *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Neisseria meningitidis* and who were sent home before blood culture results were available. None of the 46 patients who had lumbar punctures during their first visits had laboratory evidence at that point of meningitis. Nine (3%) of the 271 children, all of whom were <1 year old, acquired meningitis; seven (78%) of these nine children had lumbar punctures during their initial evaluations and two (12%) did not ($p < .001$). Treatment with antimicrobial agents may have decreased the risk of meningitis; 2 (11%) of 17 bacteremic children <1 year old who had a lumbar puncture during the initial visit and who were treated with antimicrobial agents acquired meningitis compared with five (83%) of the six patients who had lumbar punctures but were not treated with antimicrobial agents ($p = .003$). The investigators discussed two important limitations of their study. First, clinicians may be able to identify patients who are most likely to acquire meningitis. Second, patients who subsequently acquire meningitis may look sicker than other patients and, thus, clinicians may perform lumbar punctures on these patients more frequently than they do on other patients. Moreover, researchers have not determined whether data from diagnostic lumbar punctures can be extrapolated to spinal anesthesia or whether the antibacterial effect of local anesthetics *(204)* decreases the risk of infection in this context compared with the risk from injections of opioids or clonidin alone.

Jakobsen et al. *(203)* evaluated 69 patients (120 extradural catheters) who were treated for abscesses or infected wounds. three (4%) patients had inadvertent dural punctures treated with blood patches, 16 (23%) had septic episodes while their catheters were in place, and 1 (1%) patient had a positive blood culture. Twelve (10%) catheters were removed because of exit site infections, but none of these patients received antimicrobials. None of the patients acquired epidural abscesses or meningitis; 1 (1%) patient acquired a discitis caused by *S. epidermidis*.

In summary, most of the studies assessing the source of infecting microorganisms in patients undergoing regional anesthesia procedures have been small, and the source of most infections was never identified. Data from several case series and from an animal model do not indicate clearly whether or not bacteremia or infections at distal sites increase the risk of infections associated with regional anesthesia procedures or whether these procedures are contraindicated in bacteremic patients. Thus, anesthesiologists should assess the risks and benefits of various approaches to methods of providing anesthesia before performing regional blocks in patients suspected of having infections and should consider treating these patients empirically with antimicrobial agents.

Rarely, contaminated anesthetics are injected into the patient's subarachnoid or epidural space. For example, North and Brophy *(188)* reported an infection in which *S. aureus* strains with matching phage types were recovered from an abscess and a multidose lidocaine vial. Green and Pathy *(205)* questioned whether staff can draw up opioids in a sterile fashion from ampules, but did not provide evidence to support their concern. They suggested that these drugs be drawn through a filter into a syringe that is then double wrapped and sterilized in ethylene oxide. Raedler et al. *(206)* obtained cultures of 114 spinal and 20 epidural needles after use for single-injection lumbar anesthesia. Twenty-four cultures (17.9%) grew microorganisms: 15.7% coagulase-negative staphylococci, 1.5% yeasts, and 0.8% each enterococcus, pneumococcus, and micrococcus. However, no infections occurred in the study population. The anesthesiologists who performed these procedures wore "operating room dress" and used sterile gloves and sterile drapes. These authors concluded that it is easy to contaminate the needle and that anesthesiologists need to improve their hygienic measures.

Other investigators evaluated specimens from catheters or syringes. In four studies, 0% to 29% of the catheters were contaminated *(207–210)* and James et al. *(207)* found that 5 of 101 syringes used to inject an anesthetic agent were contaminated. Ross et al. *(211)* drew up bupivacaine 0.25% into control syringes and into syringes used to induce continuous lumbar epidural neural blockade (test syringe) in 18 obstetric patients. After each dose from the test syringe, cultures were obtained from the contents of both the test and control syringes. Six of 18 test syringes were contaminated with bacteria, compared with 1 of 18 control syringes. In the five studies cited above, none of the patients acquired infections *(207–211)*. Hence, the authors could not correlate contaminated catheters or syringes with infection.

Yaniv and Potasman *(212)*, Dawson *(213)*, Baer *(214)*, and Videira *(215)* reviewed infections after neuraxial anesthesia. Dawson's review of studies on infections associated with epidural anesthesia *(213)*, and two papers on postdural puncture meningitis (PDPM) *(214,215)* indicate that there is no consensus regarding patient risk factors for infectious complications and that the aseptic practices used by anesthesia providers for these procedures differ substantially. In addition, the literature includes conflicting reports about the association of the risk of infection with the duration of catheterization and with the site of the catheter. Horlocker's review of complications associated with spinal and epidural anesthesia *(216)* and Baer's review of PDPM *(214)* address several issues regarding infections after these procedures.

Infections Associated with Epidural Neural Blockade

Epidemiology Infections Associated with Epidural Anesthesia—Estimated Incidence: Data from two reviews of epidural abscesses suggest that only a small proportion of these infections are related to epidural catheters *(192,217)*. The incidence of infections after epidural neural blockade has been difficult to determine. Various groups have assessed the frequency of infections after epidural neural blockade, but their results differ substantially *(218–223)*. When reviewing 350 reports in the literature, Dawkins *(219)* found no reports of infection after thoracic or lumbar epidural block, but he identified eight reports of infection after 3,767 sacral epidural blocks used for operative procedures and for obstetrics (0.2% or 212/100,000). More recently, Dawson *(213)* reviewed the literature and found rates of deep infection ranging from 0% to 0.7% and rates of

superficial infection ranging from 1.8% to 12%. Studies by Aromaa et al. *(220)* and Wang et al. *(221)* produced very different estimates of the incidence: 3.5/100,000 procedures and 51.8/100,000, respectively. Wang *(221)* also found that the rate was substantially lower at university hospitals (17.7/100,000) than at private hospitals (125.6/100,000) ($p < .01$). The risk of persistent neurological deficit was 23/100,000 *(221)*. Ruppen et al. (224) conducted a meta-analysis of complications related to obstetric epidural blockades. They identified 11 cases of deep epidural infection in 13 studies that included 1.2 million patients for an estimated rate of 0.9/100,000. If they included only studies done after 1990, the rate was 0.77/100,000. Several studies have estimated the 95% confidence intervals for the rates of infection associated with epidural neuraxial blockade. These estimates have ranged from 0 to 10 infections per 100,000 procedures *(222)* to 0 to 30 infections per 100 *(223)*. We are not sure why the estimates vary so much. However, the methods, size, and patient populations varied substantially from study to study. In addition, readers must interpret these estimates in light of two recent studies. Ptaszynski et al. *(225)* found the incidence of spontaneous spinal epidural abscesses to be 0.88/100,000 (95% CI 0.27–1.48/100,000). Reihsaus et al. *(226)* conducted a meta-analysis and found that only 5.5% of 915 patients with spinal epidural abscess (representing an incidence estimate of 0.2–2/10,000) had a prior epidural anesthetic.

A number of case series have assessed infections associated with epidural neural blockades for short-term pain relief during and after obstetrical or surgical procedures *(210,222,223,228–239)*. We found six case series that discussed infectious complications of obstetrical epidural anesthesia. Three small series (~12,000 patients) did not identify any infections *(230–232)*. Two larger studies found rates of 0.2/100,000 *(228)* and 1/100,000 procedures *(229)*. In contrast, Brooks et al. *(240)* found four infections among 4,832 (83/100,000) patients undergoing epidural neuraxial blockades for surgical procedures or for labor and delivery. Data from other case series suggest that epidural catheters inserted for long-term pain control become infected more frequently than those used for short periods of time *(241–246)*. However, in two of these studies *(241,242)*, patients received only opioids rather than local anesthetics or a combination of drugs, which may confound the interpretation of the results. Du Pen et al. *(241)* and Coombs *(242)* found that 9% (38) to 11% (39) of patients with long-term catheters acquired superficial infections. Du Pen et al. *(241)* and Zenz et al. *(243)* found rates of deep infections of 1% (38) to 2%.

Case Reports Although infections rarely complicate short-term epidural neural blockade, case reports in the literature indicate that such infections do occur and that they can be severe. We reviewed case reports of 59 patients who acquired infections after epidural neuraxial blockade with anesthetic agents alone or anesthetic agents and steroids *(239,247–257)*. We excluded patients who received steroids alone. Among the 49 (83%) patients who had epidural catheters and for whom the duration of catheterization was specified, the median duration was 3 days (range 50 minutes to 6 weeks). The median time to onset of the first signs or symptoms of infection was 4 days (range 14 hours to 5 months) after catheter placement. Forty-two (71%) of 59 patients in these case reports acquired epidural abscesses and *S. aureus* was the predominant etiologic agent (Table 60-4). The infection prevention and control precautions used during the procedures were not specified for 31 (53%) of the patients and were described in vague terms (e.g., "aseptic technique" or "according to protocol") for 13 (22%).

In 1998, Kindler et al. *(218)* published a literature review in which they identified 42 patients with catheter-related epidural infections between 1974 and 1996. Epidural abscess was the initial diagnosis in only 15 (36%) patients. Similarly, we also found evidence that the diagnosis was delayed by at least 1 day (sometimes days to weeks) in 35 (59%) of 59 infections. Of these 35 patients, 17 (49%) recovered (fully or nearly fully), 17 (49%) had residual neurological deficits, and no information was provided about 1 patient (3%). In contrast among the 22 patients for whom there was no evidence of a delay between the onset of symptoms and the diagnosis, 15 (68%) recovered, 4 (18%) had residual neurological deficits, and no information was provided about 3 patients (14%; $p = .05$) (see the reviews by Herwaldt et al. *(239)*, Baer *(214)*, Ruppen et al. (224), and by Sarrubi and Vasquez *(258)* for further information about the cases and for information about additional cases *(214)*).

Infections Associated with Subarachnoid Neural Blockade

Epidemiology Data from a passive surveillance system and from nine case series (Table 60-5) suggest that the rate of meningitis is approximately 4.6 per 100,000 subarachnoid neural blockades *(215,222,239,259–266)*. In contrast, Aromaa and colleagues *(220)* evaluated administrative data in Finland and identified only four infections (the authors did not specify the types of infection) in 550,000 patients undergoing subarachnoid anesthesia for an incidence of 7.2/1,000,000.

Case Reports Although infections infrequently complicate subarachnoid neural blockade, case reports in the literature indicate that such infections can be serious. We reviewed reports of 26 patients who acquired infections after subarachnoid neural blockade *(239,267)*. The median time to onset of signs or symptoms of infection was 24 hours (range 1 hour to 2 months) for all infections combined. The median onset time of symptoms from meningitis was only 17 hours (range 1 hour to 10 days) compared with 4 days (range 1 day to 2 months) for other infections. Compared with infections after epidural neural blockade, infections associated with subarachnoid neural blockade were more likely to be caused by streptococci and patients were more likely to recover fully (Table 60-4). Few reports provided detailed information about the infection prevention precautions used during the implicated procedures. Eight (31%) reports did not provide any information and two (8%) provided only vague descriptions ("sterile conditions," "aseptic technique").

Infections Associated with Combined Epidural and Subarachnoid Neural Blockade

Epidemiology and Case Reports At present, there are few reports in the literature about infectious complications

TABLE 60-4

Summary of Data from Case Reports on Infections Associated with Epidural and Subarachnoid Anesthesia/Analgesia

Demographics	*Epidural (n = 59)*	*Subarachnoid (n = 26)*	*Combined (n = 10)*
Median Age	51 y	27 y	33.5 y
Female	35 (59%)	10 (39%)	7 (70%)
Health status			
Previously healthy	14 (39%)	9 (35%)	7 (70%)
One or more underlying diseases[a]	30 (41%)	5 (19%)	3 (30%)
No information provided	15 (20%)	12 (46%)	
Indication for procedure			
Obstetrical analgesia	14 (24%)	6 (23%)	7 (70%)
Surgical procedure	21 (36%)	16 (62%)	2 (20%)
Nonsurgical pain	24 (41%)	4 (15%)	
Other			1 (10%)
Type of infection			
Meningitis	7 (12%)	19 (73%)	6 (60%)
Epidural abscess	42 (71%)	4 (15%)	4 (40%)
Discitis/osteomyelitis/spondylitis	4 (7%)	2 (8%)	
Other	6 (10%)	1 (4%)	
Microorganism	(*n* = 54)	(*n* = 23)	(*n* = 10)
S. aureus	39 (72%)	2 (9%)	4 (40%)
S. species	4 (7%)	12 (52%)	3 (30%)
Pseudomonas aeruginosa	4 (7%)	4 (17%)	
Other	7 (9%)	5 (22%)	3 (30%)
Outcome			
Death	3 (5%)	1 (4%; from underlying disease)	
Neurologic deficit	20 (34%)	2 (8%)	
Complete or nearly complete recovery	31 (53%)	22 (84%)	9 (90%)
Not specified	5 (8%)	1 (4%)	1 (10%)

Note: The data in this table are summarized from references (*239*,*269*,296). Data from single-shot epidurals that did not involve placement of a catheter and steroid injections were excluded

[a]For example, coronary artery disease, hypertension, peripheral vascular disease, diabetes mellitus, chronic obstructive lung disease, cancer, trauma secondary to an automobile accident, etc.

of combined epidural and subarachnoid neural blockade. Cascio and Heath *(268)* identified one (~0.1%) case of meningitis after about 700 combined epidural and subarachnoid neural blockades. We reviewed nine case reports describing 10 infections after combined procedures *(239,268,269)*. The median age of the patients was 33.5 years. All seven female patients had obstetrical procedures; two of the male patients had surgical procedures and one had lithotripsy. The median time to onset of signs or symptoms of infection was 1.5 days (range 8 hours to 9 days) for all infections and 18 hours (range 8 hours to 3 days) for meningitis. Signs or symptoms of epidural abscesses were first noted 1 to 9 days after the procedures. Evidence of symptom progression was noted in five cases, and in three of those cases the diagnosis was delayed at least 1 day. Streptococcal species caused three (50%) of six cases of meningitis and *S. aureus* caused the four epidural abscesses. Nine (90%) patients recovered fully. Infection prevention precautions were specified for eight cases, and these reports did not note obvious breaks in technique.

In summary, infections are infrequent but serious complications of neuraxial regional anesthetic procedures. The incidence of these infections is not well defined and varies substantially by study. The case series and surveillance studies from which the estimates were derived do not discuss possible confounding factors such as the patients' comorbidities, the duration of labor or of the surgical procedures, or the frequency of distal infections such as chorioamnionitis. The investigators often did not describe the infection prevention precautions used by the anesthesiologists whose patients were described. Thus, we cannot determine whether the patient populations and the practices in the different reports were similar. Moreover, the reports did not include control patients; consequently, the investigators could not identify patient or practice factors that increase the risk of infection.

Infections Associated with Peripheral Nerve Blocks

Epidemiology and Case Reports In recent years, continuous regional anesthetic techniques using peripheral

TABLE 60-5

The Frequency of Meningitis after Subarachnoid Neural Blockade

Author (Reference)	*Year*	*Number of Patients in the Series*	*Number of Patients with Meningitis*	*Cases of Meningitis per 100,000*
Evans *(259)*	1945	2,500	0	0
Arner *(260)*	1952	21,230	1	4.7
Dripps *(261)*	1954	8,460	0	0
Scarborough *(262)*	1958	5,000	0	0
Sadove *(263)*	1961	>20,000	3	≈15
Moore *(264)*	1966	11,574	0	0
Lund *(265)*	1968	>21,000	0	0
Horlocker *(266)*	1997	4,217	0	0
Auroy *(222)*	2002	5,640 obstetrical	0	0
Auroy *(222)*	2002	35,439 nonobstetrical	1	2.8
Videira *(215)*	2002	38,128	3	7.9
Total		>173,188	8	≈4.6

nerve blocks have become more popular for postoperative pain management, especially for orthopedic procedures *(270,271)*. Auroy et al. *(222)* did not identify any infections after 43,946 peripheral blocks reported through their passive surveillance system. Bergman *(272)* identified one (0.3%) patient who acquired a local *S. aureus* skin infection after 48 hours from among 368 patients who had 405 axillary catheters. The patient recovered fully with antimicrobial treatment. Meier *(273)* evaluated 91 patients who had continuous interscalene catheters for an average of 5 days, and 8 (9%) patients acquired superficial skin infections. These investigators did not provide information about the aseptic techniques used for catheter insertion.

We reviewed two case reports of serious infections after peripheral nerve blocks. Nseir et al. *(274)* described a case of fatal necrotizing fasciitis caused by group A streptococcus following an axillary brachial plexus block in an elderly woman with insulin-dependent diabetes, hypertension, and chronic atrial fibrillation. The patient underwent right carpal tunnel decompression; an axillary brachial plexus block was used during the procedure. The patient was discharged the same day. Four days later, the patient had axillary pain and edema followed by symptoms of toxic shock syndrome; the patient expired within 48 hours despite medical and surgical management. Adam et al. *(275)* identified a *S. aureus* psoas abscess in a 35-year-old woman who had a 3-in-1 femoral blockade for an arthroscopic arthrolysis of the knee. The catheter was removed 4 days postoperatively. The following day the patient had fever and 4 days after the catheter was removed she complained of left lower quadrant abdominal pain.

Cuvillion et al. *(276)* obtained cultures of 208 femoral catheters when they removed the catheters after 48 hours; 54% were colonized with potentially pathogenic bacteria (71% *S. epidermidis*, 10% *Enterococcus* spp., and 4% *Klebsiella* spp.). These investigators also reported three episodes of transient bacteremia, but they did not identify abscesses or episodes of clinical sepsis.

Capdevila *(277)* observed 1,416 patients with continuous peripheral nerve catheters and found three patients with local inflammation and one psoas abscess caused by *S. aureus* in a diabetic woman. Wiegel et al. *(278)* described nine patients (0.6%) who had local inflammation at the catheter insertion sites and three (0.2%) who had local infections (all at the femoral sites) among patients who had 628 femoral and 549 sciatic continuous blocks. Neuburger et al. *(279)* followed patients with 3,491 peripheral nerve catheters (936 axillary, 473 interscalene, 125 vertical infraclavicular, 74 psoas compartment, 900 femoral, and 964 sciatic) and found 146 minor, 83 moderate, and 29 severe infections. The risk of infectious complications was significantly ($p < .001$) higher for interscalene blocks compared with blocks at the other sites. Infections occurred on average 4 to 5 days after catheter insertion. The authors speculated that sebaceous glands might increase the risk of infection with interscalene blocks; hence, they recommended that the skin in this area be kept wet with disinfectant for 10 minutes before the catheter is placed. However, the observations from this study may not be generalizable because the infection rate was quite high. For example, Borgeat et al. *(280)* followed 700 patients with interscalene blocks and found the rate of minor to moderate infections to be 0.8% compared with approximately 5% in the study by Neuberger et al. *(279)*. Borgeat et al. *(280)* found the rate of severe infections to be 0.1% compared with 1.3% in the study by Neuburger et al. *(279)*. If interscalene blocks are more likely to be complicated by infection than are other peripheral nerve blocks, mechanical stress secondary to catheter movement might be a factor that increases the risk of infection associated with catheters placed in this area.

Preventing Infections Associated with Central Neuraxial Blockade and with Peripheral Nerve Blocks

The literature regarding infection prevention precautions for neuraxial and peripheral nerve blocks documents that practice varies substantially and that some precautions are quite controversial (*214,281–288*,289). Nevertheless, most infections after epidural and subarachnoid neural blockade are caused by bacteria that colonize the skin, respiratory tract, or water. Consequently, we believe anesthesia staff should take precautions to limit contamination from

these sources. Hepner recently wrote the following in an editorial: "Evidence has clearly shown that aseptic techniques are effective in reducing contamination and complications in other sterile procedures such as central venous lines. Likewise, data clearly show that lack of some sterile technique such as the use of masks creates situations (higher bacterial counts) that may be potentially harmful. If we are to avoid the complications that 60 years into the future will seem obvious, we must institute uniform sterile safety practices that have been proven, or seem by common logic to be prudent, and continue to study techniques used in other areas to determine their utility" (290).

Given the very low rates of infection associated with epidural and subarachnoid neural blockade, we believe it will be very difficult to prove that infection prevention interventions—such as full-barrier precautions (i.e., the anesthesiologist wears a cap, mask, sterile gloves, and sterile gown and uses a large drape to cover the patient and the patient's bed)—reduce the risk of infection. However, these procedures are at least as invasive as placing central venous catheters and the consequences of subsequent infections are at least as bad as those for catheter-associated bloodstream infections.

In addition, risk factors for infections after neuraxial and peripheral nerve blocks have not been studied in robust epidemiological studies. The only case–control study of risk factors for infections associated with epidural neural blockade done for postoperative pain relief identified only one remediable risk factor—administering the anesthetic agent with a syringe rather than a bag [OR (for use of a bag) 0.17; 95% CI 0.02–1.34, $p = .05$] *(291)*.

Several investigators have evaluated the agents used to prepare the skin before epidural neuraxial blocks. However, these studies all had methodologic flaws *(292–295)*. For example, three of four studies that we reviewed did not report power calculations, and the study by Adam et al. *(292)* comparing 3% povidone-iodine with 1% chlorhexidine was not randomized. Kasuda et al. *(293)* randomly assigned 70 patients to receive either 0.5% chlorhexidine or 10% povidone-iodine. After a median of 49 ± 7 hours, the authors removed the catheters and obtained cultures of the insertion sites and catheter tips. The rates of positive cultures were similar in both groups. Kinirons et al. *(294)* (the only investigators who reported a power calculation) cultured catheters removed from 96 children who had epidural catheters for longer than 24 hours. Coagulase-negative staphylococci were the only microorganisms that grew and the colonization rate was lower for the catheters removed from children whose skin was prepared with 0.5% alcoholic chlorhexidine (1/52 catheters, 0.9/100 catheter days) compared with those removed from children whose skin was prepared with povidone-iodine (5/44 catheters, 5.6/100 catheter days) (relative risk 0.2; 95% CI 0.1–1.0). These investigators did not identify any epidural space infections. Sato et al. *(295)* evaluated the efficacy of 0.5% alcoholic chlorhexidine and 10% povidone-iodine in a group of 60 patients who were undergoing back operations under general anesthesia. After prepping and draping the site, the investigators obtained skin biopsies that they evaluated by culture and microscopy. Cultures from skin prepared with the chlorhexidine product were less likely to be positive (5.7%) than were cultures from skin prepared with povidone iodine (32.4%; $p < .01$). *S. epidermidis, Staphylococcus hyicus,* and *Staphylococcus capitis* grew from skin cultures. However, microscopy of the hair follicles was equally likely to be positive in skin prepared with chlorhexidine (14.3%) and skin prepared with povidone-iodine (11.8%).

Recently, the ASA (9), the American Society of Regional Anesthesia (ASRA) (14–17), and the German Society of Anesthesiology and Intensive Care (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V." [DGAI]) *(25)*, as well as Brooks et al. *(240)* and Schulz-Stubner et al. (296) have published recommendations for preventing infections associated with neuraxial procedures (Table 60-6). In addition to providing advice on preventing infections, the ASA recommended the following procedures for diagnosing and managing infectious complications associated with neuraxial techniques: (9) (i) Evaluate patients with indwelling neuraxial catheters daily to identify early signs and symptoms (e.g., fever, backache, headache, erythema, and tenderness at the insertion site) of infectious complications. (ii) Investigate signs or symptoms promptly to minimize the severity of an infection. (iii) If an infection is suspected, (a) Remove an *in situ* catheter and consider culturing the catheter tip. (b) Obtain appropriate blood tests. (c) Obtain appropriate cultures. (d) Perform imaging studies and consult with appropriate specialties promptly if the patient may have an abscess or if the patient has neurologic dysfunction. (iv) Administer appropriate antimicrobial therapy at the earliest signs or symptoms of a neuraxial infection. (v) Consider consulting a physician with expertise in the diagnosis and treatment of infectious diseases. (vi) Consult a surgeon if an abscess is identified to determine whether percutaneous drainage of the abscess or a surgical procedure (e.g., laminectomy) is warranted.

To date, guidelines for placement of catheters for peripheral nerve blocks have not been published. Given that complex catheter systems, which require several manipulations during insertion, are used for these procedures *(297)*, we believe that aseptic technique similar to that recommended for placement of central venous catheters is warranted *(298)*.

OUTBREAKS ASSOCIATED WITH ANESTHESIA PERSONNEL

Anesthesia personnel have been the reservoir of infection in at least 11 outbreaks (Table 60-7) (*112–119,299–302)*. Group A β-hemolytic streptococci disseminated from anesthesia personnel caused five outbreaks of surgical site infections and one outbreak of puerperal sepsis (see Chapters 21 and 55). Anesthesia personnel carried group A β-hemolytic streptococci in the following sites: anus (two outbreaks), anus and throat (one outbreak), throat (one outbreak), and skin lesions (two outbreaks). The source of one outbreak was particularly difficult to identify, because the carrier, an anesthesia technician, was present in the operating room only between cases and not during the operations *(119)*. In two outbreaks of *S. aureus* surgical site infections, the microorganism was disseminated by anesthesiologists with psoriasis *(112,113)*. Clearly, the barrier between the anesthesia area and the operative site does not always prevent spread of microorganisms from anesthesia personnel to patients.

TABLE 60-6

Recommendations/Practice Advisories for Prevention of Infections Associated with Neuraxial Anesthetic Procedures

Practice	*ASA (9)*	*ASRA (14,15,16–17)*	*DGAI (25)*	*CDC*	*Other*
Patient selection	Before performing neuraxial techniques, conduct a history and physical examination relevant to the procedure and review relevant laboratory studies to identify patients who may be at risk of infectious complications. Determine whether a neuraxial technique is appropriate on a case-by-case basis and include an assessment of the patient's evolving medical status when considering these techniques. Consider alternatives to neuraxial techniques for patients at high risk of infectious complications. Consider administering pre-procedure antimicrobial therapy before performing a neuraxial procedure on a patient who is known or suspected to be bacteremic. Avoid doing lumbar punctures in patients with epidural abscesses.	The decision to perform a regional anesthetic technique must be made on an individual basis considering the anesthetic alternatives, the benefits of regional anesthesia, and the risk of central nervous system infection (which may theoretically occur in any bacteremic patient; which theoretically are more likely to occur in the immunocompromised patient) (16,17). Despite conflicting results, many experts suggest that, except in the most extraordinary circumstances, central neuronal block should not be performed in patients with untreated systemic infection (16). Available data suggest that patients with evidence of systemic infection may safely undergo spinal anesthesia, provided appropriate antibiotic therapy is initiated before dural puncture and the patient has shown a response to therapy, such as a decrease in fever (placement of an epidural or intrathecal catheter in this group of patients remains controversial) (16). Available data suggest that spinal anesthesia may be safely performed in patients at risk for low-grade transient bacteremia after dural puncture (16). Central neuronal block has been shown to be safe in patients with recurrent herpes simplex infections (HSV), though exacerbations of HSV-1 have been reported in association with intrathecal and epidural opioids (17).			

		There are inadequate data available regarding the safety of spinal and epidural anesthesia in the presence of primary HSV-2 infection. However, viremia, fever, and meningitis have been reported. These findings would suggest a conservative approach (17). Minimal data suggest that neuraxial and peripheral techniques (including epidural blood patch) can be performed safely in HIV-infected patients. The presence of preexisting neurologic pathology is common in these patients and must be considered (16,17).			
Hand hygiene	Remove jewelry (e.g., rings and watches), wash hands.	Thorough hand washing greatly reduces the risk of crosscontamination and should occur before performing any regional anesthetic technique. Alcohol-based antiseptic solutions will provide maximal degree of antimicrobial activity with extended duration when compared with nonalcoholic antimicrobial or nonantimicrobial preparations. The duration and method of washing (standard hand washing vs. full surgical scrub) required to reduce infectious complications is currently unknown (14). Higher microbial counts have been identified in healthcare workers who do not remove jewelry before hand washing. Therefore, it may be prudent to remove all jewelry items (rings, watches, and so on) before hand washing to reduce the risk of contamination (14).	Hand hygiene is considered obligatory. The preferred method is an alcohol-based solution used for 60 s.	The reader is referred to the CDC's hand hygiene guideline *(31).*	Hand hygiene—preferably with an alcohol-based hand rub–should be performed before and after every patient contact and before all invasive procedures (296).

(*Continued*)

TABLE 60-6

Recommendations/Practice Advisories for Prevention of Infections Associated with Neuraxial Anesthetic Procedures (*Continued*)

Practice	*ASA (9)*	*ASRA (14,15,16–17)*	*DGAI (25)*	*CDC*	*Other*
Masks	Wear a mask covering both mouth and nose and consider changing the mask before each case.	The use of surgical masks during regional anesthesia will maximize sterile barrier precautions. Although the routine use of masks has not been found to reduce infectious complications related to regional anesthesia, they do remain a vital protective measure against blood-borne pathogen exposure as recommended by OSHA.	Masks should be worn by all members of the puncture team.	Wear a surgical mask when placing a catheter or injecting material into the spinal canal or epidural space *(30)*.	Masks should be worn during regional anesthesia procedures (296).
Barrier precautions	Wear a cap and sterile gloves. Use sterile drapes.	Sterile surgical gloves should be used and considered a supplement to, not replacement for, hand washing. The use of surgical gloves is advocated not only to protect patients from crosscontamination but also to protect healthcare workers from bloodborne pathogen exposure as required by OSHA (14). Several intensive-care unit based investigations have shown that the use of surgical gowns does not reduce colonization, infection or mortality rates beyond that achieved with gloves alone. However there is currently insufficient data to make recommendations with regard to routine use during regional techniques within the operating room environment (14).	Gowns are recommended when placing catheters for continuous regional anesthesia and large drapes should be used to prevent contamination of the sterile field.		Full-barrier precautions (i.e., the anesthesiologist wears a cap, mask, sterile gloves, sterile gown and uses a large drape to cover the patient) should be used for catheter placement, especially for catheters that will be in place > 24 h and stimulating catheters that require frequent manipulations (296).

Skin preparation	Use individual packets of antiseptics to prepare the skin. Use chlorhexidine (preferably with alcohol) for skin preparation, allowing adequate drying time. If chlorhexidine is not available, use povidone iodine with alcohol.	Alcohol-based chlorhexidine antiseptic solutions significantly reduce the likelihood of catheter and site colonization and maximize the rapidity and potency of bactericidal activity when compared to other solutions. Therefore alcohol-based chlorhexidine solutions should be considered the antiseptic of choice before regional anesthetic techniques (14).	Alcohol-based solutions should be used for 1–10 min, according to manufacturers recommendations	2% Chlorhexidine in 80% alcohol skin prep or alternatively 10% povidone iodine, 80% alcohol, or a mixture of 70–80% alcohol with povidone iodine can be used to prepare the site (alcohol should not be used for subarachnoid blocks) (296).
Dressings	Use sterile occlusive dressings at the catheter insertion site.			The exit site should be dressed with a transparent dressing and should be viewed every 8 h or as necessary *(239)*.
Tunnels or port systems				Catheters for long-term use should be tunneled or have a port system (296).
Catheter management	Limit the number of times a neuraxial delivery system is disconnected and reconnected to minimize the risk of infectious complications. Consider removing catheters that are disconnected accidentally when a healthcare worker is not present. Remove catheters when no longer clinically necessary.			Disconnected nonstimulating catheters can be cut and reconnected after disinfection (296). The anesthesiologist should evaluate whether the infusion should continue if the system becomes disconnected *(239)*.
Prophylactic antimicrobial agents		Because implanted devices used for chronic pain therapy extend to the neuraxis and infection can prove to be catastrophic, routine antimicrobial prophylaxis is warranted in all patients (15). Discitis is a deep-seated difficult infection to treat and can prove to be catastrophic, thus routine antibiotic prophylaxis is warranted (15).	Prophylaxis with antimicrobial agents is not recommended for regional anesthetic procedures.	Prophylactic antimicrobial agents should not be used routinely to decrease the risk of infections associated with regional anesthesia (296).

(*Continued*)

TABLE 60-6

Recommendations/Practice Advisories for Prevention of Infections Associated with Neuraxial Anesthetic Procedures (*Continued*)

Practice	*ASA (9)*	*ASRA (14,15,16–17)*	*DGAI (25)*	*CDC*	*Other*
Patients with infections at other sites		Available data suggest that patients with evidence of systemic infection may safely undergo spinal anesthesia, provided appropriate antimicrobial therapy is initiated before the dural puncture and the patient has responded to therapy (e.g., decreased temperature). Placement of an indwelling epidural (or intrathecal) catheter in patients with infections remains controversial (16).			Patients with documented bacteremia or distal infections who need neuraxial blocks should be treated with appropriate antimicrobial agents before the procedure is done (296).
Filters	Consider using bacterial filters during extended continuous epidural infusion	Currently the literature does not support the routine use of bacterial filters with short-term (e.g., days) epidural or perineural catheter infusions (14).	Filters are recommended; routine filter changes are not recommended.		A 0.22-μm 96-h filter should be included in the infusion system (296). A 0.22-μm 96-h filter should be included in the infusion system. The tubing, filter, and solution should be changed or the system should be discontinued every 96 h *(239)*.
Administration of the anesthetic agent					The primary anesthesia and the adjuvant bolus dose should be given with a larger syringe that remains attached to the catheter until a continuous analgesia infusion is begun *(239)*.

Medication preparation		Only freshly prepared drug solutions should be used and multi-dose vials should be avoided.	Infusions and medications should be prepared by a pharmacist or an equally qualified individual according to Community Health Accreditation Program (CHAP) standard (296).
Patient follow-up	A delay in diagnosis and treatment of major central nervous system infections of even a few hours may significantly worsen neurologic outcome (16)	The puncture site for catheters should be inspected and palpated daily. If clinical signs of infection occur, a regional anesthetic catheter should be handled similar to central venous catheters.	Anesthesia personnel should observe their patients closely for signs and symptoms of infection and should consider infection in the differential diagnosis of patients who had a regional block and subsequently present with fever or with pain at the site (296).

ASA, American Society of Anesthesiologists; ASRA, American Society for Regional Anesthesia; DGAI, Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V. or German Society of Anesthesiology and Intensive Care; CDC, Centers for Disease Control and Prevention; OSHA, Occupational Safety and Health Administration.

TABLE 60-7

Outbreaks Related to Anesthesia Personnel

Author (Reference)	*Year*	*Source*	*Incubation Period*	*Infection*	*Number of Patients*	*Microorganism*	*Comments*	*Time to Recognition*	*Time to Resolution*
Walter *(112)*	1966	Anesthesiologist	Not specified	Surgical site	10	*S. aureus*	Psoriasis of scalp and extremities, dermatitis on hands; microorganism cultured from nose, throat, hands, and perineum	Not specified	3 y
Payne *(113)*	1967	Anesthesiologist	2–20 d	Surgical site	33	*S. aureus*	Acute exacerbation of psoriasis resulting in large areas of desquamation	9 d	35 d
Jewett *(114)*	1968	Anesthesiologist	14–72 h	Puerperal sepsis	25	Group A β-hemolytic streptococci	Microorganism isolated from hand and shin lesions	6 d	11 d
Schaffner *(115)*	1969	Anesthesiologist	Not specified	Surgical site	21	Group A β-hemolytic streptococci	Disseminated from an asymptomatic anal carrier	3 wk	4 m
Gryska *(116)*	1970	Anesthesiologist	24–48 h	Surgical site	13	Group A β-hemolytic streptococci	Anal carrier with mild pruritus ani	4 d	30 d
CDC *(117)*	1976	Anesthesiologist	<48 h	Surgical site; bacteremia and meningitis	61	Group A β-hemolytic streptococci	Asymptomatic throat and anal carrier	Not specified	16 d
Paul *(118)*	1990	Anesthesiologist	24 h-16 d	Surgical site	4	Group A β-hemolytic streptococci	Asymptomatic throat carrier	Not specified	30 d
Mastro *(119)*	1990	Anesthesia technician	6–240 h	Surgical site	20	Group A β-hemolytic streptococci	Disseminated from a carrier with psoriasis and seborrhea on scalp and ears	23 m	40 m
Bosch *(299,300)*	1998, 2000	Anesthesiologist	Not specified	Hepatitis	171	Hepatitis C	Anesthesiologist addicted to morphine and infected with hepatitis C gave himself morphine injections and then gave patients the drug through the same syringe and needle.	Not specified	Not specified
Ross *(301)*	2000	Anesthesia assistant		Hepatitis	Five patients and the anesthesia assistant	Hepatitis C	Index patient may have infected the anesthesia assistant who participated in her operation. Six weeks later, the anesthesia assistant had acute icterus.	Not specified	3 m
Cody *(302)*	2002	Anesthesiologist	7 wk	Hepatitis	1	Hepatitis C	Mode of transmission is unclear. Anesthesiologist probably acquired hepatitis C from a chronically infected patient.	Not specified	Not specified

Most outbreaks are inadvertent, even if they are related to poor infection prevention and control practices. However, outbreaks such as those reported by Maki et al. *(164)* and Bosch *(299,300)* demonstrate that on occasion, hospital personnel deliberately put patients at risk. In the outbreak reported by Maki et al. *(164)*, a pharmacy technician replaced stolen fentanyl with nonsterile distilled water. The outbreak described by Bosch is even more frightening. On numerous occasions, an anesthesiologist addicted to morphine and infected with hepatitis C first gave himself morphine and then administered the remaining drug to the patients through the same syringe and needle. He thereby infected at least 171 patients *(299,300)*. In two recent outbreaks, the anesthesia provider acquired hepatitis C from a patient and spread the virus to other patients *(301,302)*.

EXPOSURE OF ANESTHESIA PERSONNEL TO PATIENTS' BLOOD AND BODY FLUIDS

Asai et al. *(303)* screened routinely all patients undergoing elective operations for blood-borne pathogens. Of 6,437 patients screened in a 2-year period, 534 (8.3%) were infected with at least one of these agents. Thus, anesthesiologists frequently care for patients who are infected with these agents.

The proportion of operative procedures in which anesthesia personnel are exposed to blood has varied by study. White and Lynch *(304)* observed 1,054 blood contacts during 8,502 operative procedures. Anesthesia personnel were exposed to blood in 82 (0.96%) of the cases. The authors noted that fingers, hands, and arms were exposed 70 times, usually when anesthesia personnel inserted intravenous catheters. The face or neck was exposed eight times by blood from the operative field. Legs or feet were exposed four times when blood or bloody irrigation fluid ran off the surgical drapes. In 75 episodes, blood contaminated intact skin, and in 2 episodes blood contaminated nonintact skin. Five (6%) punctures occurred. Panlilio et al. *(305)* observed 206 operative procedures and noted that anesthesia staff were exposed to blood in 13 (6.3%). Popejoy and Fry *(306)* observed blood contact during 190 of 684 operations (28%). Circulating nurses and anesthesia personnel contacted patients' blood more frequently than did surgeons, but surgeons had more frequent percutaneous exposures. The authors noted that "although the anesthesiology staff and circulating nurses reported the greatest number of blood contact events, they were the only individuals who did not consistently wear gloves. Independent observations suggested that they were rarely gloved during the study period."

Several prospective studies indicate that anesthesia personnel are stuck with needles in 0.13% to 0.4% of operative procedures *(306–308)*. During a 3-month period studied by Maz and Lyons *(308)*, a higher proportion of the more experienced anesthesiologists stuck themselves with needles than did the less experienced personnel: 4 of 15 consultants (27%), 2 of 7 senior registrars (29%), 1 of 6 registrars (17%), 1 of 7 senior house officers (14%), and 1 of 7 clinical assistants (14%). Six of the nine needles were contaminated, and only three of the injuries were reported to the proper hospital authorities. In contrast, Jagger et al. *(309)* observed that residents injured themselves more frequently than did attending physicians in all specialties. Moreover, Heald and Ransohoff *(310)* estimated the rate of needlestick injuries in anesthesia residents to be 2.5 injuries per resident year. This rate was lower than that for residents in orthopedics (5.6 injuries per resident year), general surgery (5.5 injuries per resident year), and obstetrics and gynecology (4.5 injuries per resident year) but higher than that for residents in internal medicine (0.75 injuries per resident year).

Greene et al. *(311)* studied percutaneous injuries reported by anesthesia personnel from nine hospitals participating in the EPINet surveillance program. All contaminated percutaneous injuries in these personnel resulted from needles, 87% (34 of 39) of which were hollow bore. Seventy-eight percent of these injuries occurred between uses or after use of the device and are, therefore, considered potentially preventable. In contrast to injuries experienced by anesthesia personnel, fewer than 30% of the injuries to nonanesthesia personnel in the operating rooms were caused by hollow-bore needles. Thus, anesthesia personnel may be less likely to experience percutaneous injuries than are surgeons; however, the needles used by the former usually have hollow bores. In addition, anesthesia personnel use hypodermic needles and large-bore cannula introducers, both of which can carry more blood than suture needles. Thus, the percutaneous injuries experienced by anesthesia personnel may be more likely to transmit blood-borne pathogens than are those experienced by surgeons. A study by Jagger et al. *(309)* confirmed these findings. Most percutaneous injuries observed in this study occurred in the operative site and to nonanesthesia staff; 1.5% of the injuries occurred at the anesthesia cart or machine. However, 16.7% of the injuries sustained by anesthesia personnel were caused by blood-filled, hollow-bore needles.

Greene et al. *(312)* evaluated contaminated percutaneous injuries (CPIs) among anesthesia personnel at 11 hospitals over a 2-year period. These investigators found that 30% of all CPIs were high-risk exposures, that is, the sharp device was a blood-contaminated hollow-bore needle. Seventy-four percent of these injuries were potentially preventable. They noted that only 26% of CPIs were reported and that reporting rates varied by job category. Student nurse anesthetists reported 64% of their injuries compared with 29% for anesthesia residents, 23% for certified nurse anesthetists, and 19% for staff anesthesiologists. After correcting for under reporting, these investigators calculated a CPI rate of 0.27 CPIs per year per person or 0.42 CPIs per year per full-time equivalent. Patel and Tignor *(313)* determined device-specific sharps injury rates. Injuries with hollow-bore needles on Luer-lock syringes occurred at a rate of 1.29/100,000 devices used for anesthesiologists compared with 7.35/100,000 devices used for surgeons. Injuries from intravenous catheters occurred at rates of 1.18/100,000 devices for anesthesiologists and 12.87/100,000 devices for surgeons.

Anesthesia personnel perform numerous procedures during which they may be exposed to patients' blood or body fluids. For example, they insert intravascular catheters, intubate and extubate patients' tracheas, and

TABLE 60-8

Blood Contact During Routine Anesthesia Procedures *(314)*

Procedure	*Percentage Associated with Blood Contact (%)*
Injecting a drug intramuscularly	8
Extubating a patient	9
Suctioning the oral cavity, pharynx, or trachea	13
Catheterizing a peripheral vein	18
Doing a lumbar puncture	23
Catheterizing the epidural space	34
Doing an arterial puncture	38
Establishing or discontinuing a blood transfusion	43
Inserting a central venous catheter	87

suction tracheal and oral secretions. Using a questionnaire, Kristensen et al. *(314)* found that 50% of anesthesiologists had contact with blood during a 1-week period, compared with approximately 40% of orthopedic surgeons and approximately 30% of general surgeons. Furthermore, Kristensen et al. *(315)* determined that anesthesia personnel contacted patients' blood or body fluids during 36% of common anesthesia procedures (Table 60-8). On the basis of a questionnaire survey, Harrison et al. *(307)* observed that 65 "anesthetic and related staff" contacted patients' blood or body fluids in 35 of 270 (13%) operations, most frequently while cannulating a vessel.

In addition to contact with visible blood from vessels, the operative site, or contaminated needles, anesthesia personnel are exposed to blood from several less obvious sources. For example, Crisco and DeVane *(316)* found blood in the mouths of 56 of 168 patients (33%) after tracheal intubation; blood was visible in 12 (7%) and occult in 44 (26%). Thirty-nine patients (23%) had blood on their cheeks, tongue, and posterior soft palate, and for 29 patients (17%) blood was noted on the laryngoscope blade. After tracheal extubation, 58 patients (35%) had overt blood and 59 (35%) had occult blood in their mouths. Blood was found on the distal tip of 113 endotracheal tubes (67%). Similarly, Kristensen et al. *(314)* noted visible blood on 16 of 29 endotracheal tubes (55%; 95% CI 36–74%) and occult blood on 6 of 29 endotracheal tubes (21%; 95% CI 8–40%). Five of 28 suction catheters (18%; 95% CI 6–37%) were contaminated by visible blood, and 10 (36%; 95% CI 19–56%) were contaminated by occult blood. Brimacombe et al. *(317)* determined that cuffed oropharyngeal airways (14%) were more likely than laryngeal mask airways) (LMAs) (3%) to be contaminated with visible blood. Parker and Day *(318)* found visible blood on 12% of LMAs and 16% of endotracheal tubes after use. However, when they tested for occult blood, these investigators found that 76% and 78%, respectively, were contaminated.

In addition, anesthesia personnel may unwittingly contact a patient's blood or body fluids when they touch the anesthetic record *(319)* or equipment such as the anesthesia machine or touch screens *(320)*. Hall *(321)* sampled surfaces on "clean" anesthesia machines, carts, and monitors. Of 418 samples, 134 were positive for occult blood and three sites were contaminated with visible blood (see section "Current Anesthesia Practice," for further studies about this topic). Perry and Monaghan *(104)* found visible and occult blood on anesthesia equipment: 35.5% of the tests were positive before the first case of the day, 29.5% were positive after the first case, and 29.5% after the second case. Occult blood was more common than visible blood. They found blood on ventilator controls (25.0%), flowmeter knobs (33.9%), vapor controls (26.8%), electrocardiography cables (64.3%), pulse oximeter probes (19.6%), and blood pressure cuffs (26.8%). Taken together, these studies indicate that anesthesiologists contaminate the environment in which they work with blood, that the equipment is not cleaned adequately, and that anesthesia personnel can unwittingly contact blood during all their activities, not just when they access the vascular system.

INFECTIONS CAUSED BY OCCUPATIONAL EXPOSURE

Hepatitis B Virus

The prevalence of serologic markers for hepatitis B virus (HBV) has ranged from 3.5% to 49% in anesthesia personnel *(322–329)* compared with only 4.4% to 13.7% in the general population *(330,331)*. The highest rate of HBV seropositivity, 49%, was noted in an inner city hospital *(327)*, where 27 of 70 anesthesiologists were from areas of the world with a high prevalence of hepatitis B infection and a large proportion of the patients were in high-risk groups. Most point prevalence studies suggest that the proportion of seropositive personnel increases with the duration of anesthesia practice *(322–324,326–328)*. However, in one multicenter point prevalence study, Berry et al. *(325)* found that hepatitis B seropositivity did not increase with additional years of practice.

Anesthesia personnel were infected with HBV during two outbreaks *(332,333)*. In both outbreaks, the index case was not known to be infected with HBV, routine precautions were taken in the operating room, and the healthcare workers denied touching the patient's blood. Thus, the mode of transmission was not identified.

Hepatitis C Virus

Anesthesia personnel have acquired hepatitis C from patients; some of these staff members subsequently transmitted this virus to patients (see "Outbreaks Associated with Anesthesia Personnel" and Table 60-7) *(301,302)*. Bakir et al. *(334)* described a 33-year-old male Tunisian anesthesiologist who acquired hepatitis C while "training abroad". While he was assisting in the care of an accident victim, he instinctively put his bare hand, which had minor cuts, onto a bleeding wound. Three months later, he had jaundice,

asthenia, hepatitis, and elevated serum transaminases. His hepatitis C serology converted to positive and the infection did not respond to treatment with interferon or ribavirin. Greene et al. *(312)* estimated that the 30-year risk for anesthesiologists acquiring hepatitis C was 0.45% per full-time equivalent (FTE). They estimated that 155 anesthesiologists would acquire hepatitis C over a 30-year period.

Human Immunodeficiency Virus

Although the absolute risk of acquiring HIV infection from occupational exposure has not been determined for anesthesia personnel specifically, one anesthesiologist was infected when he stuck himself with an HIV-contaminated needle *(335)*. Buergler et al. *(336)* used data in the literature to estimate the risk for anesthesiologists and surgeons of acquiring HIV infection over a 30-year career. They assumed that (a) the risk of needle sticks per year ranges from 0.86 to 2.5 for anesthesiologists and 3.8 to 6.2 for surgeons, (b) the risk of seroconversion from a needlestick ranges from 0.42% to 0.50%, (c) the prevalence of HIV infection in the population would remain constant during the 30-year period and would range from 0.32% to 23.6%, and (d) protective measures would be of no benefit. Using these assumptions, Buergler et al. estimated a cumulative risk for anesthesiologists of 0.05% to 4.5% compared with 0.17% to 13.9% for surgeons. Buergler's estimates have been controversial *(337,338)*. Subsequently, Greene et al. *(312)* used different assumptions and estimated the 30-year risk to be only 0.049%, with 17 HIV infections occurring in anesthesiologists during this time period. Regardless of which estimate most closely approximates reality, both estimates suggest that the risk of acquiring HIV infection is measurable. Furthermore, despite the less invasive nature of anesthesia practice, the risk for anesthesiologists overlaps with that of surgeons, and, as we noted previously, many exposures among anesthesia personnel are considered high risk because they involve hollow-bore needles that had been in the vascular space.

Herpes Simplex Virus

Herpetic whitlow, infection of the fingers with herpes simplex virus (HSV), occurs rarely in the general population but is a recognized hazard for healthcare workers (see also Chapter 44). Herpes simplex infects the fingers when breaks in the skin are exposed to secretions containing the virus. Serologic surveys indicate that 80% to 90% of the United States population has been infected with HSV *(339,340)*. Cross-sectional culture surveys indicate that, at any one time, 2% to 9% of adults and 5% to 8% of children asymptomatically shed HSV in saliva; longitudinal studies suggest that 32% of children and 80% of adults asymptomatically shed HSV in saliva at some points in their lives *(341–343)*. Anesthesia personnel frequently contact patients' oral secretions and therefore might be at increased risk for acquiring herpetic whitlow *(344)*. Although the frequency of this infection in anesthesia personnel is unknown, individual anesthesiologists and nurse anesthetists have acquired herpetic whitlow from infected patients *(345–347)*.

PREVENTION AND CONTROL OF INFECTION IN THE PRACTICE OF ANESTHESIA

Current Infection Control Guidelines and Current Anesthesia Practice

As noted previously, several agencies and societies, including the ASA (7,9), the AANA *(8)*, AORN *(10–13)*, CDC (28,*29–33*,*298*), the Australia and New Zealand College of Anaesthetists (ANZCA) *(18)*, the Australian Society of Anaesthetists *(19),* the Australian Medical Association *(20)*, the New South Wales Health Department *(21)*, and the Association of Anaesthetists of Great Britain and Ireland *(22)*, Department of Health of the Netherlands Committee on Infection Prevention *(23)*, the Societe Francaise d'Anethesie et de Reanimation *(24)*, and the German Society of Anesthesiology and Intensive Care *(25),* have published infection prevention and control guidelines for the practice of anesthesia (Tables 60-1 and 60-3). Nevertheless, several anesthesiologists have voiced concern about their colleagues' disregard for basic infection control practices. They criticize their colleagues for using common syringes, handling intravenous tubing ports and multidose vials without aseptic technique, recapping needles, failing to maintain separate clean and dirty work spaces, not cleaning and disinfecting equipment after each patient, and not wearing protective barriers *(141,142,320,348–355)*.

Crow and Green *(356)* observed 18 surgeons and 10 anesthesiologists during 36 herniorrhaphies to determine whether they complied with 44 "aseptic precautions". Anesthesiologists violated those aseptic precautions nearly twice as often as did the surgeons. During the 36 operations, anesthesiologists were observed touching the sterile field (2 occurrences), working while ill (3 occurrences), inadequately separating the operative field from the anesthesia area (3 occurrences), wearing their masks improperly (7 occurrences), leaning over the sterile field (8 occurrences), not washing their hands before the case (24 occurrences), and not covering their hair completely (25 occurrences).

Tait and Tuttle *(357)* surveyed anesthesiologists to determine how many complied with practices recommended for preventing transmission of infectious agents to patients; 493 of 1,149 (43%) completed the survey. Ninety-five percent reported washing their hands after caring for patients they considered to be at high risk for infection, but only 58% washed their hands if they felt the patient was at low risk of infection. Eighty-eight percent changed breathing circuits between patients, 99% cleaned laryngoscope blades after each patient, 69% disinfected or sterilized blades, and 60.5% never or rarely disinfected their work surfaces. Forty-seven percent acknowledged that they reused syringes, and 53% said they never reused these devices. el Mikatti et al. *(358)* did a similar survey in the United Kingdom. They had a better return rate (145 of 213 [68%]) than did Tait and Tuttle *(357)*, but a lower percentage (20%) of the respondents admitted to ever reusing syringes. In Taiwan, 6% of respondents to the survey by Or et al. *(359)* acknowledged reusing syringes frequently. Ryan et al. (289)

surveyed anesthesia providers in New Zealand and found that 2.2% admitted to occasionally using a single syringe for more than one patient. Similarly, Carbonne et al. (360) in France found that 2% of the respondents to their survey admitted using a single syringe for more than one patient. Sixty-six percent of the anesthesia providers in Iran who responded to the survey by Askarian et al. *(123)* reported that they routinely used unused anesthetic agents for subsequent patients.

The proportion of anesthesiologists who reported that they always disinfected the septum of a multidose vial (27.8% United States [Tait and Tuttle] *(357)*, 39.4% United Kingdom [el Mikatti] *(358)*) and who work while sick (upper respiratory tract infection—96% United States, 94% United Kingdom; gastrointestinal infection—60.1% United States, 42.9% United Kingdom; herpes infection—22% United States, 32.6% United Kingdom) was similar in both surveys. Both Tait and Tuttle *(357)* and el Mikatti et al. *(358)* asked anesthesiologists to describe, using a scale of 0 to 10 (0, no chance of transmission; 10, a significant chance for transmission), the potential for anesthesiologists to transmit pathogens from patient to patient. The median score for anesthesiologists surveyed by Tait and Tuttle *(357)* was 4.7 compared with only three for those surveyed by el Mikatti et al. *(358)*. Thus, the anesthesiologists responding to these surveys thought their potential to transmit pathogens was low. More recently, anesthesia providers in New Zealand rated the likelihood that they could transmit pathogenic microorganisms to patients at a "7" (289). In Iran, Askarian et al. *(123)* found that anesthesia providers' assessments of whether anesthesia could cause infection in patients was significantly related to whether or not they always cleaned oral airways.

Several investigators documented that anesthesia equipment in some institutions is not cleaned and disinfected adequately. Simmons obtained cultures of 20 "clean" handles, all of which grew microorganisms *(361)*. Although *S. epidermidis, Micrococcus* species, and *Bacillus* species were the most common microorganisms, cultures from 12 of the 20 handles grew group A streptococcus. In addition, one handle each grew *S. aureus*, enterococcus, and *P. aeruginosa* with *Citrobacter*. Phillips and Monaghan *(362)* tested 65 laryngoscope blades and handles that were "patient-ready" (i.e., had been cleaned and disinfected and were ready to use on the next patient). No visible blood was noted, however, 13 (20%) blades and 26 (40%) of the handles had positive tests for occult blood; blades and handles tested in the afternoon were significantly more likely to be positive compared with those tested in the morning. Morell et al. *(363)* found similar results; 10.5% of "clean" laryngoscope blades and 50% of "clean" laryngoscope handles were contaminated with occult blood.

Several studies suggest a possible reason that these items are contaminated with blood. Many anesthesia personnel do not routinely clean and disinfect laryngoscope blades, endotracheal tube stylets, and breathing circuits between patients (*141*,*349*,*353*,*359*,360). Esler et al. *(364)* did a postal survey of all 289 Royal College tutors in anesthesiology in Great Britain, 239 (82.7%) of whom responded. Of the respondents, 22% autoclaved laryngoscope blades after every use, 19% autoclaved them "often," 41% autoclaved them after high-risk cases, and 18% did not autoclave them. Fifty percent did not dismantle the laryngoscope before cleaning. One-third of the respondents did not clean the laryngoscope handle. Forty-nine percent cleaned the handles, 13% autoclaved the handles after high-risk cases, and 5% autoclaved the handle after each case. One-third of the respondents said they would not put a randomly selected, ready-to-use laryngoscope from their institutions into their own mouths! Of note, laryngoscope blades are semicritical items and, therefore, need to be cleaned and treated at least with high-level disinfection after each use.

It has been difficult to document that these breaches in infection control practice compromise patients' care. However, Foweraker *(99)* identified four children in a pediatric cardiology ICU who were infected with *P. aeruginosa*. All four isolates had different phage types. However, the investigators found a laryngoscope blade that had dried secretions around the bulb. *P. aeruginosa* with the same phage type as the strain infecting the one child who died was isolated from the blade. Of note, the staff in this unit did not follow their own cleaning policy. Similarly, Neal et al. *(100)* reported that eight neonates acquired infections with the same *P. aeruginosa* strain. Dried secretions were found on two neonatal laryngoscopes, and *P. aeruginosa* with the same phage and serotype as the epidemic strain was isolated from cultures of these devices. The laryngoscopes were washed in hot water and detergent and wiped with alcohol. They were then stored loose in a drawer. Nelson et al. *(365)* reported that *Listeria monocytogenes* possibly was transmitted from one neonate to another by a laryngoscope that was wiped with alcohol and not sterilized as the hospital's policy required. These studies suggest that bacterial pathogens and possibly blood-borne pathogens could be transmitted to patients or to anesthesia personnel via contaminated anesthesia equipment. Laryngoscope blades touch the oral mucosa, and thus, could transmit blood-borne pathogens from patient to patient. Laryngoscope handles and anesthesia carts and machines do not contact patients directly, and thus may not put patients at risk. However, anesthesia personnel may contaminate their hands when touching these surfaces, putting themselves at risk and putting patients at risk if the staff members do not perform hand hygiene. Further studies are needed to determine whether these items could be a source of infections for individual patients or anesthesia staff or a source for outbreaks such as that reported by Chant et al. *(93)*.

Anecdotal reports, questionnaires, and studies observing their practice consistently show that many anesthesia personnel do not routinely wear protective equipment to prevent contact with blood and body fluids (*123*,289,*307, 357,358*,360,*366,367*). Only 16% of anesthesia personnel responding to O'Donnell and Asbury's *(366)* mail survey stated that they wore gloves for routine daily work. In a similar study, only 9% of anesthesia personnel wore gloves when intubating patients, and 8% wore gloves when inserting peripheral cannulas *(306)*. However, 63% wore gloves to insert arterial lines, and 89% wore gloves to insert central venous catheters *(307)*. Tait and Tuttle *(357,367)* surveyed anesthesiologists to determine how many complied with guidelines to protect themselves from exposures to blood-borne pathogens. Only 7% of anesthesiologists reported

that they wore gowns and 49.3% reported that they always wore gloves while administering anesthesia. In contrast, only 14.5% of the anesthesiologists responding to el Mikatti et al.'s *(358)* survey said they always wore gloves. Anesthesiologists who responded to Tait and Tuttle's *(367)* survey reported that they were more likely to wear gloves if they felt the patient was at high risk for infection with blood-borne pathogens. Anesthesiologists who recently entered practice were more likely than their more experienced colleagues to wear gloves for contact with patients felt to be at low risk for infection with a blood-borne pathogen *(367)*. Eighty-eight percent reported that they sometimes and 10% reported that they always recapped needles; nearly 66% reported using a two-handed technique while recapping. Thirty-two percent of the respondents reported sustaining injuries with contaminated needles in the preceding 12 months; only 45% stated that they reported the incident or sought treatment *(367)*.

In summary, studies consistently indicate that many anesthesia personnel disregard both traditional infection prevention and control procedures and those recommended by their own societies. Furthermore, despite the risk of transmitting HBV, HCV, HIV, and other blood-borne diseases, anesthesia personnel continue to use common syringes and procedures that might transmit blood-borne pathogens. In 1990, Kempen and Treiber *(354)* pointedly stated that "the widespread reeducation of personnel regarding hygiene (universal precautions) due to the AIDS epidemic may have missed anesthetic personnel, as many prevailing anesthetic practices appear quite cavalier regarding nosocomial viral transmission." In 2001, Berry *(368)* published an editorial in which he commented on a report by Ross et al. *(301)* in which the authors described transmission of hepatitis C from a patient to an anesthesia assistant, who then spread this microorganism to other patients. Berry wrote, "The report clearly demonstrates the potential for occupational HCV transmission both from and to patients via tasks performed by anesthesiologists. The disregard of appropriate aseptic techniques and the failure to use Standard Precautions likely were responsible for the adverse outcomes" *(368)*. Little has changed!

Preventing Infections in Anesthesia Personnel

Several investigators noted that anesthesia personnel could prevent most of their contact with blood and body fluids by wearing gloves *(305–307,309,315)*. Hence, if anesthesia personnel wore gloves and used other barriers, they could protect themselves against most occupationally acquired infections including HBV, HCV, HIV, and herpetic whitlow (Table 60-9).

However, anesthesia providers often have not studied important guidelines and policies. For example, 51.5% of respondents to the survey by Ryan et al. (289) acknowledged that they had never read their hospitals' infection prevention policies and 32.4% had never read the guidelines published by the ANZCA. McNamara and Stacey *(369)* surveyed anesthesia staff at five hospitals in southeast England and found that only 49% knew the published guidelines. Only 29% of the respondents wore gloves routinely. The primary reason anesthesiologists gave for not wearing gloves was that gloves decreased their sense of feel. Some anesthesia personnel are concerned that they may increase their risk of injury and that they may contaminate their patients or the environment if they wear gloves while performing procedures. A study by Ben-David and Gaitini *(370)* suggests that these fears may be unfounded. These investigators observed fewer needlestick injuries and less environmental contamination when personnel wore gloves than when they did not. Although the differences did not reach significance, these data indicate that gloves did not increase the number of injuries or the frequency of contamination.

HBV infection can be prevented by immunizing persons at high risk and by using appropriate barriers. Hepatitis B vaccine, available in the United States since 1982 *(371)*, was accepted slowly by anesthesia personnel. In 1985, only 19% of anesthesia residents surveyed by Berry et al. *(325)* had been immunized. In 1991, approximately 90% of the anesthesia residents but only 60% of the attending anesthesiologists ($p < .001$) surveyed by Rosenberg et al. *(355)* had been vaccinated. Two other surveys of anesthesiologists conducted in the late 1980s found vaccination rates of 71% to 74% *(307,308)*, but the rate in Iran was only 61.5% in 2000 *(123)*.

A case report describes an incident in which respiratory secretions splashed into an anesthesiologist's unprotected eyes during an intubation *(372)*. Subsequently, he acquired bilateral conjunctivitis, fever, myalgia, and pharyngitis. Adenovirus type 14 was isolated from the patient and the anesthesiologist. The authors concluded that face protection would have prevented this exposure, and they recommended that anesthesia personnel wear face protection when intubating patients.

A poignant case report illustrates how performing routine tasks can put anesthesia personnel at risk for HIV infection *(335)*. An anesthesiologist with 20 years of experience inserted a central venous catheter into a patient known to be infected with HIV. After inserting the catheter, the anesthesiologist picked up the 16-gauge needle in his right hand and reached across his left arm to discard it. In the process, he stuck the contaminated needle into his left forearm. Despite beginning azidothymidine (AZT) within 2 hours of the injury, he seroconverted 10 weeks later. In an article *(335)* and videotape *(373)* describing the accident, this unfortunate anesthesiologist shared several important lessons. First, the catastrophic procedure was 1 he had performed hundreds of times. Second, he was working under adverse conditions that forced him to reach across his body with the contaminated needle. Third, and to our mind most important, the accident occurred after he had finished the procedure. He concentrated intently while inserting the line in order to complete the task successfully, but his vigilance dropped while discarding the contaminated needle. Although this is only one case, we conclude that anesthesia personnel should protect themselves by optimizing their work conditions and by concentrating intently during and after procedures, even the most routine.

In summary, numerous studies indicate that anesthesia personnel are exposed frequently to patients' blood and body fluids. Thus for their own safety, anesthesia providers must implement Standard Precautions in a manner that is appropriate for their work flow.

TABLE 60-9

Recommendations/Guidelines to Protect Anesthesia Providers

Item	*ASA (8)*	*AANA (9)*	*Other*
Standard Precautions	Use gloves, fluid-resistant mask, face shield, and gown routinely with all patients. Choose barrier commensurate with the expected extent of exposure.	Use Standard Precautions for all patients. Wear gloves, gowns, mask, and protective eyewear for contact with blood and body fluids. Use transmission-based precautions for patients known to be infected or colonized with epidemiologically important pathogens (see guidelines for specifics).	For the anesthetist's protection, protective gloves are worn whenever the hands may contact blood, saliva, or any other body fluid and are to be removed after such a procedure to minimize contamination of the work place *(18)*. Universal precautions must be adopted for all anesthetic practices *(19)*. Readers are referred to the Hospital Infection Control Practices Advisory Committee's guideline on isolation precautions *(30)*.
Hand hygiene	Wash hands after touching blood or body fluids whether or not gloves are worn. Wash hands immediately after removing gloves.	Wash hands before and after all contact with patients or specimens, after handling body substances, and after removing gloves.	Frequent hand washing by the anesthetist and the anesthetic technician is a most important infection control measure. Hands should be washed before handling a new patient or equipment to be used on a new patient, after leaving a patient, whenever they become contaminated and before any invasive procedure *(18)*. Decontaminate hands means to reduce bacterial counts on hands by performing antiseptic hand rub or antiseptic hand wash *(31)*. Decontaminate hands before having direct contact with patients. Decontaminate hands before donning sterile gloves when inserting a central intravascular catheter. Decontaminate hands before inserting indwelling urinary catheters, peripheral vascular catheters, or other invasive devices that do not require a surgical procedure *(31)*.

Handling needles	Do not recap, bend, break, or remove contaminated needles from syringes by hand. If necessary to recap a needle, use a single-handed technique or a mechanical protection device. Encourage use of needleless systems or shielded needle products. Puncture-resistant containers should be at all work locations.	Do not recap needles or manipulate them in any way. Place used syringes in nearby puncture-resistant containers that are stored upright and labeled as biohazards. Use a mechanical device or one-handed technique if no alternative is available. Alternatives to needles are available for checking sensory awareness.	
Blood exposures	Develop detailed protocol at each facility.	Each facility is obligated to provide postexposure testing, counseling, monitoring, and surveillance.	
Emergency ventilation devices	Mouth pieces, resuscitation bags, and other ventilation devices should be available.	Place equipment needed for emergency resuscitation in areas where the need for resuscitation is probable and predictable. Use ventilation devices rather than mouth-to-mouth resuscitation.	
Personnel with cutaneous lesions	Anesthesiologists should refrain from direct patient contact when they have breaks in the skin or exudative, weeping lesions unless the open area can be protected. Unprotected lesions are a risk to the healthcare worker and the patient.		Personnel with skin abrasions, cuts, or dermatitis must be excluded *(19)*.
Hepatitis B vaccine	Vaccinate all anesthesiologists who do not have documented immunity.	Refers to the OSHA standard.	Immunization Practices Advisory Committee states that healthcare workers whose work involves contact with blood should be vaccinated *(33)*.
		Offer student CRNAs the vaccine at no cost.	OSHA requires that employers offer the vaccine at no cost to individuals who are exposed to blood *(377)*.
Laser plumes	Hold evacuator nozzles close to the operative field before and 30 s after the tissue is vaporized to prevent transmission of viruses.		

ASA, American Society of Anesthesiologists; AANA, American Association of Nurse Anesthetists; CDC, Centers for Disease Control and Prevention; OSHA, Occupational Safety and Health Administration; CRNA, certified nurse anesthetist

CONCLUSION

Until recently, studies assessing the risk of infection related to anesthesia procedures had produced little objective evidence to confirm that the practice of anesthesia—general or regional—and the use of anesthesia equipment can be associated with transmission of pathogens and with HAIs. Recently, Loftus et al. (101,102) and Koff et al. (103) found that bacterial pathogens can be transmitted to the anesthesia work area and to patient's intravenous lines. They also found that improving hand hygiene could decrease environmental contamination and the incidence of HAI. They demonstrated that strategic, scientific, evidence-based approaches that are specific for a unique hospital setting and integrated into the normal work flow could improve anesthesia providers' adherence with aseptic practice and, thereby, also improve patient safety.

We hope that more anesthesia providers will do studies designed to address specific infection prevention issues associated with anesthesia practice so that the evidence base will increase. Anesthesia providers understand the unique challenges presented by the environment in which they work and by the nature of the work they do (e.g., the limited amount of work space, the rapid pace of the work, and the need to multitask). They are well suited to assess the infectious risks posed by their work and to design preventive measures specific for their work and their environment. Infection prevention staff members can support these efforts by sharing their expertise and by giving the anesthesia providers the rates of infection among patients who have had anesthetic procedures. Together, they could design and conduct studies to identify risk factors specific to the specialty and the environment and specific interventions that address these factors. Such partnerships are likely to yield better results than are campaigns that take a "one-size-fits-all" approach. We hope that this chapter will encourage anesthesia providers and infection prevention staff members to engage in this important patient safety work.

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CHAPTER 61

Healthcare-Associated Infections that Complicate Invasive Procedures in Cardiology

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Few prospective studies on healthcare-associated infections related to invasive procedures in cardiology have been done, and most studies have been done retrospectively. In very few investigations were the etiologies, pathogenesis, and epidemiology specifically addressed, primarily because most studies were retrospective. There seem to be, however, no major differences between healthcare-associated infections associated with invasive devices in cardiology and other foreign body–associated infections, which are extensively covered in Chapters 17, 18, and 65. Therefore, this chapter mainly describes the incidence rates and types of infections.

INFECTIONS ASSOCIATED WITH CARDIAC CATHETERIZATION AND PERCUTANEOUS CORONARY INTERVENTIONS

Cardiac catheterization and percutaneous coronary interventions (PCIs), the latter including percutaneous transluminal coronary angioplasty (PTCA), coronary stent implantation, intraaortic balloon pump (IBP) insertion and laser thermal angioplasty, are frequently performed examinations in modern medical care. However, besides technical complications, infections may arise.

Cardiac Catheterization

In early publications, bacteremia was reported to occur in 4% to 18% of patients undergoing cardiac catheterization *(1,2)*. However, in these studies, blood for culture was obtained from the intravascular catheter or the vessel from which the catheter was removed. Sande et al. *(3)* determined the true frequency of bacteremia during and after cardiac catheterization and the frequency of fever by obtaining 214 blood cultures from 106 patients from a vein in the arm on the side opposite to that of the catheter. All venous samples were sterile; therefore, no bacteremia could be demonstrated during cardiac catheterization.

The mortality and morbidity associated with cardiac catheterization were analyzed over a period of 9 years (1971–1979) by Gwost et al. *(4)*. No infection and only two pyrogenic reactions occurred in 1,771 patients. Furthermore, there were only three cases of bacteremia or bacterial endocarditis after 12,367 catheterization procedures reported in an early cooperative study *(5)*. Ricci et al. *(6)* found only five documented infections after review of 7,690 medical records of cardiac catheterizations over a 40-month period.

Between 1980 and 1988, 12,251 arterial punctures for cardiac catheterization, PTCA, or pure diagnostic intra-arterial angiography (IAA) were performed by Würsten et al. *(7)*. The only infectious complications documented were prolonged healing of a wound in the groin and a severe graft infection necessitating ligation of the common femoral artery.

In a retrospective study from January 1991 to December 1998, Munoz et al. (8) found a bacteremia rate of 0.11% in 22,006 invasive nonsurgical cardiologic procedures (0.24% after PTCA, 0.6% after diagnostic cardiac catheterization, 0.8% after electrophysiologic studies). Multivariate analysis identified the presence of congestive heart failure (OR 21.0; CI 95% 6.8–66.0) and age older than 60 years (OR 1.9; CI 95% 1.9–6.3) as independent risk factors for a blood stream infection after nonsurgical cardiologic procedures.

The incidence of bacteremia and other infections associated with cardiac catheterization, therefore, seems to be very low. Even if synthetic vascular grafts have to be catheterized, the infection rate is very low. Mohr et al. *(9)* investigated 109 percutaneous catheterizations of synthetic vascular grafts in 89 patients to determine the risk of major complications. Ninety-six catheterizations were performed through the inguinal portion of the aortofemoral graft. There were no instances of graft infection, and only one superficial infection developed at a cutaneous puncture site, which did not involve the graft.

A large prospective study to assess the frequency of bacteremia due to cardiac catheterization and PCI was performed by Banai et al. (10) who examined patients undergoing a total of 960 interventional procedures. They analyzed blood cultures, withdrawn from the arterial sheath immediately after arterial puncture and at the end of the procedure. A third blood culture was withdrawn from a peripheral

vein 4 hours later. The incidence of positive blood cultures immediately after the procedure was 7.3% after diagnostic catheterization and 4.6% after PCI (balloon angioplasty and stent implantation). After 4 hours, positive blood cultures were noted in 3.9% and 4.1%, respectively. However, only four cases of bacteremia were considered to be clinically significant (1 × *Staphylococcus aureus*, 3 × *Klebsiella* spp.). Moreover, all of these cases were related most likely to an intravenous line and not to the cardiac procedure itself. The data of Banai et al. suggest that clinically significant bacteremia is a rare complication of cardiac catheterization and also of PCI (explaining the low incidence of coronary stent infection; see below).

A further prospective study *(11)* investigated the frequency of bacteremia after more complex PCI in 147 consecutive patients. Procedures included balloon angioplasty, cutting balloon angioplasty, rotational coronary atherectomy, and single and multiple stent implantations. All procedures were performed via the femoral route. Blood cultures were taken immediately at the end of the procedure from the side arm of the arterial sheath. A second blood culture was taken after 12 hours prior to sheath removal. 17.7% of the patients had bacteria isolated from the first blood culture with coagulase-negative staphylococci being the most common microorganisms (57.7%). After 12 hours, 12.0% of the patients yielded microorganisms in the blood culture; 70.5% of them were coagulase-negative staphylococci. Four of the 147 patients developed a temperature >38°C; all had negative blood cultures. No patient developed clinical evidence of septicemia, endarteritis, or endocarditis during hospital stay or after discharge. The authors suggested that the relatively high incidence of bacteremia was due to the complex nature of PCI. However, the statistical analysis did not show a difference in the number of devices used in those patients with and in those without bacteremia.

Percutaneous Transluminal Coronary Angioplasty

PTCA today is one of the most common procedures in nonsurgical invasive cardiology.

No infection was reported during early and long-term follow-up (at least 1 year) of 3,079 patients after coronary angioplasty in the early 1980s *(12)*. In a prospective study, 164 PTCAs resulted in one *S. aureus* infection (0.6%) that could be related to the procedure *(13)*.

Malanoski et al. *(14)* identified a risk of 0.25% for *S. aureus* bacteremia (SAB) among 1,944 PTCA procedures performed during 25 months at one institution. Cleveland and Gelfand *(15)* summarized the reported cases of invasive staphylococcal infections associated with PTCA and described three more patients with invasive staphylococcal disease after PTCA of which two patients had received single intravenous antibiotic prophylaxis with cefazolin. This may well be explained by the fact that the predominant risk of infection may not have been the procedure itself but more likely the retention of the femoral sheath for more than 24 hours.

McCready et al. *(16)* noted that septic complications after cardiac catheterization and PTCA are quite uncommon, but they described nine cases of septic complications after this procedure resulting in two deaths. Their study suggests that repeated puncture of the same femoral artery and the femoral artery sheath being left in for more than 1 day are risk factors for septic complications *(15,16)*. Cardiac abscess after PTCA has also been described in a patient in whom a problematic and repeated procedure probably led to a direct colonization and subsequent infection of an intimal dissection of the right coronary artery *(17)*.

Siddiqui and Lester *(18)* described a case of septic arthritis and bilateral endogenous endophthalmitis associated with PTCA. Several cases of septic endarteritis with *S. aureus* after PTCA have been described by different authors *(19,20)*. In another case report, an epidural abscess occurred in a patient after PTCA. The explanation was that the residual arterial sheath, whose tip was near the aortic bifurcation, was injected with an infected bolus, thus facilitating infection through the lumbar radicular arteries *(21)*. The absence of specific signs may easily cause a delay in recognizing the infection *(18,21,22)*. As mentioned above, it has been considered that retention of the sheath for more than 24 hours could be a risk factor for infection. However, prospective studies are not available on this issue *(15,23)*. Salinas et al. *(24)* reported a case of infective coronary aneurysms 7 days after a balloon angioplasty.

Endocarditis following PTCA is such a rare complication that there are merely individual case reports. Wang et al. *(25)* reported a case of *Candida parapsilosis* endocarditis. Barbetseas et al. *(26)* reported a case of a patient with infective endocarditis of a prosthetic valve in the aortic position after receiving PTCA. Shibata et al. *(27)* reported a case of a 73-year-old man who developed infectious endocarditis caused by *S. aureus* after PTCA. A postmortem examination revealed multiple myocardial microabscesses and myocardial infarction resulting from an embolic vegetation.

Although infections after PTCA are rare, some have resulted in death *(28)*. Infections may become evident several weeks after the procedure *(14)*. Even ultrasonography and computed tomography may fail to reveal vascular infection, and, when there is clinical suspicion of infection, it may be prudent to initiate early surgical exploration *(29)*. Some authors recommend use of the contralateral inguinal site if PTCA is to follow a recent catheterization *(15–17,30,31)*, whereas others found no correlation between ipsilateral inguinal puncture and infectious complications *(13)*. At present, this question cannot be answered, because none of the cited studies have the statistical power to be able to detect significant differences between contralateral and ipsilateral repuncture.

Risk factors for bacteremia and other infectious complications during cardiac catheterization, mainly during PTCA, are age older than 60 years, congestive heart failure, duration of procedure, number of catheterizations at the same site, difficult vascular access, and an arterial sheath in place for more than 1 day (8,*16*,32,*33*,*34*). The most common microorganisms that cause PTCA-related bacteremia are *S. aureus*, coagulase-negative staphylococci, and group B streptococci (32).

Cutting Balloon Angioplasty Kobeiter et al. *(35)* monitored the long-term results in 19 patients undergoing cutting balloon angioplasty over a period of 32 months. They observed no case of infection. The authors postulate a randomized trial to be necessary to confirm the favorable results.

Coronary Stent Implantation

Gunther et al. *(36)* described in 1993 the first case of lethal complications resulting from a myocardial abscess near the stent in the right coronary artery. A second case of fatal outcome resulting from stent infection with *Pseudomonas aeruginosa,* which led to infective mitral endocarditis and saccular aneurysm of the coronary artery, was described by Leroy et al. *(37)*. Studies in a swine model suggest that metallic stents have the potential of becoming infected after bacterial challenge unlike arteries that have undergone angioplasty without stenting *(38)*. Seven stent-artery complexes implanted in the iliac arteries of 14 swine were culture positive after an intravenous bacterial challenge with *S. aureus,* whereas only 1 of 14 arteries that underwent angioplasty were positive for *S. aureus* ($p = .03$) *(38)*. The pathophysiology behind the stent infection is unknown; perhaps the stents or endothelial injury served as a nidus for bacterial adherence. Bouchart et al. *(39)* suggested that multiple repeat procedures through the same arterial sheath may increase the risk for bacterial infection of the coronary stent.

Dieter et al. *(40)* reported the case of a patient who developed an infected aortic aneurysm after placement of a coronary artery stent. They pointed out that infectious complications have been rare, but that the associated mortality is alarmingly high (41). The authors analyzed four cases of stent infections, two with *P. aeruginosa* and two with *S. aureus* as causative microorganisms. Despite aggressive measures (surgical removal of the infected stent and artery complex), three of the four patients died. The authors pointed out, that the clinician must be sensitive to fever, return of angina pectoris, and bacteremia in patients who have undergone coronary stent placement. With regard to the generally low infection rate, the prophylactic use of antibiotics is not recommended.

Recently also Schoenkerman et al. (42) described stent infections as a rare, but dramatic sequela of coronary stent implantation. They reported three cases of infections, two with mycotic aneurysms and one with purulent pericarditis. Two of these three cases were associated with drug-eluting stents (DES). In all cases, *S. aureus* was the causative microorganism. The authors suggested the possibility that recent infection with *S. aureus* within 16 days prior to PCI may be an additional risk factor for the complication of coronary stent infection.

Kaufmann et al. *(43)* reviewed all published cases of coronary stent infections, that is, all patients who presented with symptoms of infection within the first 4 weeks after PCI. They stated that, although the implantation of medical devices in general represents one of the most important risk factors for healthcare-associated infections, the reports of coronary stent infections are exceedingly rare. The authors summarized 10 case reports. One patient received a DES; all other patients had a bare metal stent (BMS) implanted. In seven patients, *S. aureus* was the causative microorganism, and in four the stent was completely or partially removed. Three patients died despite initiation of antibiotic and surgical treatment. The very low number of published cases suggests that coronary stent infections represent a rather uncommon complication of PCI. But the exact incidence of infection is unknown.

According to Kaufmann et al. *(43)*, fever is the hallmark of coronary stent infection. Chest pain is present in only half of the patients. They concluded that blood cultures should be taken in all patients presenting with fever within the first (four) weeks after stent implantation even in the absence of chest pain, ECG abnormalities, or elevation of cardiac enzymes.

Infections in Drug-Eluting Stents Kaufmann et al. *(43)* speculated that DES, introduced in the first decade, may predispose more to infection than BMS because of their immunomodulating and antiproliferative effects. They stated, however, that this seems not to be the case. There are only a few documented cases of stent infection after DES insertion. Recently, Lee et al. (44) found in their retrospective study on 1,023 consecutive patients who underwent PCI with DES a mortality of 9.4%. Of the 96 patients who died, no one died from PCI-related infection.

Aoki et al. *(45)* reviewed all published case reports of coronary artery aneurysms after DES implantation since 2004 and compared them with published case reports of aneurysms after BMS implantation. They stated that the incidence of coronary artery aneurysms after DES implantation is low within the first 9 months (aneurysms have been reported from 3 days to up to 4 years) with an incidence of 0.2% to 2.3%. This is a rate similar to the aneurysm rate after BMS implantation (0.3% to 3.9%). The clinical course is variable ranging from natural resolution to life-threatening complications.

Gonda et al. *(46)* reported the unique case of a DES infection with MRSA in a 75-year-old male 11 months after the procedure. In the cardiac magnetic resonance angiography, they found a nonenhancing fluid collection surrounding the DES, suggesting the presence of an abscess, which was confirmed in the following surgical intervention.

Intraaortic Balloon Pump

In an early study published in 1978, the overall complication rate for 100 consecutive patients treated with the IBP was 23%, with five patients developing surgical site infections and two developing septicemia *(47)*. Surgical site problems contributed to the death of one patient. Another patient died with septicemia and an infected aortotomy closure site 4.5 months after the original procedure.

Goldberg et al. *(48)* compared the percutaneous and surgical techniques of IBP insertion in 101 patients. In the percutaneous group (51 patients), no infection developed, but, in the surgical group, three patients developed sepsis with bacteremia (including one patient who required vein patch repair of the femoral artery and one patient who developed a surgical site infection requiring debridement).

An outbreak of *Pseudomonas cepacia* bacteremia associated with a contaminated water reservoir of an IBP was reported by Rutala et al. *(49)*.

Forty-five patients who died after insertion of an intraaortic balloon device were studied at necropsy *(50)*. Thirty-six percent had one or more complications related to the use of the device, one of which was a local surgical site infection not suspected during life. In two other patients in whom the balloon was implanted for septic shock, there was no evidence of bacterial seeding of either the balloon catheter or the prosthetic introducer graft. In a study of 240 consecutive percutaneous intraaortic balloon counterpulsations, Eltchaninoff et al. *(51)* identified

only one case of *S. aureus* bloodstream infection and one superficial infection. In the retrospective study by Meco et al. (52), 7 of 116 patients (6%) requiring postoperative IBP support had infection of the insertion site.

Yang et al. *(53)* investigated 112 used intraaortic balloons for physical integrity, gas leakage, mechanical performance, surface chemistry and morphology, and physical stability. These devices were all used clinically only once, and the duration of use *in vivo* ranged from 6 to 312 hours. Macroscopic examination of the balloons and the outer catheters revealed no obvious change in either shape or color. No discernible abrasions or cracks were observed. However, 61% of the balloons were creased and 40% of the central lumina and 21% of the sheaths showed visible bending flaws. Moreover, 65% of the balloons and 38% of the central lumina were contaminated by visible residual organic debris. The authors concluded that the presence of residual organic debris that cannot be eliminated is an indication that such intraaortic balloons should not be reused.

In their prospective study, Crystal et al. *(54)* found an incidence of fever of 47%, true bacteremia of 15%, and sepsis of 12% in 60 patients treated with an intraaortic balloon counterpulsation pump. The authors suggested evaluating the benefit of antibiotic prophylaxis. However, no studies addressing this issue have been published so far.

Laser Thermal Angioplasty

Laser thermal–assisted balloon angioplasty is used in the treatment of patients with advanced peripheral vascular disease and in high-risk patients who are poor candidates for operative reconstructions. White et al. *(55)* followed 28 patients, including 27 who had advanced peripheral vascular disease, for 3 years after laser thermal-assisted balloon angioplasty. Eighteen patients were successfully recanalized, but five amputations were required within 1 month and another six were needed between 8 and 12 months. Early amputations were necessitated by failure of wound healing. Whether this was due to infection, however, was not mentioned in the report.

Diethrich *(56)* reviewed his experience in treating 1,849 lesions in 894 patients and found no infection. The most common surgical procedures performed were laser angioplasty, patch angioplasty, arterectomy, thrombectomy, femoral-popliteal bypass, and profundoplasty. If laser-assisted angioplasty, however, is performed in the treatment of prosthetic graft stenosis, the wound infection rate is higher. Diethrich et al. *(57)* followed 25 symptomatic patients with 28 peripheral prosthetic arterial bypass grafts; two patients suffered from recurrent thrombosis and one developed an inexplicable graft infection 5 months after laser treatment. The latter patient, however, had undergone graft thrombectomy elsewhere 3 months before laser therapy, and the 5-month interval between angioplasty and the identification of the infection would make the laser's role in the etiology doubtful.

Vascular Closure Devices

Bacteremia after PCI is estimated to range between 4.6% (10) and 17.7% (11) depending on the complexity of the PCI performed. According to Ramsdale et al. *(11)*, these data support the routine removal of femoral artery sheaths early after PCI, now that effective femoral artery closure devices are available. However, it should be mentioned that infectious complications with percutaneous vascular closure devices are reported. Franco et al. *(58)* presented the case of a 43-year-old male patient undergoing cardiac catheterization and closure with a vascular closure device. He required a second catheterization with access gained on the same side and developed bacteremia and an infected hematoma with erosion of the femoral artery. A second case involved a 57-year-old male patient, who developed a localized infection over the accessed groin site. The authors stated that the overall infectious complication rate of closure devices was 0.3%.

A meta-analysis of 31 prospective randomized trials (59) including 7,528 patients investigated the rate of complications comparing vascular closure devices and manual/mechanical compression after diagnostic angiography and/or endovascular procedures. The use of vascular closure devices was associated with a significantly shorter time of hemostasis, but also with a significantly increased risk of groin infection (0.9% vs. 0.3%; RR 2.49, CI 95% 1.06–5.88 [12 studies including 3,210 patients]).

Prophylactic Antibiotics in PCI

With regard to the findings in their prospective study, Ramsdale et al. (see above, 11) stated that routine antibiotic prophylaxis prior to PCI is routinely not necessary. However, patients who are at increased risk of infective endocarditis such as those with valvular heart disease should receive prophylactic antibiotics prior to PCI ("single shot"). Furthermore, extra care should be taken with aseptic technique, and the femoral artery sheaths should be removed early after the procedure.

Infection Control Guidelines for the Cardiac Catheterization Laboratory

In 2006, the Members of the Catheterization Lab Performance Standard Committee for the Society for Cardiovascular Angiography and Interventions (60) published infection control guidelines for the cardiac catheterization laboratory. Based on the corresponding guidelines of the Centers for Disease Control and Prevention, this committee outlined recommendations regarding hair removal, skin cleaning and disinfection, drapes, the use of antibiotics, wound dressings, hand hygiene, the use of gloves and gowns, caps, masks, eye protection, and vaccination of the staff. Cleaning of the laboratory environment, the ventilation system, the handling of fixed and disposable laboratory equipment, and the disposal of waste are further topics that were addressed. In addition, catheterization technique, sheath removal, and vascular closure devices are laboratory-specific aspects covered by this guideline.

INFECTIONS ASSOCIATED WITH IMPLANTABLE DEVICES IN CARDIOLOGY

Pacemaker Insertion

Insertion in Children Pacemaker treatment is more complicated in children than in adults, largely because of electrode problems. If infections such as recurrent septicemia occur, the whole system usually has to be removed *(61)*.

Walsh et al. *(62)* reviewed their 21-year experience with pacemaker implantation in children. Forty-one patients

aged 11 days to 19 years at initial pacemaker implantation were followed up to 248 months. Complications included infection in six cases, and one patient died of a pacemaker-associated infection. Between 1971 and 1986, 85 pacemakers were implanted at the St. Justine Hospital in Montreal in 57 patients then aged from 1 day to 23 years (mean, 10.3 years). The patients were followed for periods ranging from 15 days to 13.5 years. Only one patient developed a pacemaker-associated infection *(63)*.

Nordlander et al. *(64)* reviewed their clinical experience of pacemaker treatment in children. Pacemaker systems had been implanted in 23 children aged 2 days to 14 years since 1983. Only three local infections developed. They concluded that endocardial pacing is the method of choice even for small children.

Pacemakers can even be implanted in newborns and very small infants. Villain et al. *(65)* implanted pacemakers in neonates. In eight children, a permanent pacemaker was implanted in the first 2 days of life, and, in six children, the pacemaker was implanted at the age of 2 to 3 months. Only one pacemaker had to be replaced because of infection at 28 months. In another investigation, 24 children, 15 kg or less in weight, underwent implantation of a permanent pacemaker using the transvenous technique. During a median follow-up period of 3 years and 6 months, two children developed infection *(66)*.

Cohen et al. (67) evaluated possible predictors of pacemaker infections in children. They reported a total of 7.8% infections (30 infections in 385 pacemaker implantations). In a multivariate analysis, trisomy 21 and pacemaker revisions were found to be predictors of infection.

Insertion in Adults Several older publications described infectious complications of pacemakers in adults *(68–73)*. The time from insertion to infection varied from 7 to 31 days, and the only causative microorganisms were *S. aureus* and *S. epidermidis*. Pocket infections usually occurred earlier than septicemia, and the incidence of septicemia was much lower than that of pocket infections. Later series have shown infection rates between 0.6% and 2.1% *(74,75)*. In their case report and review of the literature, Voet et al. *(76)* reported an incidence between 0.3% and 12.6%. This may involve infection of the pocket or the electrodes and may be associated with bacteremia with or without endocarditis. Systemic factors contributing to a higher incidence of infection are diabetes mellitus, thin skin, the use of corticosteroids, age, intravenous catheters, neoplasms, the use of anticoagulants, temporary pacing, dermatologic diseases, and other infectious foci.

In their retrospective risk factor analysis of permanent pacemaker infection in 29 case patients and 58 control subjects, Sohail et al. (77) used multivariable logistic regression analysis and observed that long-term corticosteroid use and the presence of >2 pacing leads were independent risk factors for infection. Long-term corticosteroid use was defined as ≥20 mg of prednisone (or equivalent), administered for ≥1 month during the preceding year. Twenty-four of 29 infected patients had pocket infections, and 3 had pacemaker related endocarditis. *Staphylococcus* species (69%) were the most common pathogens.

Klug et al. (78) prospectively recorded all infectious complications in 6,319 consecutive patients who were recipients of pacemakers or cardioverter-defibrillators. At 12 months, device-related infections were reported in 42 patients (0.68%). In the multivariable logistic regression analysis, the occurrence of infection was positively correlated with fever within 24 hours before the implantation (OR 5.83; CI 95% 2.0–16.98), use of temporary pacing before implantation (OR 2.46; CI 95% 1.09–5.13), and early reinterventions (OR 15.04; CI 95% 6.7–33.73). Immunosuppression, diabetes mellitus, and the use of anticoagulants or skin diseases could not be confirmed as risk factors. The median time to infection was 52 days. Implantation of a new system and antibiotic prophylaxis protected against infection.

One of the most serious infectious complications is pacemaker endocarditis. Arber et al. *(79)* reported 44 cases and reviewed the literature. Kurup et al. *(80)* reported the rare case of *Candida tropicalis* pacemaker endocarditis. Between 1980 and 2000, 7 of 1,920 patients with pacemaker implantation developed endocarditis in the study by Erdinler et al. *(81)*. The most common pathogen was *S. aureus*. Mezilis et al. *(82)* described two patients with metastatic pacemaker infections, one caused by *P. aeruginosa* 5 months after implantation and a second by *Streptococcus pneumoniae* 8 years after implantation. Pacemaker infections can also be caused by rare microorganisms such as *Staphylococcus schleiferi*, a member of the human skin flora *(83)*, or by *Mycobacterium fortuitum (84)*. A prospective study by Da Costa et al. *(85)* compared microorganisms isolated at the time of insertion and any infective complication by using ribotyping. Their study supported the hypothesis that pacemaker-related infections are mainly due to local contamination. In general, early infections after implantation tend to be caused by *S. aureus,* whereas late infections are caused by coagulase-negative staphylococci *(76)*. The same most common microorganisms were also found by Margey et al. (86) in their retrospective study over a period of 7 years and a total of 2,029 permanent pacemakers and 1,076 ICD implantations. The infection rate was 1.25%. *S. aureus* was the causative microorganism in 30.8% and coagulase-negative staphylococci in 20.5% of the cases. Important to note is that the rate of infection with methicillin-resistant *S. aureus* (MRSA) was 5.1%. In the univariate comparison of cardiac device infection survivors and those dying from infection, the presence of documented MRSA infection was significantly different between the groups with MRSA predicting mortality ($p < .004$; RR 37.0; CI 95% 5.3–250).

Although most infections have been limited to the pocket, pacemaker endocarditis accounts for approximately 10% of pacemaker infections (87).

Implantable Cardioverter-Defibrillator

The automatic implantable cardioverter-defibrillator (ICD) has been found to be useful in the management of life-threatening ventricular arrhythmias. Marchlinski et al. *(88)* reported that primary infectious complications were associated with 6% of cardioverter-defibrillator implantations. In another series by Marchlinski et al. *(89)* following 26 patients for 13 months, 1 patient developed a superficial incisional surgical site infection 14 days after device implantation and 1 patient acquired a late infection

of the generator pocket 3 months after repositioning of a migrated lead and 14 months after initial generator placement. Treatment necessitated removal of both the generator and leads. A partial removal is reserved for patients in whom the risk of complete removal is too high and infection is confined to a part of the ICD (i.e., generator only) *(90)*.

Mela et al. *(91)* stated that infection is an uncommon (0–6.7% reported in the literature) but serious complication after ICD implantation, because complete device removal is often necessary. In their review of 1,700 procedures, they found a total of 21 ICD-related infections (1.2%); one-fourth of these had systemic signs of infection. Patients with abdominal systems had significantly more infections than patients with pectoral systems (3.2% vs. 0.5%). In a prospective study, Chamis et al. *(92)* determined an incidence of 45.4% (15/33) cardiac device–associated infections among patients with an ICD or a permanent pacemaker who developed *S. aureus* bacteremia (SAB). In patients with early SAB (<1 year after device placement), they found that 75% of the events were related to the device; in patients with late SAB (>1 year), 28.5% were confirmed to be related to the ICD or pacemaker (43% were possible cardiac device infections).

The most common pathogens of infections related to ICD are coagulase-negative staphylococci and *S. aureus* (68% and 23%, respectively, in the study by Chua et al. [*93*]).

The decision whether or not to reimplant an ICD after removal of an infected one has been controversial. Some authors recommend reimplantation as early as 36 hours after explantation in patients with only local symptoms of infection. The need for reimplantation should be reassessed in every case *(93)*. With regard to infections, but also to other complications, the single-chamber ICD (SC-ICD) seems to be superior to the dual-chamber ICD (DC-ICD), which may be explainable by the longer operation time and the placement of the second lead of the DC-ICD (infectious complications: 4.1% with the DC-ICD vs. 0% with the SC-ICD) *(94)*.

The greater risk of infection concerning more complex devices (dual/triple chamber vs. single ICD and pacemaker [see below]) was also documented by Nery et al. (95) in their retrospective study on 2,417 patients who had pacemaker or ICD implantation during a period of approximately 4 years. A total of 24 infections were identified (1%): 60% of these were diagnosed within 90 days of the last surgical procedure. Frequent clinical presentations were pocket infection (15/24) and bacteremia (5/24). Besides the above-mentioned greater risk regarding more complex devices, univariate analysis showed that patients with infection were more likely to have had a device replacement, rather than a new implant, and were more likely to have had a prior lead dislodgement. Of the 24 patients with device-related infection, 2 were diagnosed with a superficial wound infection. Complete system removal was performed in the 22 patients with deep infection. The authors stated that to date, there are significant data that support the premise that device replacement and/or pocket reoperation are the strongest independent risk factors for cardiac device infection.

In their retrospective study, Remmelts et al. (96) investigated whether there is a difference in the infection rate depending on the location where an implantable cardioverter-defibrillator is inserted (operating room vs. cardiac catheterization laboratory). Infections were defined as pocket infection or device-related endocarditis. Six hundred sixty-seven consecutive patients were reviewed (366 with implantation in the operating room and 301 in the cardiac catheterization laboratory). No difference in the infection rate was found.

Antibiotic Prophylaxis before the Implantation of Pacemakers and Cardioverter-Defibrillators

Several earlier studies on the merits of antibiotic prophylaxis at the time of permanent pacemaker implantation have yielded inconclusive results. A meta-analysis by Da Costa *(97)* of all available randomized trials (up to 1998) to evaluate the effectiveness of this measure to reduce infection rates after permanent pacemaker implantation suggested that systemic antibiotic prophylaxis significantly reduces the incidence of potentially serious infective complications. The studies support the use of prophylactic antibiotics at the time of pacemaker insertion to prevent short-term pocket infection, skin erosion, or septicemia *(97)*. A recent double-blinded trial (98) examined the benefit of prophylactic antibiotics (1 g of cefazolin vs. placebo) immediately before the implantation of a pacemaker or a cardioverter-defibrillator (or generator replacement) in 1,000 consecutive patients. The primary end point was any evidence of infection at the surgical incision, or systemic infection related to the procedure. The trial was interrupted after 649 enrolled patients due to a significant difference in favor of the antibiotic arm (0.63% vs. 3.28%; RR 0.19; $p = .016$). Patients with a high risk of infection, e.g., patients with prosthetic heart valves with a potentially higher risk for endocarditis, and patients who needed early reintervention due to lead dislodgement, were excluded from this study.

Management of Cardiovascular Implantable Electronic Device (CIED) Infections—A Scientific Statement of the American Heart Association (AHA)

In 2010, the AHA (87) published a scientific statement as an update on CIED infections and their management. The evidence-based recommendations were categorized into a classification system estimating the size of treatment effect and the level of evidence.

The classification system ranges from class I (benefit >>> risk) over class IIa (benefit >> risk) and class IIb (benefit ≥ risk) to class III (risk ≥ benefit). The level of evidence is defined as level A (data derived from multiple randomized clinical trials or meta-analysis), level B (data derived from a single randomized trial or nonrandomized studies), and level C (consensus opinion of experts, case studies, standard of care).

The most important recommendations are summarized as follows:

Diagnosis of CIED and Associated Complications

- At least two sets of blood cultures should be drawn before prompt initiation of antimicrobial therapy (IC).
- Generator-pocket tissue Gram stain and culture and lead-tip culture should be obtained (IC).

- A TEE should be done in patients who have had recent antimicrobial therapy before blood cultures were obtained (IC).
- Adults suspected of having CIED-related endocarditis should undergo TEE, even if TTE has demonstrated lead-adherent masses. In pediatric patients with good views, TTE may be sufficient (IB).

Antimicrobial Management

- The antimicrobial therapy should be based on the identification and *in vitro* susceptibility results of the causative pathogen (IB).
- Duration of therapy should be 10 to 14 days after CIED removal for pocket-site infection (IC), at least 14 days after CIED removal for bloodstream infection (IC), at least 4 to 6 weeks for complicated infection (endocarditis, septic thrombophlebitis, osteomyelitis, persisting bloodstream infection despite device removal) (IB).

Removal of Infected CIED

- Device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis (IA), for all patients with CIED pocket infection (IB), for all patients with valvular endocarditis without definite involvement of the leads and/or device (IB), and for all patients with occult staphylococcal bacteremia (IB).

New CIED Implantation after Removal of an Infected CIED

- A careful evaluation whether there is need for a new device should be done (IC).
- The replacement device implantation should not be ipsilateral to the extraction site. Alternative locations include the contralateral side, the iliac vein, and epicardial implantation (IC).

Antimicrobial Prophylaxis

- Prophylaxis with an antibiotic that has *in vitro* activity against staphylococci should be administered (IA).

INFECTIONS AFTER MINIMALLY INVASIVE VALVE SURGERY

Valve surgeries, including valve repairs and valve replacements, are the most common type of minimally invasive surgery in cardiology, which is increasingly utilized. Studies comparing minimally invasive and conventional median sternotomy approaches for primary valve surgery have demonstrated similar early mortality. However, less need for transfusion and better postoperative pulmonary function have been observed with minimally invasive surgery *(99)*. In their prospective study comparing the outcome of 337 sternotomies (160 undergoing aortic valve and 177 mitral valve surgery) and 161 minithoracotomies (61 aortic valve and 100 mitral valve surgery), Sharony et al. *(99)* found a significant difference with regard to the occurrence of deep wound infections (0% in the minimal surgery group vs. 2.4% in the sternotomy group [$p = .05$]). Additionally, hospital length of stay was shorter and the 5-year survival rate was borderline favorable in the minimally invasive group.

A retrospective review of 1,005 patients who underwent minimally invasive aortic valve operations (aortic root replacement, ascending aortic replacement, reoperative surgery) was done by Tabata et al. (100). The incidence of deep sternal wound infection was 0.5%, and for pneumonia 1.3%. In the subgroup of the elderly (≥80 years), the rate of deep wound infection was 1.1% (2/179). The authors concluded that the minimal access approaches in aortic valve surgery are safe and feasible with excellent outcomes.

For mitral valve surgery and its minimal access approach, Modi et al. (101) reviewed the literature and included one randomized controlled trial and 10 case–control studies published between 1998 and 2005 in their meta-analysis. Three studies reported data for septic wound complications *(102–104)*. There was a significant difference comparing minithoracotomy and conventional sternotomy in the study of Grossi et al. (*103*) (0.9% vs. 5.7%; $p = .05$). The incidence of septic wound complications increased in the elderly (≥70 years) to 1.8% and 7.7%, respectively *(102)*. One of the three studies reported no significant difference *(104)*. In the synopsis of the available studies, Modi et al. (101) stated that minimal mitral valve surgery is associated with less morbidity in terms of reduced need for reoperation for bleeding, a trend to shorter hospital stay, less pain, and faster return to preoperative function levels than conventional sternotomy-based surgery.

A recently published propensity-matched comparison of 2,124 patients undergoing mitral valve surgery through a minimally invasive approach and 1,047 patients undergoing a conventional sternotomy found a similar infection rate between both groups regarding 590 well-matched patient pairs (56% of cases) *(105)*. Overall, the authors reported a deep sternal wound infection rate of 14/2,124 (0.66%) versus 4/1,047 (0.38%) and in the matched patients of 6/590 (1.02% in the minimally invasive group) versus 4/590 (0.68% in the conventional group). Regarding infectious complications like sepsis and septicemia, there was a significant difference overall (17/2,124 [0.8%] vs. 31/1,047 [3.0%] with $p < .0001$). This significance could not be documented regarding the propensity-matched patients (8/590, 1.4% in the minimally invasive group vs. 12/590, 2.0% in the conventional group).

REUSE OF DISPOSABLE CARDIAC CATHETERS

In Canada and many European countries, the reuse of disposable catheters has been common practice until the end of the last century. Today, the legal situation in Europe is quite diverse. In some European states, reprocessing is regulated or accepted if validated procedures/high-quality standards are strictly adhered to by reprocessors (as in Germany). Other states such as the United Kingdom or France do not recommend reprocessing. Consequently, reprocessors cannot offer their services in these states. However, it is likely that uncontrolled reprocessing is widely performed.

In the United States, this practice had been discontinued mainly because of legal concerns, but some centers have started to reuse cardiac catheters involving professional

third-party reprocessors *(106,107)*. Several studies have examined the risks of infection with reuse of catheters. Jacobson et al. *(108)* prospectively studied 341 patients who underwent cardiac catheterization and/or coronary angiography to examine the correlation of adverse effects with the number of times catheters were cleaned, sterilized with ethylene oxide (ETO), and reused (maximum of four uses and less when any defects were noted). The overall incidences of adverse reactions were hypotension 27%, fever 3%, chills 3% (all three 0.6%). There were no statistically significant increases in these reactions associated with the reuse of catheters. The authors concluded that careful processing and reuse of catheters did not obviously increase the risk of infection.

Frank et al. *(109)* prospectively studied 414 patients who had undergone cardiac catheterization or angiography to determine whether there was an increased risk of bacterial contamination or pyrogenic reactions in patients who had procedures with reused cardiac catheters. One hundred sixty-one patients were studied with 426 single-use catheters and 152 with 384 multiple-use catheters that were resterilized once or twice, and 101 patients with 325 multiple-use catheters reprocessed up to ten times. No significant differences between the three groups with respect to fever could be observed. Infectious complications associated with cardiac catheterization or angiography did not occur in any case. It was concluded that careful cleaning, disinfection, and resterilization of intravascular catheters with ETO do not increase the risk of infection. O'Donoghue and Platia *(110)* surveyed retrospectively 13,395 electrophysiologic (EP) studies using 44,950 reused pacing catheters in nine medical centers. They found one superficial skin infection and eight positive blood cultures. However, blood cultures were only performed when infection was suspected, and no information was given on the denominator. The authors concluded that infections were very rare and not significantly different in the catheter reuse group (1,245 EP studies; 3,125 catheters; 3 medical centers) compared with the single-use group and that reuse was safe and cost-effective.

Few studies in the literature provide information on specifically how reuse affects catheter material and function. Zapf et al. *(111)* presented data concerning mechanical stability of polyethylene catheters (elasticity and maximum tensile strength) when exposed up to 60 times to ETO and concluded that reuse of catheters seems to be possible without loss of mechanical safety. Bentolila et al. *(112)* studied the effects of reuse on the physical characteristics of five types of angiographic catheters with special emphasis on the possibility that reuse could be associated with blood contamination by loose particles. Samples were taken both from new catheters and from catheters used up to 10 times. Routine cleaning and sterilization procedures showed no adverse effect on the maximum tensile strength and elongation at break of catheters. Some biologic debris was occasionally present in reused catheters. On the other hand, new catheters exhibited a substantially higher loose particle count than catheters that had been properly cleaned and resterilized.

One of the main concerns with using resterilized catheters is reaction to endotoxin, which may cause chills, fever, and hypotension. Lee et al. *(113)* reported reactions in 13% (8/62) of patients undergoing cardiac catheterization over a 3-month period. New catheters, however, may also contain traces of endotoxin. To establish a baseline for the endotoxin contamination of commercially prepared angiographic catheters, Kundsin and Walter *(114)* purchased 106 catheters from three manufacturers that were packaged, sterile, and ready for insertion. All catheters contained endotoxin ranging from 6.9 to 55.6 pg per catheter. Twenty-five new sterile catheters were pyrogenic, whereas 106 were not. The authors also tested 13 catheters that were reprocessed in a cardiac catheterization laboratory. All were found to be pyrogenic, containing as much as 7,800 pg per catheter of endotoxin. Recommendations were then made for processing catheters to eliminate pyrogens.

Buchwalsky et al. *(115)* reported experience in 50,000 interventions, including PTCA, using different reprocessed cardiac catheters. Neither the duration of the intervention nor the catheter-dependent complication rates increased for reused in comparison with single-use catheters. Avitall et al. *(116)* prospectively investigated, over a period of 1 year, the electrical, mechanical, and physical changes after reuse of 69 catheters used in 336 ablation procedures and concluded that they can be reused an average of five times if careful examination of the ablation tip electrode under appropriate magnification (×30) is performed before each use. The catheters should also be tested for deflection and electrical integrity.

Recommendations for Reprocessing of Cardiac Catheters

In the United States, the Food and Drug Administration (FDA) announced in 2000 that it intended to phase in active enforcement of all its premarket and postmarket requirements for devices to ensure that the cleaning, disinfection, and sterilization of reprocessed single-use devices (SUDs) afforded the same level of safety and effectiveness for patients as new catheters did (*www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofSingle-UseDevices/default.htm*). Postmarket requirements such as registration, listing, medical device reporting, medical device tracking, medical device corrections and removals, the quality system regulation, and labeling are applicable to third-party and hospital reprocessors. This policy led to the comment of a "requiem for reuse of SUDs in U.S. hospitals" *(117)*. In Germany, the Robert Koch-Institute (RKI) issued its guideline on reprocessing of medical devices (*www.rki.de/cln_151/nn_206124/DE/Content/Infekt/Krankenhaushygiene/Kommission/kommission__node.html?__nnn=true*). According to this guideline, cardiac catheters are ranked as highly critical medical devices, which require special caution when such devices are reprocessed, and an active external quality control system is required to be in place.

Cleaning and Sterilizing of Cardiac Catheters If hospitals decide to reprocess cardiac catheters within their own facilities, the following process may be applied. If these recommendations are followed carefully and are accompanied by strict quality controls, no infectious complications or endotoxic reactions should occur. Resterilization bears the potential for residual chemical contamination with ETO *(118)*. Therefore, residual ETO levels may be substantially reduced by allowing a 14-day waiting period after resterilization or by

incorporating a detoxification period immediately after ETO exposure [repeated cycles of steam flushes *(119)*].

- Flush immediately after use with water or heparinized saline and soak for 20 to 25 minutes.
- Remove and brush the tip and soak in a detergent solution for 30 minutes.
- Push guidewire gently through the catheter lumen to remove any biologic material or debris.
- Hand wash and rinse for 5 minutes with detergent solution and rinse intensely with sterile water.
- Blow completely dry with compressed air.
- Inspect carefully for any damage or defect or the presence of organic matter or debris and mark with an indelible marking pen.
- Repackage in sealed envelope and add proper identification.
- Sterilize with ETO.
- Aerate catheters for at least 14 days at room temperature.

Reuse of Coronary Angioplasty Catheters

One of the pioneer studies on reuse of PTCA catheters was done by Plante et al. *(120)*. In this study, two centers were compared: one using new and the other reused catheters. Comparison of the centers led to the conclusion that reuse was associated with a higher rate of adverse clinical events (7.8% vs. 3.8%). This result is in contrast to findings published by Browne et al. *(106)*, who investigated the reuse of PTCA balloon catheters. The study enrolled 107 patients; 106 had a successful laboratory outcome, and 1 required coronary artery bypass graft surgery after failed rescue stenting. The authors concluded that reuse of disposable coronary angioplasty catheters after carefully controlled reprocessing appeared to be safe and effective with success rates similar to those of new products and no detectable sacrifice in performance.

With respect to reuse of PTCA equipment, Krause et al. (121) reviewed the literature, interpreted the state of knowledge (2000), and presented the main arguments in favor and against reuse. According to the authors, the following conclusions can be drawn:

1. Even assuming that no additional clinical risk is associated with PTCA-catheter reuse, the decision to adopt or reject a reuse policy has to be based on the individual situation at each hospital. Factors to consider include technical and personnel resources of the institution, frequency of PTCA procedures, and the economical and legal environments.
2. The review of the literature showed that authors tend to come to two contradictory conclusions as far as patient safety is concerned. One group of authors claimed that PTCA catheters are already being reused in many countries and that there is no evidence for an increased risk. The other group sees a risk in the presence of organic debris in reused catheters, which raises both health and legal issues.

Krause et al. stated that it is unlikely that clinical trials will ever come up with a clear answer to the problem (121).

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CHAPTER 62

Infection Risks of Endoscopy

John Holton

Endoscopic procedures are used worldwide for both diagnostic and therapeutic interventions. Considering the numbers of endoscopies that must be performed annually, the incidence of infection is comparatively low and estimated at one per 1.8 million examinations (*1,2,*3), although increasing concern has been expressed at cross-contamination during the decontamination process *(4)*. Endoscopic procedures are becoming increasingly complex, particularly in the field of keyhole surgery; however, percutaneous endoscopic surgical procedures have impacted beneficially on the postoperative wound infection rate and by reducing hospital stay have also had an economic benefit. It is therefore important that the potential cross-infectious hazards from the instruments are reduced to a minimum by correct decontamination procedures particularly as endoscopes are the commonest medical device associated with outbreaks of infection (*5,6,*7).

Many endoscopic procedures are carried out with all-metal instruments and they are thus comparatively easy to decontaminate by autoclaving. There are still, however, large numbers of endoscopies performed with instruments that are flexible and heat sensitive. It is this group of instruments that presents a considerable challenge to effective decontamination, in part because of their complex internal structure, with several very narrow bore channels and difficult to clean valves and valve seats. An additional factor to be considered is the heavy workload on a clinic and consequently a short turnaround time between patients, thereby potentially making effective decontamination problematic.

Currently, there are circumstances that set a particular challenge to the safe decontamination, not only of flexible but also rigid endoscopes, and these circumstances relate to viral and prion contamination of instruments (8). These circumstances take the emphasis for the safe reuse of instruments away from simply killing adherent microorganisms to removal of contaminating "soil" that may contain microbial nucleic acids, hazardous protein, and endotoxin. The availability of the polymerase chain reaction (PCR) has demonstrated that following decontamination procedures *(9)* it is possible to still detect the presence of microbial nucleic acid and that, although it may not be an infective hazard, it may well be hazardous for the patient by other mechanisms. These considerations and the concern regarding biofilms have led to a reevaluation of current decontamination procedures by professional organizations and to the circulation of new protocols to deal with contaminated endoscopes (10,*11*,12,13,*14–17*,18,*19*,20,*21,22*,23).

To standardize the decontamination procedure for endoscopes, the instruments are now almost universally processed in automated washer/disinfectors. This does not obviate the need for an initial manual cleaning, which is vital to the whole decontamination process, but does ensure that all endoscopes are decontaminated in an identical fashion and frees the endoscopy nurses for other duties in the clinic. There is, however, a downside to the use of automated washer/disinfectors, which relates to recontamination of endoscopes by the machine after the disinfection stage. This is due to the growth of microorganisms within a biofilm present in the tanks and pipes of the washer/disinfector and thus recontamination during the final rinse prior to removal of the instrument from the machine *(24)*. This problem has led to the reporting of pseudo-outbreaks of tuberculosis following bronchoscopy and to actual infection of patients with environmental gram-negative microorganisms. The manufacturers of automated washer/disinfectors have had to redesign the internal architecture of the machines and to otherwise modify them by including a self-disinfection cycle. The problem has also led to the development of systems for the provision of sterile water to the machine from the potable water supplies.

Aldehydes, for example, 2% glutaraldehyde, are still probably the commonest disinfectants used worldwide for flexible endoscopes *(25–29)* although in some countries, including the United Kingdom, they have been withdrawn from the market and this has of necessity led to the use of other disinfectants. Glutaraldehyde does have two major disadvantages despite its efficacy as a disinfectant. It is now recognized to be a major cause of occupational allergy, giving rise to both pulmonary and skin hypersensitivity *(30,31)*. Its other main disadvantage is that it acts as a fixative, and with concern expressed over prion proteins and the emphasis placed on soil removal from endoscopes, this characteristic in a disinfectant is unwelcome. The disinfectants that have replaced glutaraldehyde (in the United Kingdom) are very effective in killing microorganisms but are far more corrosive both to the endoscope and to the washer/disinfector.

The area of endoscope decontamination is thus currently in a state of flux, and further developments are anticipated with respect to the processes of decontamination, the nature of disinfectants, and the materials from which endoscopes are manufactured.

TYPES OF ENDOSCOPES

Endoscopes are constructed from a diverse range of materials including plastic, metal, glass, and adhesives. They generally have a complex internal construction with narrow bore channels, external ports, and valves. Many different endoscopes are now produced for a variety of medical interventions, both therapeutic and diagnostic, including bronchoscopy, arthroscopy, laparoscopy, colonoscopy, gastroscopy, and cystoscopy. The endoscopes may be flexible or rigid, the latter usually made entirely of metal and are thus relatively easily decontaminated compared to the flexible endoscopes. They may be used as direct viewing instruments or for the collection of biopsy specimens, as video endoscopes, or as endoscopes with an ultrasound attachment used for diagnostic purposes.

Endoscopes can be classified as critical instruments—those that penetrate the skin or sterile body cavities—or as semicritical instruments—those that are in contact with mucous membranes. However, this distinction is not clear-cut, as many semicritical instruments may be in contact with pathologic lesions, where the local defenses are breached, or they are used to take specimens, thus breaching local defense mechanisms.

Critical Instruments

These instruments include laparoscopes, vascular and neurological endoscopy, cystoscopes, and arthroscopes. Some of these instruments such as the cystoscopes and laparoscopes may be rigid in construction, made out of metal, and are thus autoclavable.

Laparoscopes are used for visualizing the peritoneal cavity, penetrate the skin, and are increasingly used as surgical equipment involved in intraperitoneal operations such as cholecystectomy, hysterectomy, hernia repair, and tubal ligation. Similar instruments may also be used in the thoracic cavity for some surgical procedures, in cosmetic surgery for rhytidectomy, and in general surgery for thyroidectomy. Angioscopy is used for atherectomy, embolectomy, and direct inspection of vessels. Endoscopes are used in neurology for III ventricle ventriculoscopy, in cases of hemorrhage-related obstructive hydrocephalus, and for transsphenoidal resection of pituitary adenoma. Arthroscopes are also rigid and autoclavable and are used for inspecting joint spaces and surgical procedures including meniscectomy. These instruments are also used percutaneously. Hysteroscopes are used for visualizing the uterus, for removing polyps, for biopsies, and for resection of submucous fibroids. Cystoscopes are often rigid, although ureteroscopes are flexible. These instruments are used for visualizing the urinary tract, taking biopsies, removing small tumors and calculi, and dilating stenosed regions of the urinary tract. They may be passed into the renal tract through the urethra or directly into the renal pelvis percutaneously.

In general, the flexible operative endoscopes are heat labile and should be sterilized by ethylene oxide or gas plasma. The rigid ones may be autoclaved.

Semicritical Instruments

These instruments include gastroscopes, duodenoscopes, sigmoidoscopes, proctoscopes, colonoscopes, bronchoscopes, and laryngoscopes. Gastroscopes, duodenoscopes, and colonoscopes are long, flexible instruments, usually with four channels (suction, biopsy, air, and water) and corresponding ports and valves. The suction and biopsy channels are often combined within the insertion tube. Their intricate construction makes them difficult to clean, and the materials from which they are made make them difficult to decontaminate. These instruments are inserted through one of the natural orifices of the body, which has a rich normal flora. Bronchoscopes are thus categorized as semicritical despite the fact they enter a sterile body cavity. These instruments are used both diagnostically and for minor surgical procedures such as polyp removal or diathermy.

Accessories

A wide range of accessories is available for both critical and semicritical endoscopes including forceps, snares, diathermy, bougies, sphincterotomy knives, and lasers. Many of these accessories can be autoclaved, but increasingly manufacturers are supplying single-use disposable accessories. Laser and ultrasonic probes are expensive and not able to be autoclaved.

ETIOLOGY

The commonest microorganisms that cause endoscopy-associated infections or pseudoinfections are opportunistic gram-negative bacteria and mycobacteria that are associated with moisture or biofilms on an endoscopy processing apparatus *(32,33)*. Microorganisms that have frequently been isolated include *Pseudomonas* species *(34)*, *Serratia marcescens*, *Klebsiella*, *Escherichia*, and *Salmonella* species *(35–42)*. *Salmonella* sp. is easily diagnosed as cross-infection due to a poorly decontaminated endoscope because this microorganism would not normally be found in the environment of an endoscopy room as a contaminant. Cross-contamination with *Salmonella* would be likely to cause an infection, even in relatively healthy individuals, in comparison to the environmental opportunist microorganisms commonly linked to failed endoscope decontamination, such as *Klebsiella* and *Pseudomonas*. Most of the cases of transmission of *Salmonella*, and there have been relatively few, date from the 1970s to 1980s, and in all cases, disinfectants were used that would be regarded as inappropriate by current standards. The agents that were used to decontaminate the endoscopes were skin antiseptics—chlorhexidine, cetrimide, povidone-iodine, hexachlorophene, and quaternary ammonium compounds. The majority of reported infections occurred prior to 1983, with only three more cases reported by 1992 and none to the current time. Since the late 1980s, glutaraldehyde and more recently other agents have been used to decontaminate endoscopes, with the effect that there are fewer reported incidents of cross-infection from an endoscope contaminated with enteric gram-negative bacteria.

Bronchoscopy has been associated with contamination or infection caused by *Mycobacterium tuberculosis*, *M. kansasii*, *M. chelonae,* and *M. abscessus (24,43–47)*. Cystoscopy has been associated with infections by *Escherichia*, *Enterococcus*, and *Proteus* species *(48)*. Percu-

taneous endoscopy has been associated with skin flora and *Staphylococcus aureus* surgical site infections *(49)*.

There is little evidence of viral transmission after endoscopy. Both bronchoscopes and gastroscopes become contaminated with human immunodeficiency virus (HIV) when used on patients with the acquired immune deficiency syndrome (AIDS), yet there is no evidence of transmission following endoscopy. Studies have shown that mechanical cleaning of endoscopes removes even high concentrations of HIV and that glutaraldehyde rapidly inactivates the virus *(50)*. There is a single well-documented case of hepatitis B virus (HBV) transmission between patients *(51)*, but most studies have not been able to document transmission. Of 394 patients followed up after exposure, none showed clinical evidence of infection *(52)*. There have been three reported cases of hepatitis C virus (HCV) transmission, one following endoscopic retrograde cholangiopancreatography (ERCP), and two following colonoscopy, and in all cases decontamination was found to have been ineffectively carried out *(53)*. In a study of 19 patients with HCV using molecular techniques to detect the virus, a blood sample taken from the patient was positive prior to the procedure, and 53% of the endoscopes were contaminated with the virus immediately after removal, but after both mechanical cleaning and mechanical cleaning followed by immersion in a disinfection, none were contaminated *(54)*. Thus, current decontamination procedures appear to be sufficiently robust to prevent viral transmission following endoscopy.

Less frequently identified pathogens that may be transmitted by endoscopic procedures include *Helicobacter pylori (55,56)*, *Shewanella* spp. *(57)*, *Trichosporon asahii (58)*, and *Strongyloides (59)*. Other microorganisms that may be transmitted by endoscopy include *Clostridium difficile*, *Cryptosporidia*, and enteroviruses.

PATHOGENESIS

Infections are derived either from an external source (exogenous) or from the patient's own microflora (endogenous). (Fig. 62-1) Endoscopically transmitted infection reported in the literature has been mainly exogenous, from inadequately decontaminated endoscopes, although endogenous infections have also been reported, particularly in association with urologic or percutaneous procedures.

Exogenous Spread of Infection

There are two main reasons for microorganisms being transmitted to a patient from an endoscope, which are to some extent related. On the one hand, the endoscope may be inadequately decontaminated. On the other hand, microorganisms produce and reside in a biofilm when in a moist environment, such as an endoscope or an endoscope washer/disinfector (AEW). Many bacteria secrete a carbohydrate substance, frequently called "slime," which forms the glycocalyx or matrix (the biofilm) within which the microorganisms can survive (*60*,61). Often, biofilms contain complex microbial communities. The dynamics of the biofilm are still poorly understood, but what is certain is that microorganisms within the biofilm are more resistant to biocides than adherent but non–biofilm-associated bacteria or planktonic bacteria *(62,63)*. Additionally, biofilms and the associated bacteria are resistant to hydrodynamic shear forces. Both these characteristics make eradication of microorganisms from endoscopes or endoscope washer/disinfectors difficult and predispose to failure of decontamination processes. The net result is that microorganisms are still present on the endoscope, or the endoscope becomes recontaminated following the decontamination procedure *(64,65)* by poor quality rinse water. Thus, in Fig 62-1, the endoscope (E1) will become contaminated

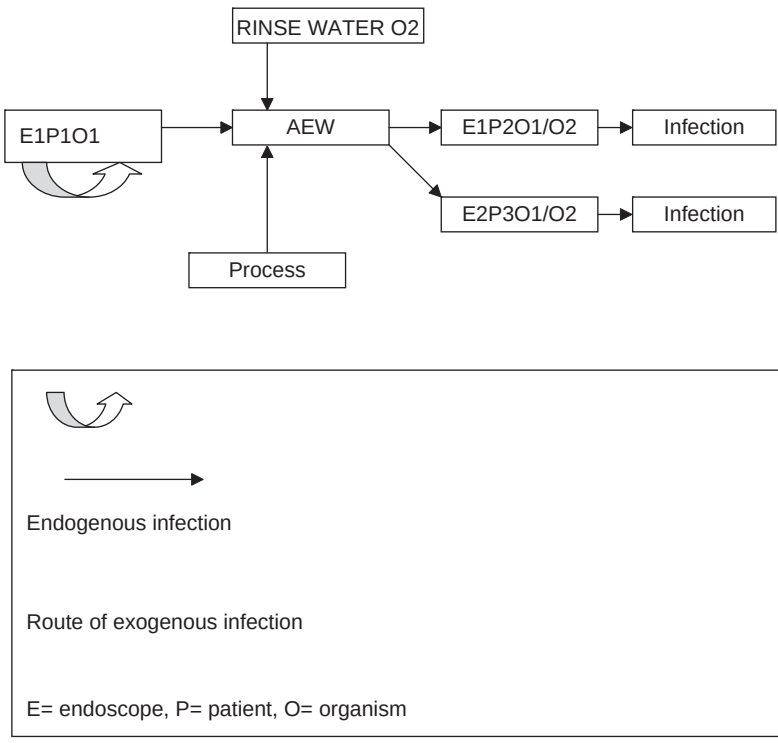

FIGURE 62-1 Routes of transmission of microorganisms by endoscopy.

during the procedure with microorganisms (O1) from the first patient (P1). The endoscope will then be decontaminated in an Automated Endoscope Washer/Disinfector (AEW) and if the procedure is inappropriate or poorly carried out the microorganism will not be removed or killed and when the same endoscope is used on another patient (E1P2O1) an infection may occur. The AEW may also act as a source of contamination of endoscopes. Microbes derived from patients (O1) or from contaminated rinse water (O2) may reside in the biofilm and contaminate endoscopes processed in the machine thereby infecting other patients (E2P3O1/2).

Airborne infection from staff members in the endoscopy room during percutaneous surgical procedures, although possible, is unlikely owing to the small incision produced. During endoscopic surgery, the video screen may act as a source of contamination of the surgeon's hands, as the electrostatic field generated by the screen facilitates the transfer of microorganisms from the screen to the gloved hands of the surgeon *(66)*.

On the other hand, spread of infection from the patient to the staff is a very real risk during bronchoscopy, particularly when dealing with patients who have tuberculosis. Similar concern has been expressed about staff members acquiring infection with HIV when performing endoscopy on patients who are infected *(67)*. In one study of 427 urologic procedures, contamination of the surgeon's skin or mucous membranes occurred in 32%. Thirty-three percent were endoscopic procedures and in these, contamination of the face or eyes occurred in 46% *(68)*. Although in practice the risks of infection are small, the risks of contamination in some procedures are high, and appropriate physical precautions have been almost universally introduced.

In addition to the transfer of microorganisms to the patient, who may then become colonized, whether or not the patients develop an infection is due to other contributory factors such as their underlying medical condition, the treatment they may be receiving, and whether they already have a focus of infection such as an obstructed bile duct *(69)*.

Endogenous Spread of Infection

Endogenous infection may be due to transfer of microorganisms from one site to another during the insertion or removal of the endoscope. Mouth flora may be transferred to the stomach or to the bronchi during gastroscopy or bronchoscopy. Mouth, stomach, or duodenal flora may be transferred to the biliary or pancreatic system during ERCP. Intestinal flora may contaminate the oral cavity on removal of a gastroduodenoscope or ERCP. Similarly, skin flora may be introduced into the peritoneal cavity, pleural cavity, or joint; vaginal flora may be introduced into the uterus; and fecal, skin, or urethral flora may be introduced into the bladder or kidneys during urological procedures.

INFECTIONS ASSOCIATED WITH ENDOSCOPY

The insertion, manipulation, or removal of the endoscope may be associated with bacteremia, usually with the patient's own microflora but rarely from microorganisms contaminating the endoscope. More usually, pseudoinfections have been reported in the literature, due to contamination of a patient's specimen by a microorganism derived from the endoscope. Percutaneous procedures may be followed by surgical site infections or joint infections, peritonitis, bacteremia, or empyema.

Between 1974 and 2004, there were 140 outbreaks related to endoscopy reported in the world literature (70). Forty-nine percent were from the United States and 51% from 19 countries other than the United States. Bronchoscopy accounted for 47% of infections and 94% of pseudoinfections in the United States and 21% of infections and 76% of pseudoinfections outside the United States. Gastrointestinal endoscopy accounted for a similar percentage of infections, but only 6% of pseudoinfections within the United States and 76% of infections and 24% of pseudoinfections outside the United States. Overall, bacteria were the principal cause of infections and pseudoinfections.

The commonest cause of toxic reactions was glutaraldehyde, which has now been withdrawn from use in the United Kingdom. The most frequent cause of outbreaks related to inadequate decontamination practices followed by contamination of the AEW in the United States and the use of contaminated water outside the United States. Over this period of study, the primary cause of decontamination failure fell from 72% to 47% in the United States and 81% to 70% elsewhere. Since 1990, equipment malfunction has been identified as a cause of failure in the United States (8%) and elsewhere (4%) and AEW contamination accounting for 25% and 4% in the United States and elsewhere, respectively. A key outcome of this study was that by better adherence to decontamination guidelines, 90% to 97% of the outbreaks could have been prevented both within and outside the United States. During this period of study, there were 14 deaths, 1.9% of the total number of exposed patients in the United States and 6 deaths elsewhere (1% of contaminated patients). The mean length of an endoscopy-related outbreak was 182 days in the United States and 202 days elsewhere.

These data represent an underestimate as an unknown number of endoscopy-related incidents may go unreported, and in about half of the reported cases insufficient data was recorded and particularly the denominator (number of patients undergoing endoscopy) is unknown. Since this study, there have been nine further outbreaks reported from 2005 to 2008 that occurred outside the United States *(71)*.

Endoscope-Assisted Surgery

Laparoscopic Surgery Surveys of infective complications following minimally invasive procedures are few, and there is little evidence to show they are due to contaminated endoscopes as opposed to complications of the procedure. Surveys between 1975 and 1980 of, in one case, over 100,000 laparoscopies *(72)* showed an infection rate of 3% to 4%, with only seven possibly being due to nonsterile equipment. In a second survey of over 10,000 laparoscopies *(73)*, three cases of surgical site infection were reported, none of which were thought to be due to contaminated equipment. In 1991, a prospective study

of 1,518 laparoscopic cholecystectomies showed an infection rate of 0.9% to 2.0% *(74)*. In 1999, a retrospective survey of 1,702 laparoscopic cholecystectomies *(75)* showed an infection rate of 2.3%, with a surgical site infection rate of 0.4%. The commonest infective complication following this procedure is septic complications after spillage of gallstones in the peritoneal cavity *(76–78)*, and not due to a failure of decontamination procedures. In 2002, a Cochrane Review of laparoscopic appendectomy compared to open appendectomy covering 45 studies *(79)* showed that wound infection following the laparoscopic procedure was half as likely as with the open procedure, but that intra-abdominal abscess was three times as likely. It was not suggested that failed decontamination procedures were the cause of any of the infective complications.

In a report from India, local skin infection with *M. tuberculosis* followed laparoscopic surgery in eight patients *(80)*. The endoscopes were soaked in an open tray for 20 minutes, a technique no longer used in developed countries and that emphasizes the importance of correct modern decontamination procedures.

In a study of 801 patients treated by laparoscopic distal pancreatectomy, an infection rate of 0.6 was recorded. Fewer patients have undergone total pancreaticoduodenectomy, and of 85 so reported although the morbidity was high (34%) the rate of infection was not reported *(81)*.

Minimally invasive surgery has so far involved percutaneous entry into the abdominal cavity to perform the operative procedure with a lower infection rate compared to conventional surgery. However, the development of natural orifice transluminal endoscopic surgery (NOTES) where flexible endoscopes are used to perform intra-abdominal and intrathoracic operations may alter that, as entry into the abdominal cavity is via the vagina *(82)* or stomach *(83)*. As the endoscope transverses a heavily colonized mucosal site, the procedure may be associated with a higher postoperative infection rate as there is a potential to introduce microorganisms into a sterile cavity. However, in both series, no infections were recorded and the transvaginal approach is frequently used by gynecologists without adverse infection risks. This suggests that terminal sterilization of surgical endoscopes is not required, although a protocol has been developed to sterilize these surgical endoscopes using peracetic acid *(84)* Further, a single-port endoscopic procedure for cholecystectomy (SPEC) has been developed in pigs *(85)* as an alternative to NOTES, and as there are fewer breaks in the skin, this may even further reduce the possibility of infection.

Arthroscopy

Infections following arthroscopy are uncommon, with, in one survey of 12,505 procedures, an infection rate of 0.04% being reported *(86)*. Postprocedure infections do occur, usually with skin flora and usually due to environmental contamination rather than poor decontamination of the arthroscope. In one study, three joint infections occurred in 155 arthroscopies *(87)*, but following alteration of environmental factors, there were no subsequent infections in 222 procedures. In one more recent study, *Candida albicans* infection occurred following arthroscopy. Infectious complications can also follow other endoscopic orthopedic procedures, and in one case lumbar discitis occurred following laparoscopic sacrocolpopexy *(88)*, although there was no indication this was due to failed decontamination. Infection has also been reported following meniscus repair performed by arthroscopy. Three patients developed a septic arthritis with *Staphylococcus epidermidis*, and the likely source was the cannulae. *In vitro* studies demonstrated these cannulae could only be sterilized by an ultrasonic bath, jet washing of the lumen, and steam sterilization. *(89)*.

Cystoscopy

Cystoscopes were among the first endoscopes to be used, and initially inadequate disinfection was responsible for infection. Many of the cystoscopes can be autoclaved, although flexible heat-sensitive cystoscopes are also used. In the 1950s, it was shown that patients were developing infections within a few days of the procedure *(90)*. A number of disinfectants were introduced, and since the use of 2% glutaraldehyde and antibiotic prophylaxis, the postprocedure infection rate is small. In a study of 161 cystoscopies, an infection rate of 7.5% was reported with microorganisms derived from endogenous flora, giving no suggestion that failed decontamination procedures were to blame *(91)*. In a study of 420 patients following flexible cystoscopy, 110 patients donated a postprocedure urine specimen 3 days following the investigation, with 2.7% showing evidence of infection *(92)*. Percutaneous urologic procedures, such as nephrostomy or insertion of a ureteral endoprosthesis, in one study had a complication rate of 7%, with 0.87% being due to urinary tract infection. Minor complications of skin inflammation occurred in 5.3%, but in no case was it thought to be due to poor decontamination procedures *(93)*. An outbreak of *Pseudomonas aeruginosa* infection following cystoscopy was identified in New Mexico involving 23 patients. Most of the patients had a urinary tract infection postprocedure, but 4 also had bacteremia. A multivariate analysis indicated cystoscopy was the most likely common factor (OR: 46.5). On examination, the cystoscope was positive for the microorganism and there were several breaches of the decontamination protocol identified *(94)*. Another study in a urology unit indicating inadequate disinfection as a cause of an outbreak demonstrated that forceps were the likely source. In this case, 10 isolates of *Pseudomonas* recovered from the forceps were indistinguishable by pulse-field gel electrophoresis *(95)*.

Endoscopic Vascular Surgery

Infections are also a complication of cardiovascular cannulation, although there is no suggestion that these infections are due to failed decontamination procedures, as the cannulas are sterile, single-use items. In a retrospective study between 1991 and 1998 of 22,006 procedures, there were 25 cases of bacteremia (0.11%) with 0.24% following percutaneous transluminal coronary angioplasty, 0.06% following cardiac catheterization, and 0.08% following electrophysiologic studies. The majority of the infections were with gram-negative bacteria *(96)* (see also Chapter 61).

In one study, 103 patients undergoing coronary artery bypass graft (CABG) had the saphenous vein removed by minimally invasive endoscopic procedure. Eight

point seven percent of the standard operative control population (9/105) developed a wound infection, whereas only 2 out of 103 developed an infection after in the endoscopic procedure *(97)*. A further study demonstrating the lower infection rate using minimally invasive endoscopic procedures compared open surgical repair of the abdominal aorta compared to endovascular repair. The patient with an open procedure was twice as likely to develop an infection compared to the one having endovascular repair *(98)*.

Endoscopic Neurosurgical Procedures

Third ventricular endoscopy (ETV) has been used for obstructive hydrocephalus of several etiologies including removal of tumors, Chiari malformation, aqueduct narrowing, spina bifida, and following a cerebral hemorrhage. In one study of 34 procedures for obstructive hydrocephalus following cerebral hemorrhage, spanning a 15-year period of endoscopic neurosurgery, no cases of infection were reported postprocedure *(99)*. Although this study is small, if the general trend of lower post procedure infection rates for other types of surgery is observed, then ETV will compare well with placement of an extraventricular drain (EVD) where infection rates of 10% are common *(100)*. Further, some studies report infection rates as high as 45% for EVD. In another study of 190 patients treated by EVT for obstructive hydrocephalus *(101)*, there were no cases of postprocedure infection reported, and in many cases an EVD or VP shunt was not needed, thus avoiding recognized infectious complications. In a study of ETV for colloid cyst removal in 55 patients, the infection rate was 0% compared to 5 of 27 patients in the control surgical procedure *(102)*. Finally, after endoscopic removal of subcortical tumors in 21 patients, only one postoperative infection was identified. *(103)*. The use of endoscopic procedures in neurosurgery not only results in a lower infection rate postprocedure, but there are no reports of contaminated endoscopes linked to outbreaks.

Miscellaneous Endoscopic Surgical Procedures

In a study of 251 patients who underwent thyroidectomy using an endoscopic transcervical approach, the infection rate was 2.6% compared to 7.35% in conventional surgery *(104)*. A 10-year prospective study of endoscopic rhytidectomy in 54 patients did not record any case of postoperative infection or of cross-infection *(105)*.

Semicritical Endoscopes

Gastrointestinal Endoscopy Infections associated with gastrointestinal endoscopy are uncommon, and several surveys dating from the 1970s have shown a rate of <1%. In a survey of over 240,000 gastrointestinal endoscopies, only 24 infective complications were reported, including four fatal cases, two of cholangitis and two of pancreatitis *(106)*. In a further study, 116 infective complications were reported, which included bacteremia, hepatitis B, endocarditis, aspiration pneumonia, and Creutzfeldt-Jakob disease (CJD) *(25)*. The microorganisms isolated included enteric gram-negative bacteria such as *Serratia* and *Salmonella*, environmental bacteria such as *Pseudomonas*, and gram-positive bacteria such as *S. aureus*. In a survey in the United Kingdom of 164,000 endoscopies, the infection rate was 0.74% for ERCP, but of those infected, there was a high mortality rate of 26% *(107)*. Percutaneous endoscopic gastrostomy (PEG) is a procedure for establishing enteral feeding *(108)*. In one study of 166 PEG procedures, the complication rate was 16.3%, with wound infections occurring in 5.4%, including one case of necrotizing fasciitis. Esophagoscopy has been linked to the transmission of *Pseudomonas* with, in some cases, evidence of infection and death following septicemia *(109)*. In a study of 760 children undergoing PEG between 1994 and 2005, there was a 4% complication rate (skin infection) postprocedure in hospital rising to 20% out of hospital *(110)*.

Lower respiratory tract infection has also followed gastroscopy, again with *Pseudomonas*, which probably relates to aspiration of oral secretions associated with a contaminated endoscope *(111)*.

Following sigmoidoscopy, a 10% prevalence of bacteremia that was detectable over a period of 15 minutes has been reported, although no obvious infective complications were noted *(112)*. Transient bacteremia has also been reported in other studies *(113–116)*. A false sense of security may be given if using disposable rigid sigmoidoscopes as microorganisms may contaminate the nondisposable bellows or light head. In one study of 21 sigmoidoscopies, a number of enteric bacteria were detected in these two locations *(117)*.

Procedures involving sclerotherapy with *N*-butyl-2 cyanoacrylate have been shown to have a high rate of bacteremia and peritonitis, ranging from 5% to 53% and 0.5% to 3%, respectively *(118)*, and in some cases endocarditis or abscess has occurred following endoscopy *(119–121)*. An alternative approach is the use of a covered needle (Clisco needle) whose tip does not become contaminated during insertion of the endoscope *(122)*. Culture of the tip of covered needles compared to noncovered needles showed a lower contamination rate for the covered needle and by implication this may lower the rate of postprocedure bacteremia. However, endoscopic variceal ligation is replacing sclerotherapy as the method of choice to control bleeding. This procedure has a 3% to 14% risk of bacteremia, with 11/67 patients developing bacteremia and 2/67 developing peritonitis *(123)*.

Endoscopic Retrograde Cholangiopancreatography

Infection following ERCP is more common than with other forms of gastrointestinal endoscopy, particularly when the biliary tree is obstructed. A postal survey of 10,000 endoscopies showed an infection rate of 3%. Most complications were due to pancreatitis, but cholangitis and cases of infected pancreatic pseudocyst also occurred, as did a small number of cases of aspiration pneumonia *(124)*. Exogenous infection leading to septicemia, following the use of a contaminated endoscope for ERCP, has also been reported. The microorganism isolated from the patient's blood, the endoscope, and the water reservoir was *P. aeruginosa (125)*. In a survey of 690 ERCPs, fever occurred in 12 patients and 5 of these died of septicemia *(126)*. Microorganisms isolated were *Pseudomonas*, *Klebsiella*, *Proteus*, and *Escherichia*. Several other reports have documented infections following ERCP, frequently in association with biliary stasis, and thus likely to be of endogenous origin, but also following the use of inappropriate disinfectants as mentioned previously, or more recently, incidents have been reported

following recontamination of the endoscope from the endoscope washer/disinfector. In both cases, outbreaks due to *Pseudomonas* have been reported *(127–130)*. In one report, the post-ERCP infection rate in one hospital increased from 1.6% to 3.6% following the use of a new automated washer/disinfector. The microorganisms causing the bacteremia were *Pseudomonas* and enteric gram-negative bacteria. Seven epidemic strains causing infection were genomically related as shown by macrorestriction DNA analysis and accounted for 55% of the episodes. Effective decontamination of the washer/disinfector led to a reduction in the infection rate to preincident levels *(131)*.

In a report from the United States, *Pseudomonas* was isolated from 10 patients following ERCP. Five developed sepsis and one died *(132)*. The same strain (serotype 10) was isolated from the endoscope and persisted in the unit for 9 months. Factors involved in its persistence were probably inadequate decontamination of the endoscope, recontamination from the rinse water of the washer/disinfector, and inadequate drying of the endoscope. *Pseudomonas* has also been implicated in other cases of infection in association with high counts of the microorganism in the biopsy channel and samples of rinse water from the washer disinfector immediately after disinfection with glutaraldehyde *(64,133,134)*. The mechanism of persistence in this case was lack of circulation of the disinfectant to all areas in the washer/disinfector and the formation of a biofilm containing the microorganism, which acted as a source of recontamination.

Bronchoscopy

A bronchoscope is less complex than a gastrointestinal endoscope, having fewer channels to decontaminate. However, bronchoscopes are used to obtain bronchoalveolar lavage (BAL) specimens in which the pulmonary tree is washed out with saline. There is thus the potential to contaminate the specimen from an inadequately decontaminated endoscope, giving a false clinical impression that the patient is infected.

The most frequently reported pseudoinfection is with mycobacterial species, but they have also been reported with *Pseudomonas* found in bronchial washings following bronchoscopy *(32)*. In a study in 1982, 11 of 19 specimens were contaminated with the same serotype 10, which was also isolated from the bronchoscopy channels *(135)*. In another study, 82/103 BAL specimens were contaminated by *P. aeruginosa (136)*, but again no infections were reported. As with gastrointestinal endoscopy in the 1970s and early 1980s, the disinfectants used were inappropriate. Other outbreaks involving multiresistant *P. aeruginosa* have also been reported more recently *(137–139)*.

Microorganisms other than *Pseudomonas* have also been linked to outbreaks of pseudoinfections as well as true infective complications. Following bronchoscopy on a patient with *S. marcescens* pneumonia, the microorganism was found in the tracheal washings of three other patients *(140)*. Other sources of outbreaks of pseudoinfection have been linked to contaminated sterile water *(141)* and lens cleaner *(142)*. In one case, incorrect connectors had been used to link the machine to the bronchoscope. Also, defects in the bronchoscope may be involved. In one report, three outbreaks were identified involving 418 patients contaminated by various Enterobacteriaceae (*Klebsiella* sp., *Proteus* sp., and *Morganella* sp.). The likely source of the contamination was traced to a faulty biopsy channel port *(143)*. Proteus species have also been associated with pseudoinfections following bronchoscopy *(144)*, and bronchoscopes have also been the vehicle for a pseudo-outbreak with *Legionella pneumophila,* which became contaminated from tap water *(145)*.

Gram-negative bacteria are relatively susceptible to disinfectants, compared to the more hardy mycobacteria. Additionally, mycobacteria are also found in water supplies and can grow in biofilm in pipe work. It is therefore not surprising that infections with *M. tuberculosis* and many pseudoinfections with other mycobacterial species have been reported. A retrospective survey of 8,750 bronchoscopies showed that contamination occurred in eight, but there was no evidence of infection *(146). M. tuberculosis* has been isolated from washings of a bronchoscope after it had been decontaminated in povidone-iodine, and transmission was documented from one patient to another in a separate episode. In this case, the bronchoscope had also been disinfected in povidone-iodine, and *in vitro* studies showed that this was an ineffective agent for mycobacteria *(147)*. In 1 month in 1999, five *M. tuberculosis* BAL specimens were reported in one hospital that overall had a low rate of tuberculosis. A retrospective survey for the whole year showed that 19 bronchoscopies had been performed with 10 of 18 BAL specimens positive. Two patients were infected prior to endoscopy and two became infected after the procedure. Six patients had positive specimens but did not develop infection. The majority of the isolates were indistinguishable on restriction fragment length polymorphism analysis. In one of the three endoscopes that was used during this period, a small hole was discovered in the sheath, and as leak testing had not been performed regularly, this had allowed a contaminated endoscope to be unwittingly used *(148)*.

There have been numerous reports of pseudoinfections with other mycobacterial species, and on some occasions this has led to inappropriate treatment. In one study, *M. xenopi* was isolated from 13 clinical specimens, although none had clinical evidence of mycobacterial infection. Five of these patients received antituberculosis therapy *(149)*. An important factor was rinsing bronchoscopes with tap water and gargling with tap water prior to sputum collection. In another study over a period of 37 months, 35% of mycobacterial isolates were *M. xenopi*. Four of the patients had *M. xenopi*–associated disease; the remaining were pseudoinfections. An important risk factor was rinsing bronchoscopes after disinfection in tap water *(150)*. Other mycobacterial species have also been associated with bronchoscopy. A pseudo-outbreak of *M. abscessus* occurring in 15 patients was traced to the use of an automated washer/disinfector *(24)*. Pseudo-outbreaks in association with the use of automated washer disinfectors have also been reported with *M. chelonae* and *Methylobacterium mesophilicum (151)*. Colonization by the microorganisms was linked to bronchoscopy, and the microorganisms were also isolated from the endoscopes, washer disinfectors, and glutaraldehyde taken from the washer/disinfector. Some strains of *M. chelonae* are known to be resistant to glutaraldehyde.

A pseudo-outbreak of nontuberculous mycobacteria involving 41 patients over a 6-month period yielded 16 specimens with acid-fast bacilli that were mainly *M. chelonae* or *M. gordonae*, although one specimen was *M. avium* and one *M. tuberculosis*. Of the apparently positive patients, four were treated for suspected tuberculosis. The source of the contamination for most of the isolates was the water reservoir in the machine, although the source of two of the *M. gordonae* isolates was a laboratory solution *(152)*. In one study 13 strains of *M. chelonae* were isolated from BAL fluid where the bronchoscopes were decontaminated in the same machine as colonoscopes. The outbreak was stopped by manually decontaminating the instrument *(153)*.

True infections following bronchoscopy are uncommon. The complication rate of 24,521 bronchoscopic procedures assessed from 192 replies of a questionnaire was 0.08% with a mortality of 0.01% *(154)*, with fever in eight patients and pneumonia in two. In a prospective study of 100 bronchoscopies, fever occurred in 16% and lung infiltration in 6% *(155)*. In a prospective study of fever and bacteremia following bronchoscopy in immunocompetent children, of 91 children investigated, 48% developed fever within 24 hours, but bacteremia was not detected *(156)*. In those children who developed fever, 40.5% of the BAL specimens had a significant bacterial growth.

These cases emphasize the importance of correct use and regular maintenance of the AEW, and adherence to recognized guidelines for reprocessing the instrument. Also, defects in the bronchoscope may be involved and should be guarded against by regular maintenance of the endoscope.

Miscellaneous Microorganisms and Sources

Bacillus species have been found in bronchial washing in one hospital, although none of the patients were infected. The source seemed to be the automatic suction valve *(157)*. Fears have been raised that anthrax may be transmitted by endoscopy, although studies of the efficacy of current disinfectants indicate that they would be effective in killing the microorganism *(158)*. An outbreak of *Aeromonas hydrophila* pseudoinfection was reported. The endoscopes were decontaminated with a disinfectant containing a quaternary ammonium compound and glutaraldehyde phenate. The use of 2% glutaraldehyde eradicated the problem *(159)*. *Strongyloides stercoralis* has been transmitted by gastroscopy *(59)*, and also cross-infection with *H. pylori* may occur *(55,56)*. Fungal infections and pseudoinfections have been reported with *Trichosporon* species *(58)* and *Aureobasidium* species; the latter was linked to the reuse of plastic stopcocks *(160)*. Finally, in 169 patients following ERCP, 12.7% were positive for *Cryptosporidium* oocytes *(161)*. This is a particular risk for AIDS patients, especially as the microorganism is resistant to most disinfectants. (See Chapter 9 for more information on pseudoinfections.)

CONTROL OF INFECTION

As mentioned, endoscope-associated infection can be either endogenous or exogenous in origin. Endogenous infections may be prevented by appropriate skin preparation or chemoprophylaxis prior to the procedure. As indicated by recent reviews, several aspects of the prevention of exogenous infection from endoscopes have taken on current importance *(162–169)*. Exogenous infections would be prevented by effective decontamination procedures. In this latter category, infections that have followed endoscopy have arisen from the use of inappropriate disinfectants, breakdown in the decontamination process, or recontamination from an automated washer/disinfector.

Two common reasons associated with transmission is failure to conform to an adequate decontamination process and equipment failure (*71*,170). Important hazard points in the reprocessing of endoscopes are provision of trained endoscope decontamination staff, regular AEW and endoscope maintenance, adherence to effective decontamination protocols, drying of the endoscopes, machine decontamination at the start of a session, endoscope reprocessing at the start of a session and sterile rinse water. Also important for identifying and mapping outbreaks is surveillance such as tracking of instruments and accessories and surveillance cultures (Fig. 62-2).

Key factors aimed at reducing the already low case-to-case transmission of microorganisms is the development of endoscope channels that can be adequately manually cleaned prior to the automated phase of the decontamination process, including the removal of biofilm, the development of flexible materials that can withstand pressurized steam, and the rapid detection of contamination prior to use. The key factor, however, in relation to decontamination failure is lack of adherence to accepted protocols. This is emphasized by a study in which a questionnaire was sent to 367 Society of Gastroenterology Nurses and Associates (SGNA) members in the United States, which showed that there was a wide variation in quality assurance practices (particularly in the manual decontamination steps) and the use of disposable accessory equipment *(171)*.

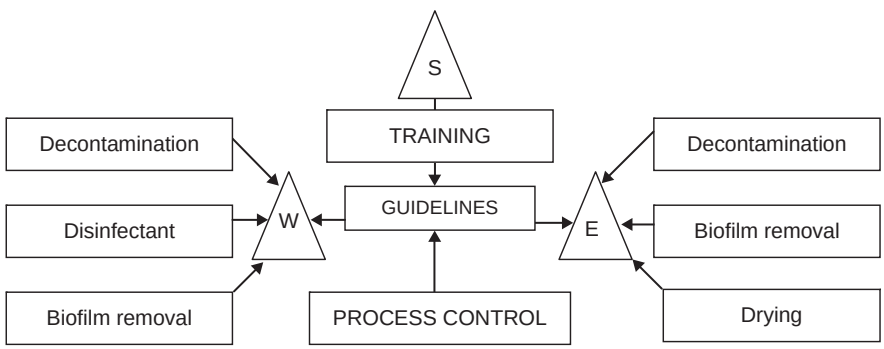

FIGURE 62-2 The three critical areas related to transmission of exogenous infection and the main components of the decontamination cycle. W, the AEW as a source; S, process control as a source; E, the endoscope as a source.

A review of case-to-case transmission of infections in the United States as a result of mainly reprocessing errors has been reported *(172)* and the resultant clinical and economic effects of infection demonstrated. The main type of endoscopy reported to transmit infection in this study was bronchoscopy. The reasons for the failure were processing faults, equipment compatibility problems, and AEW failure, and although there was no evidence of cross-transmission or infection, it was indicative of the need to be stringent in the application of policy guidelines.

In the United Kingdom, a study of decontamination failures was stimulated by an incident where an auxiliary channel of an endoscope had not been identified since the endoscope had been purchased and had been used undecontaminated on 1,300 patients. As a result of this incident, a look back of the 1,300 patients was instigated *(173)*, and an Endoscopy Task force was established to examine decontamination failures in the United Kingdom between 2003 and 2004 *(174)*. In the initial case, none of the 1,300 patients had any evidence of being infected with a bloodborne virus. A further eighteen incidents were investigated: eight incidents were failure to decontaminate auxiliary channels (incompatibility of endoscope with the AEW (4); manual cleaning only of the auxiliary channel (3); detergent not flushed down the channel (1); seven incidents were related to use of an AEW (4) in which the incorrect detergent had been used and in three there had been a fault of the machine alarm); in one incident the endoscope had only been cleaned manually; in another the reprocessing of a bronchoscope was incorrect and in the final incident a single use item was reused. In all these incidents, over 23,000 patients had been exposed. As a result of this investigation, an NHS National Decontamination Training Programme was established.

In another case, a faulty pump of an AEW used to inject disinfectant into the endoscope channels led to exposure of 236 individuals of which 197 patients were followed up. Despite the prevalence of HIV (23%), HCV (39%), and HBV (33%) in this cohort prior to exposure, analysis and testing of potential chain of transmission did not reveal any seroconversions despite there being acute cases of HIV, HCV, or HBV in the population *(175)*. A similar episode occurred with a failed AEW in France leading to the exposure of 72 patients of which 59 patients were followed up and there were no cases of seroconversion at 3 and 6 months *(176)*.

A further report noted an increase in *Pseudomonas* isolated from BAL specimens from 10% to 30%. In 414 patients, 39 developed respiratory infections or bacteremia and the cause of the failed decontamination was a loose biopsy port cap *(177)*. A similar problem with ill-fitting biopsy port caps led to contamination with *S. marcescens* and *P. aeruginosa* in 60 patients *(178)*.

In Britain, there is a particular concern that CJD may be transmitted on endoscopes, and this has led to interest in the efficacy of soil removal from endoscopes. Additionally, as current decontamination procedures incorporate the use of automated washer/disinfectors and as there have been pseudoinfections linked to recontamination of an adequately disinfected endoscope from a washer/disinfector, attention has focused on the provision of sterile water for the final rinse of the endoscope. One final event in Britain has been the removal of 2% glutaraldehyde from the marketplace due to problems with sensitization. This has led to the realization that monitoring of staff health is an important issue, as is the assessment of new disinfectants.

Flexible endoscopes are complex, reusable instruments that require unique consideration with respect to decontamination. In addition to the external surface of the endoscope, their internal channels are exposed to body fluids and other contaminants. In contrast to rigid endoscopes and some reusable accessories, flexible endoscopes are heat labile and cannot be autoclaved or washed ultrasonically. The main obstacle to effective decontamination of instruments is the complex internal structure of the channels and the inevitable damage that occurs to the channel lining, which then provides a source of microbes during the decontamination process (*179*) and the development of biofilm in the channels.

The scheme introduced by Spaulding *(180)* to separate medical devices into critical, semicritical, or noncritical categories depending on their relationship with mucosal surfaces or sterile body cavities does not adequately cover the issues raised by the development of complex, heat-sensitive endoscopes, some of which are introduced into body cavities. This has led to difficulties in sometimes choosing an adequate disinfection regimen and to controversy over the correct regimen for others. According to the Spaulding scheme, arthroscopes and laparoscopes, because they are critical items, should be sterilized. However, mostly these items are decontaminated by high-level disinfection, and the data show that infection following the use of these items is minimal. There is no evidence to suggest that sterilization of these items will reduce the rate of infection, and to do so would involve the use of either ethylene oxide or gas plasma.

Decontamination of Endoscopes

Decontamination is a process that renders the endoscope safe to use on another patient and consists of a mandatory cleaning step followed either by a disinfection or sterilization process. Cleaning removes many of the microorganisms as well as biologic fluids from the surfaces of the endoscope. Thorough cleaning with a detergent (neutral or enzymatic) is one of the main requirements for the effective reprocessing of endoscopes and accessories and is essential to maximize the effectiveness of the subsequent disinfection or sterilization step. Cleaning should comprise an initial mechanical cleaning of the endoscope once removed from the patient, followed by an obligatory clean in an automated washer or washer/disinfector followed by sterilization or high-level disinfection. The cleaning step should include all channels and valves as well as the insertion tube. The channels should be vigorously brushed and the brush sterilized or discarded *(181)*. The decontamination of reusable accessories was found to be cheaper in one study compared to the use of disposable accessories *(182)*; however, the advantage of using disposable accessories is the lower risk of cross-contamination and the avoidance of the need to track the accessories and record their use in the patient's notes.

Sterilization is defined as the destruction or removal of all viable microorganisms including spores. The Food and Drug Administration (FDA) defines sterilization as a 12-log

reduction in the bacterial spore count. The adherence of prions presents a special challenge. In practice, assessment of sterilization in the laboratory requires the killing of spores of *Bacillus subtilis* or *Bacillus stearothermophilus*. According to the Spaulding criteria, cystoscopes, arthroscopes, and laparoscopes should be sterile, but in practice high-level disinfection is frequently used. However, wherever possible, instruments that penetrate a sterile body cavity should be sterilized.

Disinfection is more difficult to define. It implies the removal or destruction of vegetative microorganisms excluding spores; the process reduces the bioload on the endoscope to a safe level, although this may vary with circumstances. In laboratory tests, the disinfectant must pass one of the National tests, which usually involves the reduction of a panel of vegetative microorganisms including viruses and mycobacteria by 10^5 in 5 minutes in either clean or dirty conditions, that is, without or with the addition of an organic soil.

Surface Contamination of Endoscopes

Microbiological Assessment of Endoscope Contamination: Surveillance Cultures The use of surveillance cultures is incorporated into many guidelines. However, some consider them to be onerous without any benefit and have suggested fewer sampling times and also rejecting the need to assess endotoxin levels. Routine surveillance cultures are of necessity *post hoc*, but if carried out regularly can identify potential problems and allow remedial action early. Samples are taken from specific locations in both the AEW and the ready-to-use endoscopes and cultured to assess the presence of viable bacteria and are used as an assessment of contamination levels.

After removal of the endoscope from a patient, it is inevitably contaminated with microorganisms and organic matter. An important consideration is how effectively the decontamination process reduces this contamination. In a study in Italy over a 2-year period, surveillance of contamination of gastroscopes demonstrated that 60.5% were contaminated on the outer surface and the channels were contaminated in 41.3% *(183)*. Similar figures were found for colonoscopes. The microorganisms most frequently isolated were *Pseudomonas* and *Staphylococcus* species. A study investigating the contamination of the air and water channels in endoscopes when they were either brushed or not brushed prior to reprocessing showed that the air channel in 42 endoscopes in both groups was not contaminated and the water channel in only one endoscope was contaminated in the group that was not brushed prior to reprocessing *(184)*. There was, however, organic matter present in both channels as determined by amido black staining. This was markedly reduced by effective brushing of the channels. Investigations using sterile, single-use biopsy forceps that had been passed through the channel of an endoscope at different stages of the decontamination cycle showed the effectiveness of the decontamination process *(185)*. The endoscopes were tested prior to use, directly postprocedure, after manual cleaning, and after manual cleaning and exposure to 2% glutaraldehyde, and showed overwhelming contamination with microorganisms immediately after removal from the patient. Microorganisms were present in 25% of cases after manual cleaning and 0% after exposure to glutaraldehyde.

In a study of 312 surveillance cultures taken between 1992 and 1994, 11.6% (15/129) of cultures were positive, the majority (93%) from duodenoscopes. However, between 1995 and 1997, 14.5% (18/124) were positive of which only one-third were from duodenoscopes and 55.6% were from upper GI endoscopes. The latter residual contamination was due to faulty cleaning by nontrained staff *(186)*.

A prospective study of the efficacy of decontamination by assessing ready-to-use endoscopes showed that both gastroscopes ($n = 1{,}376$, contamination rate 1.8%) and colonoscopes ($n = 987$, contamination rate 1.9%) were equally contaminated with oro/faecal flora in low numbers. HCV was detected on one occasion by using PCR on the washings. Significant findings were: (i) the more frequently used an endoscope, the more likely it was to be contaminated postdecontamination, (ii) colonoscopes used on patients with gastrointestinal disease were more likely to be contaminated postdecontamination, and (iii) of the culture-negative endoscopes, 40% were positive by PCR for coliforms—this as a surrogate marker for the presence of biofilm (187).

If surveillance cultures on endoscopes are performed, it is important that retrograde flushing of the channels is undertaken as the number of positive samples increases from 3–8% to 25–31% compared to antegrade flushing *(188)*. The cost of surveillance cultures has been analyzed over a 5-year period during which 2,374 screening tests (287 from the AEW, 631 from bronchoscopes for mycobacteria, and 1,456 from all endoscopes) were taken at a cost of 51,000 Eu. Only six samples were positive, and the authors suggest that process control would be more cost-effective than product control (189). The problem is, however, unlike autoclaving where temperature and pressure are monitored, the parameters for chemical disinfection are more insubstantial because of nonuniformity during the process and accuracy of values measured.

Alternative, more rapid methods to assess efficacy of decontamination have been suggested, by using ATP levels or utilizing PCR *(190)*. Using the assessment of ATP levels, in one study 109 endoscopes were sampled (from the surface of the insertion tube and the channel orifice at the tip, at various times during the reprocessing cycle (predecontamination, postmanual cleaning, postdisinfection, and during storage). Although the level of ATP (as detected by a luminometer) fell during reprocessing, there was a poor correlation between the luminometer reading and the level of bacterial contamination as assessed by culture. Also, the test only detected rather high levels of bacteria (10^5–10^6 CFU) *(191)*. An alternative study sampled 63 endoscopes from eight locations, and recognizing that the coefficient of variance of ATP was lower than that of culture, did not correlate luminometer values with colony counts but set benchmarked values for contamination. Using these values, the main sites of contamination were suction channels predisinfection and endoscope tips postdisinfection *(192)*.

Microorganisms may reside in endoscopes even though they have undergone disinfection, and one report detailed an outbreak associated with *Pseudomonas* where the channels were heavily soiled with biofilm *(193)*.

Biofilm Despite the adherence to guidelines for reprocessing endoscopes, biofilm will develop in the endoscope and the AEW. There is no simple recognized

way of detecting the presence of biofilm or of determining reduction or eradication of the biofilm after attempted removal. Techniques do exist for assessing the biofilm and the spatial distribution of bacteria therein by the use of florescent *in situ* hybridization and 2/3D image analysis, and these have been applied to medical specimens *(194,195)*. An alternative method to assess microbes in biofilm is by the use of Syto 13 nucleic acid stain *(196)*. Specific biofilm-detaching agents have been investigated, and in one study the surface covered by the biofilm was assessed by crystal violet and the quantification of microorganisms by culture. The agent, which was 0.5% solution containing minerals, phosphates, amylases, lipases and proteases, was more active than current detergents at removing biofilm *(197)*.

Infection Risk and Drying of the Endoscope Another area of dispute is the need for reprocessing after storage in which there are differences between National Guidelines. If the endoscopes are not dried, then there is a growth of *Pseudomonas* that could present a potential source of infection. However, if stored in a drying cabinet, then the number of microorganisms fell with time, whereas if not stored in a drying cabinet, the number remained stable or even increased *(198)*. In another study, all ready-to-use endoscopes were assessed before reprocessing and after overnight storage. Out of 194 endoscopes tested, the contamination rate was 15.5%, and the median time from reprocessing the previous day was 18 hours. The most frequent microorganism isolated was coagulase-negative staphylococci, and the authors suggested that reprocessing at the beginning of the list is omitted *(199)*. In a further study of the effect of drying on the bioburden of duodenoscopes, endoscopes that had been processed in an automatic washer were sampled through the suction channel at 2, 24, and 48 hours postdisinfection (200). Fifty percent of the endoscopes were contaminated mainly with *Pseudomonas* species and mainly after 48 hours. After an additional drying period was introduced, the contamination fell to 0%, thus emphasizing the importance of drying the endoscope, particularly the channels, prior to storage. Similar results were obtained in a different study *(201)*. In this case, the bioburden following removal of the endoscope was 7.0×10^9, which was reduced to 1.3×10^5 by cleaning. Gram-negative bacilli were the most numerous contaminants (*E. coli* and *Bacteroides*) found immediately after removal and *Pseudomonas* after cleaning. In addition to microbial contamination, the endoscopes are also contaminated with organic matter. An investigation of the suction channel from a variety of endoscopes (bronchoscope, duodenoscope, colonoscope) was assessed immediately after removal from the patient and after mechanical cleaning but prior to disinfection or sterilization (202). The highest level of soiling was not unexpectedly found immediately after removal from the patient with high levels of protein, sodium, hemoglobin, bilirubin, carbohydrate, endotoxin, and bacteria. Colonoscopes were the most contaminated. After mechanical cleaning, the levels of most contaminants fell by 5- to 10-fold with a 3- to 5-log reduction in bacterial contamination. Although cleaning does reduce the level of bioburden and organic contamination, a significant amount still remains.

Transmissible Spongiform Encephalopathies and Endoscopy

Transmissible spongiform encephalopathies (TSE) are a group of neurologic conditions that lead to dementia and are caused by a protein agent called a prion, PrP^{sc}, which is an abnormal variant of a normal cellular protein PrP^{c} *(203)*. Prion proteins are resistant to inactivation by a wide range of sterilization and disinfection processes. The best known of the TSEs is CJD and a modified variant (vCJD) that was first reported in the United Kingdom in 1996 and that has different clinical and histopathologic appearances. This new-variant CJD is thought to have been transmitted to the human population via food products from beef cattle that were suffering from bovine spongiform encephalopathy (BSE or mad cow disease). Cattle are thought to have contracted BSE by having been fed on processed animal feed. The prion protein of vCJD is found in a wide distribution in the body including muscle, blood, and lymphoid tissue. Patients with vCJD do not give a history of contact with neurological tissue (dura mater, growth hormone), and because they may be asymptomatic, present a special risk for endoscopic procedures *(204)*. Thus, they are of particular concern in endoscopy in which biopsies are taken from the small intestine where there is a high concentration of Peyer's patches or ear, nose, and throat (ENT) endoscopy involving the tonsillar tissue *(205)*. The European Society of Gastrointestinal Endoscopy and the UK government have issued advice on preventing transmission of vCJD by endoscopy (8,206). The particular concern is the contamination of endoscopes by proteins that are resistant to removal or destruction, because current routine methods of sterilization or high-level disinfection are incapable of inactivating the prion. This places a greater emphasis on the physical cleaning steps prior to sterilization/disinfection and an argument for the use of disposable accessories, particularly biopsy forceps (see also Chapters 47 and 80).

Methods to destroy the prion protein are too harsh (e.g., autoclaving, concentrated sodium hydroxide) to be used on endoscopes. Some processes can inactivate the prion protein but can be damaging to instruments, particularly flexible ones. Autoclaving at 134° to 137°C for 18 minutes may be effective in some cases. Immersion in 1 N sodium hydroxide or 20,000 parts per million (ppm) free chlorine or 96% formic acid for 1 hour will inactivate prions but in the routine situation are not practicable (see also Chapter 80).

Alternative methods of inactivation and removing prions have been advocated: (i) Vaporized hydrogen peroxide (1.5 mg/L at 25°C for 3 hours) in conjunction with an enzymatic agent (Klenzym—0.8% at 43°C for 5 minutes); (ii) an alkaline cleaner (HAMO 100 detergent—1.6% at 43°C for 15 minutes); and (iii) a phenolic agent (EnvironLpH—5% at 20°C for 30 minutes) can reduce infectivity by >5.6 log. Neither the enzymatic cleaner on its own nor 20% peracetic acid at 55°C for 12 minutes have any effect on reducing infectivity, but vaporized hydrogen peroxide, on its own, reduces infectivity by 66% *(207)*. Another study *(208)* demonstrated that proteinase K + Pronase + sodium dodecyl sulfate (incubation at 40°C for 60 minutes) effectively removed prion proteins from steel. This study, however, used a concentrated human vCJD preparation compared to a preparation of the scrapie agent used by Fichet et al. (*207*).

A combination of copper sulfate and hydrogen peroxide (500 μM/L/7.5% 30 minutes) is also effective in decontaminating prions, reducing them by >5.25 log and can be used on thermosensitive endoscopes. It is also active against a wide range of viruses (adeno and polio virus), bacteria (*Pseudomonas*, *Enterococcus*, and *Mycobacteria*), and fungi (*Candida*) (209). More recently, a broad-spectrum agent consisting of 0.2% SDS + 0.3% NaOH + 20% 1 propanol has been reported and reduces prion infectivity by >5.5 log and is also active against a wide range of bacteria, viruses, and fungi *(210)*.

Washer/Disinfectors and Sterile Water

Washer/disinfectors are now recommended as part of the decontamination process rather than a manual wash, as they are more effective and more consistent, and reduce the potential contact with sensitizing agents *(211,212)*. Owing to both the reports of outbreaks of pseudoinfection with gram-negative bacteria and mycobacteria and the importance of removing contaminating organic material from endoscopes, the key role of the washer/disinfector has become an issue. Guidelines have been promulgated on the purchase of washer/disinfectors and the criteria that should be taken into consideration (213). Essentially, the machine must clean, disinfect, and rinse all channels, provide a supply of sterile water for terminal rinsing, contain and filter disinfectant fumes, be equipped with a self-disinfection cycle that irrigates all channels of the washer/disinfector, and finally provide a readout that can be incorporated into the patient's notes.

A controversial issue is the provision of sterile water for the terminal rinsing of endoscopes. In the United Kingdom, HTM 2030 *(214)* provides precise details on the routine testing of washer/disinfectors to achieve sterile rinse water, even down to the level of allowable endotoxin. However, doubt has been expressed as to its importance, particularly with respect to gastrointestinal endoscopes *(215)*, and concerns have been expressed as to the suitability and practicality of the standards *(216)*. The concern is the ability to actually obtain sterile rinse water, given the difficulty in controlling the formation of biofilm, which makes eradication of the microorganism from the internal channels of the washer disinfector very difficult *(217)*. A study of a new washer/disinfector that was fitted with a water-filtration system to provide a supply of sterile water showed that only 24% of the samples of final rinse water were culture negative over a 6-month period *(218)*. In some cases, fungal contamination was found *(219)*. Current methods of trying to obtain sterile water for rinsing include the use of pharmaceutical grade water (which is expensive and impractical), filters, UV light, raised water temperature, and the addition of a biocide.

Decontamination Processes

Items penetrating a sterile body cavity ideally should be sterile, although, as discussed above, there is some controversy over this. Nevertheless, rigid instruments can be autoclaved. Alternative methods include ethylene oxide, gas plasma, and low-temperature steam/formaldehyde or prolonged insertion in a disinfectant. In a cost analysis of sterilization methods for endoscopic instruments, ethylene oxide was the most expensive with gas plasma next and formaldehyde the cheapest. However, plasma sterilization was the quickest with the fastest turnaround time *(220)*.

If instruments have been used on a case of CJD, the UK recommendations are that they should be incinerated or kept in reserve for future use on a known case of CJD. For operations on known CJD patients, disposable equipment should be used as far as possible. If there is some doubt whether a patient has CJD or not, the instrument or endoscope should be quarantined until a histological diagnosis is available.

High-Level Disinfection of Flexible Endoscopes

High-level disinfection of flexible endoscopes involves initial manual cleaning, followed by the use of an automated washer/disinfector that initially mechanically washes the endoscope followed by a period of immersion in a suitable disinfectant. Until recently, 2% glutaraldehyde has been the most commonly used disinfectant. Its advantages are a long in-use life, a broad spectrum of activity, and compatibility with equipment. Its disadvantages are its capacity to cause sensitization in healthcare staff and that it fixes proteins to surfaces. This latter characteristic is unwanted in the light of concerns about prions. Further, some reports have highlighted the emergence of glutaraldehyde-resistance mycobacterial species from the biofilm in washer/disinfectors *(221)*.

Several other agents are now available for high-level disinfection of flexible endoscopes *(222,223)*. Generally, they are more active than glutaraldehyde, providing shorter contact times, but they are also more corrosive to equipment, more expensive, and have a shorter in-use life.

Orthophthalaldehyde

Orthophthalaldehyde (OPA) is a substitute for 2% glutaraldehyde. It has a lower vapor pressure than glutaraldehyde and is thus less likely to cause adverse reactions in healthcare staff, although it does have the same sensitization capacity as glutaraldehyde to exacerbate dermatitis or asthma. It has a similar spectrum of activity to glutaraldehyde, inactivating a broad range of bacteria, viruses, and fungi. It is active against HIV and HBV and is more active than glutaraldehyde against mycobacterial species *(224)*. Its activity against *Cryptosporidia* is, like glutaraldehyde, poor *(225)*. It is similar to glutaraldehyde in its in-use life and in its capacity to fix proteins. An environmental survey of 17 decontamination rooms where OPA was used was undertaken. In some of the rooms, open trays of OPA were used and in others decontamination was with an AEW. As one might anticipate, the environmental levels of OPA were higher in the rooms with open trays compared to the AEW (1.43 ppb compared to 0.35 ppb, respectively). Occupational exposure was also highest in these rooms (0.66 ppb compared to 0.33 ppb). Disinfection-related complaints were skin complaints (10%), eye complaints (9%), and respiratory complaints (16%) *(226)*.

Peracetic Acid

Peracetic acid is available as a liquid disinfectant or as part of a decontamination system incorporating a washer/disinfector (Steris Corporation, Mentor, OH) *(227,228)*. Peracetic acid has a broad spectrum of activity and has greater mycobactericidal activity than glutaraldehyde and is active against glutaraldehyde-resistant mycobacteria *(227,229–232)*. In a comparison with ethylene oxide, peracetic acid

was more effective at decontaminating lumina *(233)*, and in a prospective study of contamination in bronchoscopes there was no incidence of cross-contamination in 220 procedures. Additionally, artificial contamination with *M. gordonae* was effectively inactivated by peracetic acid *(234)*. It has a shorter in-use life and must be replaced daily. It also is corrosive to flexible endoscopes, and washer/disinfectors have to be modified in order to use the disinfectant.

In situ generation of peracetic acid linked to an AEW was assessed by artificially contaminating endoscopes (externally and internally) with *P. aeruginosa*, a glutaraldehyde-resistant *M. chelonae*, spores of *Clostridium difficile*, a vancomycin-resistant *Enterococcus* sp, and an MRSA *(235)*. In all cases, the process reduced all microorganisms to undetectable levels. This is particularly encouraging for *C. difficile* spores as spores are, by their nature, more resistant to disinfectants than vegetative bacteria. Moreover, a review of the literature on the transmission of *C. difficile* by endoscopy did not reveal any case of transmission linked to endoscopy *(236)* as long as accepted guidelines are adhered to.

Chlorine Dioxide

Chlorine dioxide is an effective disinfectant that has a broad spectrum of activity including spores and mycobacteria and some modest activity against cysts of gastrointestinal pathogens such as *Giardia* and *Cryptosporidia (237–240)*. It is corrosive and gives off irritant fumes, and some endoscope manufacturers do not recommend that chlorine dioxide be used on their products.

Superoxidized Water

Superoxidized water is the anodal product of the electrolysis of a salt solution. It is vital that the parameters of the electrolysis are adhered to, as an effective agent is only produced by electrolysis of a 0.05% solution of saline at 950 mV. The disinfectant has a broad range of activity *(241,242)* but is inactivated in the presence of organic matter and adversely affects the polymer coating of some endoscopes. The polymer of endoscopes can be protected with a coating of Optiflex or Scope Protection System (Sterilox Technologies Inc., Mount Olive, NJ). Its active half-life is <24 hours and should be used only once and then discarded. The disinfectant could be ideally tailored to be a component of an endoscope/washer disinfector and be continuously produced at the point of use.

Hydrogen Peroxide

Hydrogen peroxide has also been advocated as a disinfectant for endoscopes. In this study, 2% accelerated hydrogen peroxide (AHP) was used, which is a stabilized form and has a shelf life of 2 weeks and provides high-level disinfection within 5 minutes but only has sterilizing activity after 6 hours. It is a broad acting biocide and hydrolyzes to water and oxygen with a reduced occupational sensitivity hazard *(243)*.

Other Agents

Alcohol is an effective antimicrobial against vegetative bacteria including mycobacteria and viruses except for enteroviruses *(237,244)*. Alcohol does not have activity against bacterial spores. Because of the risk of fire, alcohol is not used as a primary disinfectant for endoscopes, but it is useful for flushing the channels as it enhances the drying of the endoscope. Prolonged exposure to alcohol can damage the polymer of the endoscope as well as the lens cement. Other compounds such as iodophors, peroxygen compounds, and quaternary ammonium compounds have been used in the past to decontaminate endoscopes and have been associated with cross-contamination. Newer formulations of some of these agents have been developed, but few data are available on their efficacy, and they are currently not recommended for high-level disinfection of flexible endoscopes.

Gas Plasma Technology

The Sterrad sterilization system (Johnson & Johnson, Irvine, CA) is a low-temperature method that utilizes hydrogen peroxide converted to a plasma, in a vacuum, by MHz electromagnetic radiation. The equipment resembles an autoclave, and like an autoclave a vacuum is drawn prior to injection of hydrogen peroxide. This is then converted to a plasma, and the free radicals kill a wide range of microorganisms including spores and mycobacteria *(245–247)*. For sterilization of endoscopes that have narrow channels, special adaptors are required for the end of each channel, or the channels will not be effectively decontaminated *(241)*. An organic load can also lead to the failure of decontamination *(248)* (see also Chapters 80 and 81).

A comparison of the four models of Sterrad (ASP Johnson & Johnson) indicated that the 50, 100, 100S, and 200 models were all comparable in sterilizing endoscopes *(249)*.

CONCLUSION

Infective complications of endoscopy are relatively rare. Few problems of infection occur with operative endoscopes that are sterilized or given high-level disinfection even though they penetrate sterile sites. The majority of infections associated with percutaneous and operative endoscopes relate to endogenous infection. These are principally bacteremia, endocarditis, or abscesses.

Although the incidence of crossinfection is low, outbreaks related to contaminated endoscopes are still reported in the literature. The principal cause of these cases is failure to adhere to recognized and accepted guidelines, and in order to reduce the already low risk of transmission this is an issue that can be addressed by education and continuous refresher training. Another main concern relates to biofilm, whether in the automated reprocessor or in the endoscope, and this problem is being addressed by development of agents, which will remove biofilm. Another important consideration is the ability to remove prions from the endoscopes, and again, agents are being developed that can destroy and or remove them. A third reason for failed reprocessing of endoscopes is a manufacturing fault in the endoscope. This is a problem more difficult for the end user to address.

Important for monitoring the reprocessing cycle, surveillance cultures of the reprocessor and the endoscope will give early warning of a failure and allow remedial action. Additionally, the tracking of instruments, which should be mandatory in any process control, will facilitate epidemiological investigation.

High-level disinfectants that have replaced aldehydes in some countries are more rapidly acting than glutaraldehyde

but have a shorter shelf life and are more corrosive. The long-term effects of these new disinfectants on staff are unknown, reinforcing the need for continual staff monitoring of the long-term health effects. Similarly, long-term follow-up of patients in the community will provide a more accurate assessment of the burden of postendoscopy infection.

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CHAPTER 63

Control of Infections Associated with Hemodialysis

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In 2007, there were approximately 340,000 maintenance hemodialysis patients receiving care at some 5,240 outpatient hemodialysis facilities (1). This represents about 92% of the end-stage renal disease (ESRD) population receiving renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation) in the United States. Approximately 2,999 (1%) hemodialysis patients perform self or assisted therapy in their homes. The ESRD program is administered by the Centers for Medicare and Medicaid Services (CMS) of the Department of Health and Human Services and is the only Medicare entitlement that is based on the diagnosis of a medical condition.

Maintenance hemodialysis patients are at increased risk for infection because uremia is known to make patients with ESRD more susceptible to infectious agents through defects in cellular immunity, neutrophil function, and complement activation *(2,3)*. In addition, since the process requires vascular access for extended periods and an extracorporeal circuit in an environment where multiple patients receive hemodialysis concurrently, repeated opportunities exist for transmission of infectious agents. Transmission of infectious agents, directly or indirectly through contaminated devices, equipment, supplies, dialysis fluids, injectable medications, environmental surfaces, or hands of healthcare personnel have all been demonstrated. Furthermore, hemodialysis patients require frequent hospitalizations and surgery, which increases their opportunities for exposure to healthcare-associated infections. This chapter describes (a) the major infectious diseases that can be acquired in the maintenance dialysis center setting, (b) important epidemiologic and environmental microbiologic considerations, and (c) infection control strategies.

MICROBIAL CONTAMINANTS IN HEMODIALYSIS SYSTEMS

Hemodialysis systems are complex and have components that contain a variety of fluid pathways that transport water, dialysate, dialysate effluent, and blood. These systems can become colonized or contaminated with a variety of microorganisms. There are many situations where certain types of water bacteria (gram negatives, environmental mycobacteria, and other gram positives) and fungi can persist and actively multiply in aqueous environments associated with hemodialysis equipment. This can result in the production of massive concentrations of microorganisms, primarily gram-negative bacteria, which can directly or indirectly affect patients by septicemia or endotoxemia *(4–17)*.

Gram-negative water bacteria are commonly found in water supplies used for hemodialysis. These bacteria, in conjunction with fungi, can adhere to surfaces and form biofilms (glycocalyces), which are virtually impossible to eradicate *(6,18–24)*. Control strategies are designed not to eradicate bacteria but to prevent establishment of biofilms *(25)*, reduce bacterial concentration to relatively low levels, and prevent their regrowth.

Although certain genera of gram-negative water bacteria (e.g., *Burkholderia*, *Delftia*, *Enterobacter*, *Flavobacterium*, *Hydrogenophaga*, *Methylobacterium*, *Pseudomonas*, *Ralstonia*, *Serratia*, *Sphingomonas*, and *Stenotrophomonas*) are most commonly encountered, virtually any bacterium that can grow in water can be a problem in a hemodialysis unit. Several species of environmental mycobacteria may also contaminate water treatment systems, including *Mycobacterium chelonae*, *M. abscessus*, *M. fortuitum*, *M. gordonae*, *M. mucogenicum*, *M. scrofulaceum*, *M. kansasii*, *M. avium*, and *M. intracellulare*; these microorganisms do not contain bacterial endotoxin but are comparatively resistant to chemical germicides *(26–31)*. Some investigators have also reported isolating fungi from water used to prepare dialysate (*18*,*19*,32,*33*).

Gram-negative water bacteria can multiply even in water containing relatively small amounts of organic matter, such as water treated by distillation, softening, deionization, or reverse osmosis, reaching levels of 10^5 to 10^7 microorganisms/mL *(6)*; these levels are not associated with visible turbidity. When treated water is mixed with dialysis concentrate, the resulting dialysis fluid is a balanced salt solution and growth medium almost as rich in nutrients as conventional nutrient broth *(6,34)*. Gram-negative water bacteria growing in dialysis fluids can reach levels of 10^8 to 10^9 microorganisms/mL, without producing visible turbidity.

Bacterial growth in water used for hemodialysis depends on the types of water treatment system used, dialysate distribution systems, dialysis machine type, and

The findings and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

TABLE 63-1

Factors Influencing Microbial Contamination in Hemodialysis Systems

Factors	*Comments*
Water Supply (Water Source)	
Ground water	Contains endotoxin and bacteria
Surface water	Contains high levels of endotoxin, bacteria, and other microorganisms
Water treatment at the dialysis center	
None	Not recommended
Filtration	
Prefilter	Particular filter to protect equipment; does not remove microorganisms
Absolute filter (depth or membrane)	Removes bacteria but unless changed frequently or disinfected, bacteria will accumulate and grow through the filter; acts as a significant reservoir of bacteria and endotoxin
Granular activated carbon (GAC)	Removes organics and available chlorine or chloramine; significant reservoir of water bacteria and endotoxin
Water treatment devices	
Ion exchange (softener, deionization)	Softeners and deionizers remove cations and anions, contaminants from source water; significant reservoir for bacteria and endotoxin
Reverse osmosis	Removes bacteria, endotoxin, chemicals, and must be cleaned and disinfected; most systems employed for dialysis applications operate under high pressure
Ultraviolet germicidal irradiator	Kills most bacteria, but there is no residual, some UV-resistant bacteria can develop
Ultrafilter	Removes bacteria and endotoxin; operates on normal line pressure; can be positioned distal to storage tank and deionizer; must be disinfected or changed
Water and dialysate distribution system	
Distribution pipes	
Size	Oversized diameters and length decrease fluid flow and increases bacterial reservoir in the form of biofilms for both treated water and central delivery systems (bicarbonate concentrate or bicarbonate dialysate)
Materials	Pipe materials influence bacterial colonization and biofilm formation, as well as what types of chemical disinfectants can be used
Construction	Rough joints, dead ends, and unused branches can act as bacterial reservoirs
Elevation	Outlet taps should be located at highest elevation to prevent loss of disinfectant
Storage tanks	Generally undesirable because of large surface area and can act as a reservoir for water bacteria; a properly designed tank can minimize this risk
Dialysis machines	
Single pass	Disinfectant should have contact time with all parts of the machine that are in contact with treated water or dialysate
Recirculating single pass, or recirculating batch	Recirculating pumps and machine design allow for massive contamination levels if not properly disinfected. Overnight disinfection has been recommended

method of disinfection (Table 63-1) *(6,20,26,35,36)*. Each component is discussed separately below.

Microbial Contamination of Water

Water used for the production of dialysis fluid must be treated to remove chemical and microbial contaminants. The Association for the Advancement of Medical Instrumentation (AAMI) has published guidelines and recommended practices for the chemical and microbial quality of water used to prepare dialysis fluid and reprocess hemodialyzers (Table 63-2) (*37*,*38*,39). Some components of the water treatment system may allow for amplification of water bacteria (Table 63-1). For example, ion exchangers such as water softeners and deionizers do not remove endotoxin or microorganisms, and provide many sites for significant bacterial multiplication *(40–42)*. Granular activated carbon adsorption media (i.e., carbon filters) are used primarily to remove certain organic compounds and available chlorine (free and combined) from water *(43–45)*, but they also significantly increase the level of water bacteria, yeast, fungi, and endotoxins *(46–48)*.

A variety of filters are marketed to control bacterial contamination of water and dialysis fluids. Most are inadequate, especially if they are not either routinely disinfected or frequently changed. Particulate filters, commonly called prefilters, operate by depth filtration, which allows

TABLE 63-2

AAMI Microbial Quality Standards for Dialysis Fluids

	Microbial Bioburden		*Endotoxin*	
Type of Fluid	*Maximum Contaminant Level*	*Action Level*	*Maximum Contaminant Level*	*Action Level*
Water for all purposes	200 CFU/mL	50 CFU/mL	2 EU/mL	1 EU/mL
Conventional dialysate	200 CFU/mL	50 CFU/mL	2 EU/mL	1 EU/mL
Ultrapure dialysate	1 CFU/10 mL		0.03 EU/mL	
Dialysate for infusion	1CFU/1,000 L[a]		0.03 EU/mL	

[a]Compliance with a maximum bacterial level of 10^{-6} CFU/mL cannot be demonstrated by culturing, but by processes developed by the machine manufacturers.

larger particles to be trapped near the surface of the filter while smaller particles penetrate the larger open areas to be trapped nearer the center of the filter in the smaller openings. Depth filters remove larger particulates from the water but do not remove bacteria or endotoxin; these filters can become colonized with gram-negative water bacteria, resulting in higher levels of bacteria and endotoxin in the filter effluent than in the feed water. Absolute filters, including membrane types, remove 100% of particles above the stated pore sizes (≥1 μm) and temporarily remove bacteria from passing water; however, some of these filters tend to clog, and gram-negative water bacteria can "grow through" the filter matrix and colonize downstream surfaces within a few days. Further, absolute filters do not reduce levels of endotoxin in the effluent water. All of these filters should be changed regularly in accordance with the manufacturer's directions and disinfected in the same manner and at the same time as the rest of the water distribution system.

Ultraviolet germicidal irradiation (UVGI) is sometimes used to reduce microbial contamination in water, but the use of UVGI has some special considerations. The lamp should be appropriately sized for the flow rate of water passing through the device, and the energy output should be monitored to insure effectiveness of the lamp. Manufacturers of the lamp may require a routine replacement schedule. Some bacterial populations may develop resistance to UVGI *(49)*. In recirculating dialysis distribution systems, repeated exposure to UVGI is used to ensure adequate disinfection; however, this approach allows for selection of UVGI-resistant microorganisms. In addition, bacterial endotoxins are not affected.

Reverse osmosis is an effective water treatment modality that is used in more than 97% of US hemodialysis centers, either alone or in combination with deionization *(50)*. Reverse osmosis possesses the singular advantage of being able to remove a variety of substances including microorganisms and endotoxin from supply water based primarily on particle size and adsorption to the membrane. However, low numbers of microorganisms may penetrate the membrane or by other means (leaks around seals) colonize downstream portions of the water distribution system. Consequently, the reverse osmosis unit must be disinfected routinely.

A water treatment system that produces chemically adequate water while avoiding high levels of microbial contamination is highly recommended. The components in a typical water system should include (a) prefilters, (b) a water softener, (c) carbon adsorption tanks (at least two in series), (d) a particulate filter or absolute filter (to protect the reverse osmosis membrane), and (e) a reverse osmosis unit. If one includes a deionization unit as a polisher (postreverse osmosis unit) or a storage tank, the final component in the system should be an ultrafilter to remove both microorganisms and endotoxin *(51,52)*. As the incoming tap water passes through the system components, it becomes more chemically pure, but the level of microbial contamination increases, which is why the use of reverse osmosis and ultrafiltration is important. Additional components or processes may be included in the pretreatment chain (Table 63-1) depending on the pH, potable water disinfectant, and the chemical quality of the incoming municipal water *(52)*. If the system is adequately disinfected and properly maintained, the microbial content of water should be well within the recommended limits.

Distribution Systems

Water that has passed through the water distribution system (product water) is then distributed to individual dialysis machines, where it is combined with dialysate concentrates (bicarbonate and acid concentrates), and to a reprocessing area if a facility reprocesses hemodialyzers for reuse. It may also be combined with concentrates at a central location where the resulting dialysis fluid is supplied to the individual machines. Plastic pipe (most often schedule 80 polyvinyl chloride) is then used to distribute water or dialysis fluids to the dialysis machines. Distribution systems should include the use of a loop-based system and no dead end pipes (dead legs). Outlets to dialysis machines should have a relatively short path with the least amount of fittings and the use of valves with minimal dead space. Voids, dead ends, and large surface areas serve as sites for microbial colonization. Large-diameter pipes decrease fluid velocity and increase the wetted surface area available for microbial colonization *(34,53)*, and long pipe runs increase the available surface area for colonization; therefore, both of these situations should be avoided if possible. Gram-negative water bacteria in fluids remaining in pipes overnight can rapidly multiply and colonize wetted surfaces of the distribution system, producing microbial populations and endotoxin in quantities proportional to the total volume of the surface area. Such colonization results in the formation of protective biofilm, which is difficult to remove and protects the bacteria and other microorganisms from disinfection (54).

Routine disinfection of the water or dialysate distribution system should be performed on a regular basis so that the microbial quality of the fluids is within the acceptable standards range. The minimum frequency of disinfection may be at least monthly *(34,51)*. However, AAMI standards and recommended practices are community consensus standards, and do not specify a schedule for disinfection other than to suggest that routine disinfection be conducted. In many instances, microbiologic monitoring can be used to determine the frequency of testing and disinfection of the distribution system *(51,52)*.

To prevent disinfectant from draining from pipes by gravity before adequate contact time, distribution systems should be designed with all taps at equal elevation and at the highest point of the system. Furthermore, the system should be free of rough joints, dead ends, oversized pipes, and long pipe runs. Fluid trapped in such stagnant areas can serve as reservoirs for bacteria and fungi that later contaminate the rest of the distribution system *(55)*.

Storage tanks greatly increase the volume of fluid and surface area of the distribution system. If used, these should be designed with a conical-shaped bottom so that water exits the storage tank at its lowest point (and allows the tank to be drained), fitted with a tight sealing lid, and equipped with a spray head, and possesses an air vent containing a bacteriologic filter. Storage tanks should also be routinely cleaned, disinfected, and drained. In order to remove biofilm, use of strong oxidizers may aid in stripping biofilm from surfaces; however, physical scrubbing of the inner surfaces of the tank may be necessary. When using a storage tank, an ultrafilter should be incorporated before water is pumped into the distribution system *(51,52)*.

Hemodialysis Machines

In the 1970s, most dialysis machines were of the recirculating or recirculating single-pass type; their design contributed to relatively high levels of gram-negative bacterial contamination in dialysis fluid. Currently, virtually all dialysis machines in the United States are single-pass machines. Single-pass machines tend to respond to adequate cleaning and disinfection procedures and, in general, have lower levels of bacterial contamination than do recirculating machines. Levels of contamination in single-pass machines depend primarily on the microbiologic quality of the incoming water and the method of machine disinfection *(6,51)*.

Disinfection of Hemodialysis Systems Routine disinfection of isolated components of the dialysis system frequently produces inadequate results. Consequently, the total dialysis system (water treatment system, distribution system, and dialysis machine) should be included in the disinfection procedure.

Disinfection of dialysis systems usually employs sodium hypochlorite solutions, hydrogen peroxide solutions, commercially available peracetic or peroxyacetic acid (PAA) disinfectants, ozone, and in some systems hot-water pasteurization. Sodium hypochlorite solutions are convenient and effective in most parts of the dialysis system when used at the manufacturer's recommended concentrations. Also, the test for residual available chlorine to confirm adequate rinsing is simple and sensitive. However, because chlorine is corrosive, it is usually rinsed from the system after a relatively short dwell time of 20 to 30 minutes. The rinse water invariably contains microorganisms that can multiply to significant levels if the system is permitted to stand overnight *(34)*. Therefore, disinfection with chlorine-based disinfectants is best performed before the start of the first patient treatment session rather than at the end of the day. In centers dialyzing patients in multiple shifts with either batch or recirculating hemodialysis machines, it may be reasonable to disinfect with chlorine-based disinfectants between shifts and with another disinfectant or process (e.g., PAA) at the end of the day. Single-pass machines may be disinfected at the end or beginning of the treatment day.

Aqueous formaldehyde, PAA, hydrogen peroxide, or glutaraldehyde solutions can produce good disinfection results *(20,56,57)*. These products are not as corrosive as hypochlorite solutions and can be allowed to dwell in the system for long periods of time when the system is not in operation. However, formaldehyde, which has good penetrating power, is considered an environmental hazard and potential carcinogen and has irritating qualities that may be objectionable to staff *(58)*. The U.S. Environmental Protection Agency (EPA) has also limited the amount of formaldehyde that can be discharged into the wastewater stream, which has drastically reduced the use of this chemical in the dialysis community as a disinfectant. PAA and hypochlorite-based products are commercially available and are designed for use with dialysis machines when used according to the manufacturers' labeled instructions. Glutaraldehyde use is limited because it is considered to be a sensitizer and may pose a risk to healthcare workers; it is more frequently used for dialyzer reprocessing and only in a minority (<4%) of facilities in the United States (59).

Some dialysis systems (both water treatment and distribution systems, some hemodialysis machines) use hot-water disinfection (pasteurization) for control of microbial contamination. In this type of system, water heated to >80°C (176°F) is passed either through the water distribution system and the fluid pathway of the hemodialysis machine, or just through the hemodialysis machine at the end of the day. These hot-water systems are excellent for controlling microbial contamination.

Monitoring of Water and Dialysis fluid

Microbiologic and endotoxin standards for water and dialysis fluids were originally based on the results of culture assays performed during epidemiologic investigations *(34,35,52,53,60)*. However, as knowledge improved about the long-term effect of dialysis fluids on patient inflammatory responses, the recommended microbial standards have been revised (Table 63-2) (*37,38,*39). There is increasing evidence that the microbial quality of hemodialysis fluids plays a role in the chronic inflammatory response syndrome impacting anemia management, serum albumin level, and rate of loss of residual renal function in dialysis patients (61,*62–66*,67,*68*,69,*70–75*). Increasing data suggest that use of ultrapure water and dialysate would benefit maintenance dialysis patients. However, there have been no randomized controlled studies to evaluate and confirm the impact on health outcomes.

Water samples should be collected from a source as close as possible to where water enters the dialysate proportioning unit. In most cases, this is the tap (not from the hose

connecting the tap to the dialysis machine) at the dialysis station, but may also be a sampling port on the hemodialysis machine. Water samples should be collected at least monthly (more frequent monitoring may be necessary) from several locations within the dialysis unit. Samples should also be collected after any modifications or maintenance has been made to the water treatment system or water distribution system. Dialysate samples should be collected during or at the end of the dialysis treatment from a source close to where the dialysis fluid either enters or leaves the dialyzer. Dialysate samples should be collected at least monthly from a representative number of dialysis machines. Samples of water and dialysate should also be collected whenever pyrogenic reactions are suspected *(53)*. If centers reprocess hemodialyzers for reuse on the same patient, water used to prepare disinfectant and rinse dialyzers should also be assayed monthly. The maximum contaminant levels are 200 CFU/mL and 2 EU/mL (Table 63-2) (*37*,*38*,39).

Specimens should be assayed within 30 minutes of collection or refrigerated at 4°C and assayed within 24 hours of collection. Conventional laboratory methods, such as the spread plate or membrane filter technique, can be used. Calibrated loops should not be used because they sample only a small volume, are inaccurate, and often do not have the sensitivity to detect the current action or maximum contamination limits. Blood and chocolate agar media should not be used because the microorganisms have adapted to nutrient-poor environments and thus require specific media designed for the recovery of microorganisms from water. In addition, microorganisms that are found in bicarbonate dialysis fluids require a small amount of sodium chloride. Consequently, to cover both conditions needed, trypticase soy agar (soybean casein digest agar) is currently recommended; however, standard methods agar, plate count agar, or tryptose glucose yeast extract agar may also be used (39,*76*,*77*). The assay should be quantitative, not qualitative, and a standard technique for enumeration should be used. Colonies should be counted after 48 hours of incubation at 36°C (39,*51–53*,*78*,*79*). Total viable counts are the objective of plate counts. Endotoxin testing should be conducted using either the *Limulus* amebocyte lysate assay, Gel-clot method, or one of the kinetic methods.

In an outbreak investigation, the assay methods may need to be both qualitative and quantitative; detection of nontuberculous mycobacteria and, in some cases, fungi in water or dialysate may be desirable. In such instances, plates should be incubated for 5 to 14 days at both 36°C and 28°C to 30°C.

DIALYSIS-ASSOCIATED PYROGENIC REACTIONS

Gram-negative bacterial contamination of dialysis water or components of the dialysis system (water, dialysate, water used for reprocessing) can cause pyrogenic reactions. Pyrogenic reactions are defined as objective chills (visible rigors), fever (oral temperature ≥37.8°C [100°F]), or both in a patient who was afebrile (oral temperature up to 37°C [98.6°F]) and had no signs or symptoms of an infection before the start of the dialysis treatment session *(11,80,81)*. Depending on the type of dialysis system and the level of contamination, fever and chills may start 1 to 5 hours after dialysis has been initiated. Other symptoms may include hypotension, headache, myalgia, nausea, and vomiting. Pyrogenic reactions can occur without bacteremia; because presenting signs and symptoms cannot differentiate bacteremia from pyrogenic reactions, blood cultures are necessary.

During 1990 to 2002, an annual average of 20% to 24% of the hemodialysis centers in the United States reported at least one pyrogenic reaction in the absence of septicemia in patients undergoing maintenance dialysis (*50*,59,*82–90*). Pyrogenic reactions can result from passage of bacterial endotoxin (lipopolysaccharide [LPS]) or other substances in the dialysate across the dialyzer membrane (*91–94*,95) or from the transmembrane stimulation of cytokine production in the patient's blood by endotoxin in the dialysate *(92,96–98)*. In other instances, endotoxin can enter directly into the bloodstream with fluids that are contaminated with gram-negative bacteria *(99)*. The signs and symptoms of pyrogenic reactions without bacteremia generally abate within a few hours after the dialysis has been stopped. If gram-negative sepsis is associated, fever and chills may persist, and hypotension is more refractory to therapy *(4,99)*.

When a pyrogenic reaction occurs, the following steps are usually recommended: (a) careful physical examination of the patient to rule out other causes of chills and fever (e.g., pneumonia, vascular access infection, urinary tract infection); (b) blood cultures, and other diagnostic tests (e.g., chest radiograph), and other cultures as clinically indicated; (c) collection of dialysate from the dialyzer (downstream side) for quantitative and qualitative microbiological culture; and (d) recording of the incident in a log or other permanent record. Determining the cause of these episodes is important, because they may be the first indication of a remediable problem.

The higher the level of bacteria or endotoxin in dialysis fluid, the higher is the probability that the bacteria or their products will pass through the dialyzer membrane, thus producing bacteremia or a pyrogenic reaction by stimulating cytokine production in a patient. In an outbreak of febrile reactions among patients undergoing hemodialysis, attack rates were directly proportional to the level of microbial contamination in the dialysis fluid *(6)*. Prospective studies also demonstrated a lower pyrogenic reaction rate among patients when they underwent dialysis with dialysis fluid from which most bacteria had been removed, compared to patients who underwent dialysis with fluid that was highly contaminated (mean 19,000 CFU/mL) *(5,80,100)*.

Among nine outbreaks of bacteremia, fungemia, and pyrogenic reactions not related to dialyzer reuse investigated by the Centers for Disease Control and Prevention (CDC), inadequate disinfection of the water distribution system or dialysis machines was implicated in seven (Table 63-3) *(4,9,55,101–105)*. The most recent outbreaks occurred at dialysis centers using dialysis machines that had a port (waste-handling option or WHO port) that allowed disposal of the extracorporeal circuit priming fluids. One-way check valves in the WHO had not been maintained, checked for competency, or disinfected as recommended, thus allowing backflow from the effluent dialysate path into and contamination of the port and the attached blood line (103,*104*,*105*).

TABLE 63-3

Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008

Description	*Cause(s) of Outbreak*	*Corrective Measure(s) Recommended*	*Reference*
Bacteremia, Fungemia, or Pyrogenic Reactions not Related to Dialyzer Reuse			
Pyrogenic reactions in 49 patients	Untreated city water contained high levels of endotoxin	Install a reverse osmosis system	*(4)*
Pyrogenic reactions in 45 patients	Inadequate disinfection of the fluid distribution system	Increase disinfection frequency and contact time of the disinfectant	(55)
Pyrogenic reactions in 14 patients; 2 bacteremia; 1 death	Reverse osmosis water storage tank contaminated with bacteria	Remove or properly maintain and disinfect the storage tank	*(35)*
Pyrogenic reactions in six patients; seven bacteremias	Inadequate disinfection of water distribution system and dialysis machines; improper microbial assay procedure	Use correct microbial assay procedures; disinfect water treatment system and dialysis machines following manufacturer's recommended procedures	*(301)*
Bacteremia in 35 patients with central venous catheters (CVCs)	CVCs used as facilities primary vascular access; median duration of infected catheters was 311 d; improper aseptic techniques	Uses CVCs when only absolutely necessary for vascular access; use appropriate aseptic technique when inserting and performing routine catheter care	*(302)*
Three pyrogenic reactions and 10 bacteremias in patients treated on machines with a port for disposal of dialyzer priming fluid (waste-handling option or WHO port)	Incompetent check valves allowing backflow of fluid from the waste side of the machine into attached blood tubing; bacterial contamination of the WHO	Routine disinfection and maintenance of the dialysis machine including the WHO; check competency of WHO prior to patient treatment	(103)
Bacteremia in 10 patients treated on machines with WHO port	Incompetent backflow to allow backflow from dialysate effluent side of the machine in the WHO port and attached bloodlines	Routine maintenance, disinfection, and check for valve competence of the WHO port	*(104)*
Outbreak of pyrogenic reactions and gram-negative bacteremia in 11 patients	Water distribution system and machines were not routinely disinfected according to manufacturer's recommendations. Water and dialysate samples were cultured using a calibrated loop and blood agar plates—results were always as no growth	Disinfect machines according to manufacturer's recommendations and include reverse osmosis water distribution system in the weekly disinfection schedule; microbiological assay should be performed via membrane filtration or spread plate using Trypticase Soy agar	*(9)*
Phialemonium curvatum access infections in four dialysis patients; two of these patients died of systemic disease	Observations at the facility noted some irregularities in site prep for needle insertion. All affected patients had synthetic grafts. One environmental sample was positive for *P. curvatum* (condensate pan of HVAC serving the unit)	Review infection control practices and clean and disinfect HVAC system where water accumulated. Perform surveillance on all patients	*(303)*
Phialemonium curvatum blood stream infections in two patients	Water system and dialysis machines with WHO ports not routinely maintained; water system contained dead legs and lab used wrong assays	Conduct routine maintenance and disinfection of machines and WHO ports; redesign water system to eliminate dead legs; have a routine schedule for disinfection of the water system	*(105)*
Bacteremia/Pyrogenic Reactions Related to Dialyzer Reprocessing			
Mycobacterial infections in 27 patients	Inadequate concentration of dialyzer disinfectant	Increase formaldehyde concentration used to disinfect dialyzers to 4%	*(27)*
Mycobacterial infections in five high-flux dialysis patients; two deaths	Inadequate concentration of dialyzer disinfectant and inadequate disinfection of water treatment system	Use higher concentration of peracetic acid for reprocessing dialyzers and follow manufacturers labeled recommendations; Increase frequency of disinfecting the water treatment system	*(304)*

(*Continued*)

TABLE 63-3

Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008 (*Continued*)

Description	*Cause(s) of Outbreak*	*Corrective Measure(s) Recommended*	*Reference*
Bacteremia in six patients	Inadequate concentration of dialyzer disinfectant; water used to reprocess dialyzers did not meet AAMI standards	Use AAMI quality water; insure proper germicide concentration in the dialyzer	CDC unpublished data
Bacteremia and pyrogenic reactions in six patients	Dialyzer disinfectant diluted to improper concentration	Use disinfectant at the manufacturers' recommended dilution and verify concentration	*(79)*
Bacteremia and pyrogenic reactions in six patients	Inadequate mixing of dialyzer disinfectant	Thoroughly mix disinfectant and verify proper concentration	*(10)*
Bacteremia in 33 patients at two dialysis centers	Dialyzer disinfectant created holes in the dialyzer membrane	Change disinfectant (product was withdrawn from the market place by the manufacturer)	*(305,306)*
Bacteremia in six patients; all blood isolates had similar plasmid profiles	Dialyzers were contaminated during removal and cleaning of headers with gauze; staff not routinely changing gloves; dialyzers not reprocessed for several hours after disassembly and cleaning	Do not use gauze or similar material to remove clots from header; change gloves frequently; process dialyzers after rinsing and cleaning	*(307)*
Pyrogenic reactions in three high-flux dialysis patients	Dialyzer reprocessed with two disinfectants; water for reuse did not meet AAMI standards	Do not disinfect dialyzers with multiple germicides; more frequent disinfection of water treatment system and conduct routine environmental monitoring of water for reuse	*(308)*
Pyrogenic reactions in 14 high-flux dialysis patients; one death	Dialyzers rinsed with city (tap) water containing high levels of endotoxin; water used to reprocess dialyzers did not meet AAMI standards	Do not rinse or reprocess dialyzers with tap water; use AAMI quality water for rinsing and preparing dialyzer disinfectant	*(309)*
Pyrogenic reactions in 18 patients	Dialyzers rinsed with city (tap) water containing high levels of endotoxin; water used to reprocess dialyzers did not meet AAMI standards	Do not rinse or reprocess dialyzers with tap water; Use AAMI quality water for rinsing and preparing dialyzer disinfectant	*(11)*
Pyrogenic reactions in 22 patients	Water for reuse did not meet AAMI standards; improper microbiological technique was used on samples collected for monthly monitoring	Use the recommended assay procedure for analysis of water and dialysate; disinfect water distribution system	*(8)*
Bacteremia and candidemia among patients in seven dialysis units (MN and CA)	Dialyzers were not reprocessed in a timely manner; some dialyzers refrigerated for extended periods of time before reprocessing; Company recently made changes to header cleaning protocol	Reprocess dialyzers as soon as possible; follow joint CDC and dialyzer reprocessing equipment and disinfectant manufacturer guidance for cleaning and disinfecting headers of dialyzer	CDC unpublished data
Transmission of Viral Agents			
26 patients seroconvert to HBsAg+ during a 10-mo period	Leakage of coil dialyzer membranes and use of recirculating bath dialysis machines	Separation of HBsAg+ patients and equipment from all other patients	*(181)*
19 patients and 1 staff member seroconvert to HBsAg+ during a 14-mo period	No specific cause determined; false-positive HBsAg results caused some susceptible patients to be dialyzed with infected patients	Laboratory confirmation of HBsAg+ results; strict adherence to glove use and use of separate equipment for HBsAg+ patients	*(310)*
24 patients and 6 staff seroconverted to HBsAg+ during a 10-mo period	Staff not wearing gloves; surfaces not properly disinfected; improper handling of needles/sharps resulting in many staff needlestick injuries	Separation of HBsAg+ patients and equipment from susceptible patients; proper precautions by staff (e.g., gloves; handling of needles and sharps)	*(181)*

TABLE 63-3

Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008 (*Continued*)

Description	*Cause(s) of Outbreak*	*Corrective Measure(s) Recommended*	*Reference*
13 patients and 1 staff member seroconvert to HBsAg+ during a 1-mo period	Extrinsic contamination of intravenous medication being prepared adjacent to an area where blood samples were handled	Separate medication preparation area from area where blood processing for diagnostic tests is performed	*(186)*
Eight patients seroconverted to HBsAg+ during a 5-mo period	Extrinsic contamination of multidose medication vial shared by HBsAg+ and HBV-susceptible patients	No sharing of supplies, equipment, and medications between patients	(CDC, unpublished data)
Seven patients seroconverted to HBsAg+ during a 3-mo period	Same staff caring for HBsAg+ and HBV-susceptible patients	Separation of HBsAg+ patients from other patients; same staff should not care for HBsAg+ and HBV susceptible patients	*(181)*
Eight patients seroconverted to HBsAg+ during 1 mo	Not consistently using external pressure transducer protectors; same staff members cared for both HBsAg+ patients and HBV-susceptible patients	Use external pressure transducer protectors and replace after each use; same staff members should not care for HBV-infected and susceptible patients on the same shift	*(300)*
14 patients seroconvert to HBsAg+ during a 6-wk period	Failure to review results of admission and monthly HBsAg testing; inconsistent hand washing and use of gloves; adjacent clean and contaminated areas; <20% of patients vaccinated	Proper infection control precautions for dialysis facilities; routine review of serologic testing; hepatitis B vaccination of all patients	*(184)*
Seven patients on the same shift seroconvert to HBsAg+ during a 2-mo period	Same staff members cared for HBsAg+ and HBV-susceptible patients on the same shift; common medication and supply carts were moved between stations, and multidose vials were shared; no patients vaccinated	Dedicated staff for HBsAg+ patients; no sharing of equipment or supplies between any patients; centralized medication and supply areas; hepatitis B vaccination of all patients	*(184)*
Four patients seroconverted to HBsAg+ during a 3-mo period	Transmission appeared to occur during hospitalization at an acute-care facility; no patients vaccinated	Hepatitis B vaccination of all patients	*(184)*
11 patients seroconverted to HBsAg+ during a 3-mo period	Staff, equipment, and supplies were shared between HBsAg+ and HBV-susceptible patients; no patients were vaccinated	Dedicated staff for HBsAg+; no sharing of medication or supplies between any patients; hepatitis B vaccination of all patients	*(184)*
Two patients converted to HBsAg+ during a 4-mo period	Same staff cared for HBsAg+ and HBV-susceptible patients; no patients vaccinated	Hepatitis B vaccination of all patients; dedicate staff for the care of HBsAg+ patients; no sharing of supplies or medication between patients	*(184)*
Six patients converted to HBsAg+ during a 6-mo period	Transmission occur during hospitalization at an acute-care facility; same staff cared for HBsAg+ and HBV-susceptible patients; no patients vaccinated	Hepatitis B vaccination of all patients; review HBsAg status of chronic hemodialysis patients who require hospitalization; no sharing of equipment, supplies, or medication between patients	*(187)*
36 patients with liver enzyme elevations consistent with Non-A, Non-B hepatitis	Environmental contamination with blood	Utilize proper precautions (e.g., gloving of staff; environmental cleaning); monthly liver function tests (e.g., ALT)	*(308)*
35 patients with elevated liver enzymes consistent with Non-A, Non-B hepatitis during a 22-mo period; 82% of probable cases were anti-HCV+	Inconsistent use of infection control precautions, especially hand washing	Strict compliance to aseptic technique and dialysis center precautions	*(311)*

(*Continued*)

TABLE 63-3

Outbreaks of Dialysis-Associated Illnesses Investigated by the Centers for Disease Control and Prevention, 1975–2008 (*Continued*)

Description	*Cause(s) of Outbreak*	*Corrective Measure(s) Recommended*	*Reference*
HCV infection developed in 7/40 (18%) HCV-susceptible patients; shift specific attack rates of 29–36%	Multidose vials left on top of machine and used for multiple patients; routine cleaning and disinfection of surfaces and equipment between patients not routinely done; arterial line for draining prime dripped into a bucket that was not routinely cleaned or disinfected between patients	Strict compliance with infection control precautions for all dialysis patients; routine HCV testing	(*252*,253)
HCV infection developed in 5/61 (8%) HCV-susceptible patients	Sharing of equipment and supplies between chronically infected and susceptible patients; gloves not routinely used; clean and contaminated areas not separated	Strict compliance with infection control precautions for all dialysis patients; CDC does not recommend separation of equipment/supplies between HCV-infected and susceptible patients	(*252*,253)
HCV infection developed in 3/23 (13%) HCV-susceptible patients; shift specific attack rate 27%	Supply carts moved between stations and contained both clean and blood-contaminated items; medications prepared in the same area used for disposal of used injection equipment	Strict compliance with infection control precautions for all dialysis patients	(*252*,253)
HCV infection developed in 7/52 (13%) HCV-susceptible patients; shift specific attack rates 4–21%	Medication cart moved between stations and contained both clean and blood-contaminated items; single-dose medication vials used for multiple patients; cleaning and disinfection of surfaces and equipment between patients not routinely done	Strict compliance with infection control precautions for all dialysis patients	(*252*,253)
HCV infection developed in 9/90 (10%) HCV-susceptible patients.	Cleaning and disinfection of surfaces and equipment between patients not routinely done; gloves not routinely used; medications not stored in separate clean area	Strict compliance with infection control precautions for all dialysis patients; routine HCV testing	*(254)*
HCV infection developed in 8/107 (7.5%) HCV-susceptible patients	Poor medication handling and infusion practices	Proper training of personnel on aseptic technique and compliance with infection control precautions for dialysis setting	*(255)*

Hemodialyzer Reuse

From 1976 to 1997, the percentage of maintenance dialysis centers in the United States that reported reuse of disposable hollow-fiber dialyzers increased steadily; the largest increase (126%) occurred during the period between 1976 and 1982, when percentage of facilities reprocessing dialyzers increased from 18% to 43%, and the percentage of facilities reprocessing peaked at 82% in 1997 (*90*). However, the percentage of facilities reporting reusing dialyzers had declined to 63% in 2002 (59). This decline was primarily driven by a large dialysis chain's decision to discontinue the practice of reuse and to only use single-use dialyzers.

In 1986, AAMI Standards for reprocessing hemodialyzers *(106)* were adopted by the United States Public Health Service (USPHS) and were incorporated into regulation by the CMS. In general, dialyzer reuse appears to be safe if performed according to strict and established protocols *(22)*. In the United States, dialyzer reuse has not been associated with the transmission of blood-borne pathogens such as hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) *(107,108)*. However, the reprocessing of dialyzers has been associated with pyrogenic reactions *(107)*. These adverse events may be the result of the use of incorrect concentrations of chemical germicides, failure to maintain appropriate water quality, or improper cleaning (e.g., header cleaning practices). Manual reprocessing of dialyzers that does not include a test for membrane integrity, such as a pressure-leak test, may fail to detect membrane defects and may be a cause of both pyrogenic reactions and bacteremia *(107,108)*.

The procedures used to reprocess hemodialyzers generally constitute high-level disinfection rather than sterilization *(22,109)*. There are several liquid chemical germicides that have been used for high-level disinfection of dialyzers. Formaldehyde is a chemical solution from chemical supply houses and is not specifically formulated for dialyzer disinfection. There are commercially available chemical germicides specifically formulated for this purpose (e.g., PAA, chlorine-, and glutaraldehyde-based products) that are approved by the U.S. Food and Drug Administration (FDA) as sterilants or high-level disinfectants for reprocessing hemodialyzers. During the period between 1983 and 2002, the percentage of centers using formaldehyde for reprocessing dialyzers decreased from 94% to 20%, while the percentage using PAA increased from 5% to 72%. Only a minority of facilities (4%) reported using either glutaraldehyde or heat disinfection (59).

In 1983, most centers used 2% aqueous formaldehyde with a contact time of approximately 36 hours to disinfect dialyzers *(110)*. In 1982, a dialysis center using this regimen experienced an outbreak of infections caused by nontuberculous mycobacteria *(27)*. It was subsequently shown that the 2% formaldehyde regimen was not effective against nontuberculous mycobacteria. Rather, a regimen of 4% formaldehyde with a minimum contact time of 24 hours was required to inactive high numbers of these microorganisms and was recommended as the minimum solution for reprocessing dialyzers *(22,107,109)*. A similar outbreak of systemic mycobacterial infections in five hemodialysis patients, resulting in two deaths, occurred when high-flux dialyzers were contaminated with *M. abscessus* during manual reprocessing and disinfected with a commercial disinfectant prepared at a concentration that did not ensure complete inactivation of mycobacteria *(28)*. These two outbreaks of infections in dialysis patients emphasize the need to use dialyzer disinfectants at concentrations that are effective against more chemically resistant microorganisms, such as mycobacteria.

Outbreaks of pyrogenic reactions have often resulted from reprocessing hemodialyzers with water that did not meet AAMI standards (Table 63-3). In most instances, the water used to rinse dialyzers or to prepare the dialyzer disinfectants exceeded the allowable AAMI microbial or endotoxin standards, because the water distribution system was not disinfected frequently, the disinfectant was improperly prepared, or routine microbial assays were improperly performed.

High-Flux Dialysis and Bicarbonate Dialysate

High-flux dialysis uses dialyzer membranes with hydraulic permeability that is 5 to 10 times greater than conventional dialyzer membranes. There has been concern that bacteria or more likely endotoxin in the dialysate may penetrate these highly permeable membranes.

Another concern is that high-flux membranes require the use of bicarbonate rather than acetate dialysate. Acetate dialysate is prepared from a single concentrate with a high salt molarity (4.8 M) that does not support the growth of most bacteria. Bicarbonate dialysate, however, must be prepared from two concentrates, an acid concentrate (acetic acid) with a pH of 2.8 that is not conducive to microbial growth and a bicarbonate concentrate with a relatively neutral pH and a salt molarity of 1.2 M. Because the bicarbonate concentrate will support rapid growth *(79)*, its use can increase microbial and endotoxin concentrations in the dialysate and theoretically may contribute to an increase in pyrogenic reactions, especially when used during high-flux dialysis.

Some of the concern appeared justified by results of surveillance data during the 1990s showing a significant association between use of high-flux dialysis and reporting of pyrogenic reactions among patients during dialysis *(111)*. However, a prospective study of pyrogenic reactions in patients receiving more than 27,000 conventional, high-efficiency, or high-flux dialysis treatments with dialysate containing high concentrations of bacteria and endotoxin found no association between pyrogenic reactions and the type of dialysis treatment *(5)*. Although there seem to be conflicting data on the relationship between high-flux dialysis and pyrogenic reactions, centers providing high-flux dialysis should ensure that dialysate meets AAMI microbial standards (Table 63-2).

BACTERIAL AND FUNGAL INFECTIONS

Annual adjusted mortality rates among hemodialysis patients are between 203.3 (patients on dialysis <2 years) and 245.1 (patients on dialysis >5 years) deaths per 1,000 patient years at risk (1). Infection is the second leading cause of mortality in this patient population (32.7/1,000 patient years at risk); septicemia is the leading cause of infectious mortality *(112)*. In a number of published studies that have evaluated bacterial infections in outpatient hemodialysis, bacteremia occurred in 0.6% to 1.7% of patients per month and vascular access infections (with or without bacteremia) in 1.3% to 7.2% of patients per month (*113–123*). A review of four studies published during 2002 estimated that 1.8% of hemodialysis patients have bacteremia each month, amounting to at least 50,000 cases nationally per year *(124)*.

Because of the importance of bacterial infections in hemodialysis patients, CDC initiated a voluntary ongoing surveillance project in 1999 in which all US maintenance hemodialysis centers are eligible to enroll *(122)*. Bloodstream infections as well as hospital admissions and intravenous antimicrobial administrations are counted. Since infections treated with outpatient oral antimicrobials are excluded, this system likely only detects more severe infections. During 2006, 32 dialysis centers reported data on 28,047 patient months (125). Bloodstream infection rates per 100 patient months were reported as 0.5 (AV fistula), 0.9 (grafts), 4.2 (cuffed catheters), and 27.1 (temporary catheters) (125). Previous infection rates per 100 patient months in hemodialysis patients have been reported as 3.2 for all vascular access infections (including access infections both with and without bacteremia), 1.8 for vascular access–associated bacteremia, 1.3 for wound infections not related to the vascular access, 0.8 for pneumonias, and 0.3 for urinary tract infection. Among patients with fistulas or grafts, wounds were the most common site for infection *(122)*. Among patients with hemodialysis catheters, infections of the vascular access site were the most common site for infection (*122*,125).

In a study of 27 French hemodialysis centers, 28% of 230 infections in hemodialysis patients involved the vascular access, whereas 25% involved the lung, 23% the urinary tract, 9% the skin and soft tissues, and 15% other or unknown sites *(119)*. Thirty-three percent of infections involved either the vascular access site or were bacteremia of unknown origin, many of which might have been caused by unrecognized access infection or colonization. Thus, the vascular access site was the most common site for infection but accounted for only one-third of infections.

Pathogens causing infection can either be exogenous (i.e., acquired from contaminated dialysis fluids, injectable medication, hands of healthcare workers, equipment, etc.) or endogenous (i.e., caused by invasion of bacteria present in or on the patient). Exogenous pathogens have caused numerous outbreaks, most of which resulted from inadequate dialyzer reprocessing procedures (e.g., contaminated water or inadequate disinfectant concentration) or inadequate disinfection and maintenance of the water treatment and distribution system. During 1995 to 2006, five outbreaks were traced to contamination of the WHO port on one type of dialysis machine (103,*104*,*105*, *126–128*). Recommendations to prevent such outbreaks are published elsewhere *(129)*. The endogenous infection category includes pathogens such as *Staphylococcus aureus*, which cause a greater number of intravascular infections. An increase in incidence of these infections above baseline might be less likely to be recognized as an outbreak, but is often due to suboptimal infection control practices and aseptic technique.

Contaminated medication vials are also a source of bacterial infection for patients. In 1999, an outbreak of *Serratia liquefaciens* bloodstream infections and pyrogenic reactions among hemodialysis patients was traced to contamination of vials of erythropoietin. These vials, which were intended for single use, were contaminated by repeated puncture to obtain additional doses and by pooling of residual medication into a common vial (130).

Vascular Access Infections

Access site infections are particularly important, because they can cause disseminated bacteremia or loss of the vascular access. Local signs of vascular access infection include erythema, warmth, induration, swelling, tenderness, break down of skin, loculated fluid, and purulent exudates *(116,117,122,131)*. In the CDC surveillance project, the initial reported rate of access-associated bacteremia per 100 patient months was 1.8 overall and varied by access type: 0.25 for fistulas, 0.53 for grafts, 4.8 for permanent (tunneled, cuffed) catheters and 8.7 for temporary (nontunneled, noncuffed) catheters *(122)*. A more recent 10-year summary of the data collected through this surveillance system (1995–2005) reported that the overall vascular access infection rate was 3.1 per 100 patient months and varied from 0.6 for fistulas to 10.1 for temporary catheters *(132)*.

Vascular access infections are caused (in descending order of frequency) by *S. aureus* (32–53% of cases), coagulase-negative staphylococci (CNS: 20–32% of cases), gram-negative bacilli (10–18%), gram-positive cocci other than staphylococci (including enterococci; 10–12%), and fungi (<1%) *(122,132)*. The proportion of infections caused by *S. aureus* is higher among patients with fistulas or grafts, and the proportion caused by CNS is higher among patients dialyzed through catheters (125).

The primary risk factor for access-related infection is access type, with catheters having the highest risk for infection, grafts having intermediate risk, and native arteriovenous (AV) fistulas having the lowest risk (*115*,*116*,120,125,*132*). Other potential risk factors for vascular access infection include (a) location of the access in the lower extremity; (b) recent vascular access surgery; (c) trauma, hematoma, dermatitis, or scratching over the access site; (d) poor patient hygiene; (e) poor needle insertion technique; (f) older age; (g) diabetes mellitus; (h) immune suppression; (i) iron overload, (j) intravenous drug use; and (k) the chronic inflammatory state (*116*,*117*,*133–138*).

Based on relative risk of both infectious and noninfectious complications, it is recommended that native AV fistulas be used more commonly and hemodialysis catheters less commonly; a goal of no more than 10% of patients maintained with permanent catheters is recommended *(139–143)*. To minimize infectious complications, patients should be referred early for creation of an implanted access, thereby decreasing the time they are dialyzed through a temporary catheter. Additionally, catheters should be used only in patients for whom a permanent access is impossible. During the period between 1995 and 2002, the percentage of patients dialyzed through fistulas increased from 22% to 33%, with most of the increase occurring after 1999 (59). During the same period, use of grafts decreased from 65% to 42%, and the use of catheters increased from 13% to 33%. However, data from CMS's ESRD Clinical Performance Measures (CPM) project indicate that 75% of new dialysis patients begin dialysis using a hemodialysis catheter; in 2006, 93.1% of patients with no pre-ESRD nephrologist care started dialysis with a catheter, while 76.9% of patients who had seen a nephrologist for 1 year or less and 65.2% of patients who saw a nephrologist for 1 year or more started dialysis with a catheter *(112)*.

Recommendations for preventing vascular access infections have been developed by the National Kidney Foundation *(139–143)* and CDC (144). Selected recommendations for preventing hemodialysis catheter-associated infections include (a) not using antimicrobial prophylaxis before insertion or during use of the catheter; (b) not routinely replacing the catheter (in the absence of infection); (c) using sterile technique (cap, mask, sterile gown, large sterile drape, and sterile gloves) during catheter insertion; (d) limiting use of noncuffed catheters to 3 to 4 weeks; (e) using the catheter solely for hemodialysis unless there is no other alternative; (f) restricting catheter manipulation and dressing changes to trained personnel; (g) replacing catheter-site dressing at each dialysis session or if damp, loose, or soiled; (h) disinfecting skin before catheter insertion and dressing changes (a chlorhexidine-based preparation is preferred); and (i) ensuring catheter-site care is compatible with catheter material (144,*145*).

There have been a number of studies looking at the use of various antimicrobial locks to prevent catheter-related bloodstream infection (CRBSI) among hemodialysis patients. Two recent meta-analyses of these studies concluded that (a) antimicrobial catheter lock solutions reduce CRBSIs and the (b) use of these lock solutions should be

considered in routine clinical practice in conjunction with other prevention modalities (146,147). However, the long-term consequence of using antibiotics routinely in catheter locking solutions is unknown. While results of these studies appear to be promising, CDC does not recommend the routine use of antimicrobial lock solutions for hemodialysis catheters, because antimicrobial use can lead to antimicrobial resistance (144,148).

The Infectious Diseases Society of America (IDSA) previously recommended treatment with nasal mupirocin in hemodialysis patients who were documented *S. aureus* carriers, had catheter-related blood stream infections with *S. aureus*, and continued to need a hemodialysis catheter *(149,150)*. However, updated IDSA guidance, published in 2009 *(151)*, no longer recommends intranasal antimicrobial/decolonization based on studies suggesting this is not effective in preventing infections and concerns about emerging resistance. In CRBSI due to *S. aureus*, *Pseudomonas* spp., or *Candida* spp., the catheter should always be removed and a temporary catheter inserted at another site. If no alternative sites are present, the infected catheter should be exchanged over guidewire. Once blood cultures are negative, a new permanent catheter maybe placed. For uncomplicated CRBSI due to pathogens other than *S. aureus, P. aeruginosa, Bacillus* spp., *Micrococcus* spp., proprionibacteria, mycobacteria, or fungi, treatment should be attempted without catheter removal, with the use of both systemic and antimicrobial lock therapy *(151)*.

Pneumonia

Hospital admissions for pneumonia have been declining overall for dialysis patients; however, pneumonia rates for hemodialysis patients are 1.8 to 2.2 times those of transplant recipients or peritoneal dialysis patients. Hospital admissions for pneumonia are also 102% higher among hemodialysis patients when compared to the general population (1). In one study of a group of 433 dialysis patients over a 9-year period, pneumonia was the third most common type of infection (following vascular access infections and infections below the knee) and accounted for 13% of all infections *(152)*. One- and five-year survival probabilities are 0.55 and 0.17, respectively. Pneumonia is common among hemodialysis patients, carries a poor prognosis, and is often the antecedent to cardiovascular death *(153,154)*. A recent analysis of new hemodialysis patients found pneumonia to be associated with chronic obstructive pulmonary disease, inability to transfer or ambulate, hemodialysis as initial therapy, advanced age (≥75 years), and body mass index ≥30 kg/m *(154)*.

Antimicrobial-Resistant Bacteria

Hemodialysis patients have been in the forefront of the epidemic of antimicrobial resistance, especially vancomycin resistance. One of the earliest reports of vancomycin-resistant enterococci (VRE) was from a renal unit in London, United Kingdom, in 1988 *(155)*. The prevalence of VRE stool colonization among dialysis patients has varied from 1.5% among pediatric dialysis patients in the United Kingdom *(156)* and 2.4% of adult dialysis patients at three dialysis centers in Indianapolis, IN *(157)*, to 9.5% at a University hospital in Baltimore, MD *(158)*. In one center with a prevalence of 9%, (10/111) three patients developed VRE infections in the following year *(159)*. It appears that hospital acquisition of VRE contributes substantially to the increasing prevalence of VRE in the chronic hemodialysis patient population *(160)*. Among enterococci causing blood stream infections in hemodialysis patients, up to 26% have been reported to be resistant to vancomycin *(122,161,162)*.

Vancomycin resistance in staphylococci has also been reported in dialysis patients. Five of the first six US patients infected with vancomycin intermediate-resistant *S. aureus* were receiving either peritoneal dialysis or hemodialysis *(163,164)*. Additionally, the first patient found to be infected with a fully vancomycin-resistant *S. aureus* (VRSA) strain was a maintenance hemodialysis patient; the VRSA was isolated from a diabetic foot wound and from a temporary catheter exit site *(165)*. In the period between 2002 and 2009, there was a total of nine cases of VRSA identified in the United States; three of the case patients had chronic renal failure and two were hemodialysis patients *(166,167)*. Five of the seven VRSA cases occurred in southeastern Michigan and contained a plasmid carrying the *vanA* gene, which had been donated from a VRE *(168)*.

The percentage of hemodialysis facilities reporting methicillin-resistant *S. aureus* (MRSA) infection or colonization among patients in the facility has increased from 40% in 1995 *(89)* to 76% in 2002 (59). In a recent CDC study assessing invasive MRSA infection among dialysis patients, the incidence was found to be 42.5 cases/1,000 population (169), 100-fold higher than the incidence of these infections in the general population (0.2–0.4 cases/1,000 population). Additionally, a study in the United Kingdom of vascular access infections found that MRSA was responsible for 30% of all catheter-related infections *(170)*.

In order to combat emerging antimicrobial resistance in dialysis patients, one must understand the transmission kinetics involved with each microorganism. For certain patients, including those infected with MRSA or VRE, Contact Precautions are used in the hospital setting (171). However, for several reasons, Contact Precautions are not recommended in hemodialysis centers for patients infected or colonized with pathogenic bacteria. First, although contact transmission of pathogenic bacteria is well documented in hospitals, similar transmission has not been well documented in hemodialysis centers. At least one study demonstrated that significant transmission and acquisition of pathogens occurred when hemodialysis patients were admitted to the acute-care setting, while similar transmission was not documented in the hemodialysis centers *(160)*. However, it is possible that transmission of pathogenic bacteria in dialysis centers is less likely to be recognized, possibly because it occurs less frequently than in the acute-care setting or results in undetected colonization rather than overt infection. Furthermore, because dialysis patients are frequently hospitalized, determining whether transmission occurred in either the outpatient or inpatient setting may be difficult. A second reason that Contact Precautions are not recommended in outpatient maintenance hemodialysis centers is that contamination of the patient's skin, bedclothes, and environmental surfaces with pathogenic bacteria is less likely to occur in these settings (where patients may spend up to 9–15 hours per week), as compared to hospitals (where patients spend 24 hours a day). Finally, the routine use of infection control practices

recommended for hemodialysis facilities, which are more stringent than the Standard Precautions routinely used in hospitals, should prevent transmission of these pathogens.

HEPATITIS B VIRUS

Recommendations for the control of HBV transmission in hemodialysis settings were first published in 1977 *(172)* and, by 1980, their implementation was associated with a sharp decrease in the incidence of HBV infection among both patients and staff members *(173,174)*. In 1982, the hepatitis B vaccine was recommended for all susceptible hemodialysis patients and staff members *(175)*.

Epidemiology

During the early 1970s, HBV infection was endemic in maintenance hemodialysis units and outbreaks were common. Subsequently, the incidence and prevalence of HBV infection among maintenance hemodialysis patients in the United States have declined dramatically, and by 2002, were 0.12% and 1%, respectively (59). Newly acquired HBV infections were reported by 2.8% of U.S. hemodialysis centers, and 27.3% of centers reported one or more patients with chronic HBV infection (59).

The chronically infected patient provides a reservoir for maintenance of the disease in the population and is central to the epidemiology of HBV transmission. HBV is transmitted by percutaneous (i.e., puncture through the skin) or mucosal (direct contact with mucus membranes) exposure to infectious blood or body fluids. All hepatitis B surface antigen (HBsAg)-positive persons who are also positive for hepatitis B e antigen (HBeAg) have an extraordinary level of HBV circulating in their blood, approximately 10^8 to 10^9 virions/mL *(176,177)*. With virus titers this high in blood, body fluids containing serum or blood may also contain high levels of HBV and are potentially infectious. Furthermore, HBV at titers of 10^2 to 10^3 virions/mL can be present on environmental surfaces in the absence of any visible blood and still cause infection *(176,178–180)*.

HBV is relatively stable in the environment and has been shown to remain viable for at least 7 days on environmental surfaces at room temperature *(176,178,180)*. HBsAg has been detected in dialysis facilities on hemostats, scissors, dialysis machine control panels, and door knobs *(180)*. Thus, blood-contaminated surfaces that are not routinely cleaned and disinfected represent a source for HBV transmission, even in the absence of visible blood. Dialysis staff members can transfer virus from these surfaces to susceptible patients, resulting in patient infection *(176,178,180)*.

Most HBV outbreaks among hemodialysis patients (Table 63-3) were caused by cross-contamination to patients via (a) environmental surfaces, supplies (e.g., hemostats, clamps, etc.), or equipment that were not routinely cleaned and disinfected after each use; (b) multiple-dose vials or intravenous solutions that were not used exclusively for one patient; (c) medications for injections that were prepared adjacent to areas where blood samples were handled; and (d) staff members who simultaneously provided care for both infected (HBsAg-positive) patients and susceptible patients *(99,181–187)*. Once the factors that promote HBV transmission among hemodialysis patients were identified, recommendations for control were published in 1977 *(172)*. These recommendations included: (a) serologic screening of patients for HBV infection, including monthly testing of all susceptible patients for HBsAg; (b) isolation of all HBsAg-positive patients in a separate room during hemodialysis; (c) assignment of staff members to HBsAg-positive patients and not to HBV-susceptible patients during the same shift; (d) assignment of dialysis equipment to HBsAg-positive patients that is not shared with HBV-susceptible patients; (e) assignment of a supply tray to each patient (regardless of serological status); (f) cleaning and disinfection of nondisposable items (e.g., hemostats, clamps, scissors) before use on another patient; (g) glove use whenever patient or hemodialysis equipment is touched and glove changes between each patient (and station); and (h) routine cleaning and disinfection of equipment and environmental surfaces.

The segregation of HBsAg-positive patients and their equipment from HBV-susceptible patients resulted in a 70% to 80% reduction in the incidence of HBV infections among hemodialysis patients *(174,188,189)*. The success of isolation practices in preventing transmission of HBV infection is linked to other infection control practices, including routine serologic surveillance and routine cleaning and disinfection. Frequent serologic testing for HBsAg detects patients recently infected with HBV so that isolation procedures can be implemented before cross-contamination can occur. Environmental control by routine cleaning and disinfection procedures reduces the opportunity for cross-contamination, either directly from environmental surfaces or indirectly by hands of personnel.

Since the publication of recommendations for HBV control, HBV infection outbreaks have continued to occur in maintenance hemodialysis centers (*179–187*,*190*, *191*,192,*193*,*194*). Investigations of these and other outbreaks have documented failures to use recommended infection control practices, including (a) failure to routinely screen patients for HBsAg or routinely review results of testing to identify infected patients; (b) assignment of staff members to the simultaneous care of both infected and susceptible patients; (c) sharing of supplies, particularly multidose medication vials, among patients *(184)*. In addition, annual surveillance data from the United States in 2002 found only about 56% of hemodialysis patients have received the hepatitis B vaccine *(58)*. A more recent survey of 1,052 dialysis facilities found that 62% of patients had received three or more doses of the vaccine series *(195)*. Factors among maintenance hemodialysis patients for acquiring HBV infection include the presence of ≥1 HBV-infected patient in the hemodialysis facility who was not isolated, as well as a vaccination rate <50% among patients *(82)*.

HBV infection among maintenance hemodialysis patients has also been associated with hemodialysis provided in the acute-care setting *(184,187)*. Transmission appears to stem from the sharing of staff members, multiple-dose medication vials, and other supplies and equipment among patients with chronic HBV infection and susceptible patients. These episodes were recognized only after the patients had returned to their outpatient dialysis facilities, and routine HBsAg testing was resumed. Transmission from HBV-infected maintenance hemodialysis

patients to patients undergoing hemodialysis procedures for acute renal failure has not been documented, possibly because these patients are dialyzed for short durations and have limited exposure. However, such transmission could go unrecognized because acute renal failure patients are unlikely to be tested for HBV infection.

Other risk factors for acquiring HBV infection include injection drug use, sexual and household exposure to HBV-infected contacts, exposure to multiple sexual partners, male homosexual activity, and perinatal exposure. Dialysis patients should be educated about these and other risks and, for those patients with active HBV infection (HBsAg positive), informed that their sexual partners and household contacts should be vaccinated *(196–198)*.

Screening and Diagnostic Tests

Several well-defined antigen-antibody systems are associated with HBV infection, including HBsAg and antibody to HBsAg (anti-HBs); hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc); and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Serologic assays are commercially available for all of these except for HBcAg because no free HBcAg circulates in the blood. One or more of these serologic markers are present during different phases of HBV infection (Table 63-4) *(199)*. HBV infection can also be detected using qualitative or quantitative tests for HBV DNA *(200,201)*; these tests are most commonly used for HBV-infected patients being managed with antiviral therapy *(202–206)*.

The presence of HBsAg is indicative of ongoing HBV infection and potential infectiousness. In newly infected individuals, HBsAg is present in serum on average 30 days (range 6–60 days) after exposure to HBV and persists for variable periods. Transient HBsAg positivity (typically lasting <18 days, but documented for up to 28 days) can be detected in some patients following vaccination and is clinically insignificant *(207–210)*. Anti-HBc develops in all HBV infections, appearing at the onset of symptoms or liver test abnormalities in acute HBV infection, rising rapidly to high levels, and persisting for life. Acute or recently acquired infection can be distinguished by presence of the immunoglobulin M (IgM) class of anti-HBc, which persists for approximately 6 months. However, persons with exacerbations of chronic HBV infection can test positive for IgM anti-HBc *(211)*. The positive predictive value of the IgM anti-HBc test is low in asymptomatic persons; therefore, its use for diagnosis of acute hepatitis B should be limited to persons with evidence of acute hepatitis, an epidemiologic link to a person with HBV infection *(212)*, or to assess an isolated anti-HBc positive (i.e., anti-HBc positive, HBsAg negative, and anti-HBs negative) test result in a hemodialysis patient (171).

In individuals who recover from HBV infection, HBsAg and HBV DNA are usually eliminated from the blood, and anti-HBs appears. The persistence of anti-HBs indicates immunity from HBV infection. After recovery from natural infection, most individuals will be positive for both total anti-HBc and anti-HBs, whereas only anti-HBs develops in patients who are successfully vaccinated against hepatitis B. Individuals who do not recover from HBV infection and become chronically infected remain HBsAg positive (and total anti-HBc positive) and HBV DNA positive, although a small proportion of these patients (0.3–2%) eventually clear HBsAg and might develop anti-HBs *(213)*.

In some individuals, the only HBV serologic marker detected is total anti-HBc (i.e., isolated anti-HBc). Among most asymptomatic persons in the United States tested for HBV infection, an average of 2% (range: <0.1–6%) test positive for anti-HBc *(214)*; among injecting drug users, however, the rate is 24% to 28% *(215,216)*. In general, the frequency of isolated anti-HBc is directly related to the prevalence of previous HBV infection in the population and can have several explanations. This pattern can occur after HBV infection among individuals who have recovered but whose anti-HBs levels have waned; or among individuals who have failed to develop anti-HBs. Individuals in the latter category include those who circulate HBsAg at levels not detected by commercial serological assays

TABLE 63-4

Interpretation of Serological Test Results for Hepatitis B Virus Infection

Serologic Markers				
HBsAg[a]	*Total Anti-HBc*[b]	*IgMc Anti-HB*[c]	*Anti-HBs*[d]	*Interpretation*
–	–	–	–	Susceptible, never infected
+	–	–	–	Acute infection, early incubation[e]
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Past infection, recovered and immune
+	+	–	–	Chronic infection
–	+	–	–	False-positive (i.e., susceptible), past infection, or low-level chronic infection
–	–	–	+	Immune if titer ≥10 mIU/mL

[a]Hepatitis B surface antigen.
[b]Antibody to hepatitis B core antigen.
[c]Immunoglobulin M.
[d]Antibody to hepatitis B surface antigen.
[e]Transient HbsAg positivity (typically lasting ≤18 d) might be detected in some patients following vaccination.

(low-level chronic HBV infection). However, HBV DNA has been detected in <10% of these individuals with isolated total anti-HBc. In many persons with isolated anti-HBc, the result appears to be a false-positive reaction (217). Data from several studies have demonstrated that a primary anti-HBs response develops in most of these individuals after a three-dose series of hepatitis B vaccine *(218,219)*. Infected individuals who are positive only for anti-HBc are unlikely to be infectious to others except under unusual circumstances in which they are the source for direct percutaneous exposures to large quantities of virus (e.g., blood transfusion or organ transplant) *(220–222)*.

A third antigen, HBeAg, can be detected in the serum of individuals with acute or chronic HBV infection. The presence of HBeAg correlates with viral replication and high levels of virus (i.e., high infectivity). Anti-HBe correlates with loss of replicating virus and with lower levels of virus. However, all HBsAg-positive patients should be considered potentially infectious, regardless of their HBeAg or anti-HBe status.

HEPATITIS C VIRUS

HCV is a single-stranded RNA virus that belongs to the family *Flaviviridae (223)*. HCV was first recognized as non-A, non-B hepatitis virus (NANBH) in 1974 until cloning of the etiologic agent in 1989 *(224–226)*. HCV is another efficiently transmitted blood-borne viral pathogen in the dialysis setting. It is not as efficiently transmitted as HBV in this setting, and recommended infection control practices prevent transmission among hemodialysis patients without the need for isolation (171,*227–229*). Despite recommendations for HCV control in hemodialysis centers, both outbreaks and new acquisition of HCV infection continue to occur among maintenance hemodialysis patients.

Epidemiology

Data are limited on the current incidence and prevalence of HCV infection among maintenance hemodialysis patients. In 2002, 63% of dialysis centers tested patients for anti-HCV. In the facilities that tested for anti-HCV, the incidence rate in 2002 was 0.34%, and the prevalence of anti-HCV among patients was 7.8%, a decrease of 25.7% since 1995 (59). Only 11.5% of dialysis facilities reported having at least one patient who became anti-HCV positive during 2002 (i.e., tested positive in 2002 but has previously been anti-HCV negative). Higher incidence rates have been reported from cohort studies of dialysis patients in the United States (<1–3%), Japan (<2%), and Europe (3–15%) *(230–237)*. Higher prevalence rates (10% to 85%) also have been reported in individual facilities in the United States and other countries *(233,237–242)*.

HCV is moderately stable in the environment, and can survive drying and environmental exposure to room temperature for at least 16 hours *(243)*. HCV is most efficiently transmitted by direct percutaneous exposure to blood, and like HBV, the chronically infected patient is central to the epidemiology of HCV transmission. Risk factors associated with HCV infection among hemodialysis patients include blood transfusions from unscreened donors, low staff-to-patient ratios, and years on dialysis *(230,236,244–248)*. The number of years on dialysis is the major risk factor that is independently associated with higher rates of HCV infection. As the time patients spent on dialysis increased, their prevalence of HCV infection increased from an average of 12% for patients receiving dialysis <5 years to an average of 37% for patients receiving dialysis >5 years (*240,247–252*,253).

These studies, as well as investigations of dialysis-associated outbreaks of HCV infection, indicate that HCV transmission most likely occurs because of inadequate infection control practices (253). During 1998 to 2009, eight outbreaks of HCV infection were reported among patients in chronic hemodialysis centers in the United States; six of these were investigated by CDC (253,*254–256*). In these outbreaks, multiple transmissions of HCV occurred during periods ranging from 6 months to 7 years (attack rates: 7.5–17.5%), and HCV seroconversions were associated with receiving dialysis immediately after or at a machine adjacent to a chronically infected patient. Multiple opportunities for cross-contamination among patients were observed, including (a) equipment and supplies that were not cleaned and disinfected between patient use; (b) use of common medication carts to prepare and distribute medications at patient stations; (c) sharing of multiple-dose vials, which were placed at patients' stations on the top of the hemodialysis machine; (d) contaminated priming buckets that were not routinely changed or cleaned and disinfected between patients; (e) machine surfaces that were not routinely cleaned and disinfected between patients; and (f) blood spills that were not cleaned up promptly. In one of these outbreaks, there were multiple infections clustered among patients treated on the same dialysis shift (attack rate of 27%), suggesting a common exposure event. Multiple opportunities for cross-contamination from chronically infected patients also were observed in the unit where this outbreak occurred. In particular, supply carts were moved from station to station and contained both clean supplies and blood-contaminated items, including small biohazard containers, sharps disposal boxes, and used vacutainers containing patients' blood.

Other risk factors for acquiring HCV infection include injection drug use, exposure to an HCV-infected sexual partner or household contact, and perinatal exposure *(257–259)*. The efficiency of transmission via sexual or household exposure to infected contacts is low *(259)*, and the magnitude of risk and the circumstances under which these exposures result in transmission are not well defined.

Screening and Diagnostic Tests

FDA-licensed or approved anti-HCV screening tests used in the United States include three immunoassays: two enzyme immunoassays (EIA) and one enhanced chemiluminescence immunoassay (CIA) *(260–263)*. Although no true confirmatory test has been developed, supplemental tests for specificity are available. The FDA-licensed or FDA-approved supplemental tests include a serologic anti-HCV assay, the strip immunoblot assay (Chiron RIBA HCV 3.0 SIA, Chiron Corp., Emeryville, CA), and a nucleic acid test for HCV RNA (including reverse transcriptase polymerase chain reaction [RT-PCR] amplification and transcription mediated amplification [TMA]) *(264)*.

Anti-HCV testing includes initial screening with an EIA immunoassay. However, interpretation of the results of EIAs that screen for anti-HCV is limited by several factors:

(a) these assays will not detect anti-HCV in approximately 10% of persons infected with HCV, (b) these assays do not distinguish between acute, chronic, or past infection, (c) in the acute phase of hepatitis C, there may be a prolonged interval between onset of illness and seroconversion, and (d) in populations with a low prevalence of infection, the rate of false positivity for anti-HCV is high. Among hemodialysis patients, the proportion of false-positive screening test results averages approximately 15% *(260,262)*. For this reason, one should not rely exclusively on a positive anti-HCV screening test to determine whether a person has been infected with HCV. If the screening test is positive, supplemental testing with a test with high specificity should be performed to verify the results *(260)*. Alternatively, laboratorians can choose to perform reflex supplemental testing based upon the result of screening test-positive signal-to-cutoff ratios.

Routine testing of hemodialysis patients for anti-HCV on admission to a unit and every 6 months has been recommended since 2001 (171). For routine HCV testing of hemodialysis patients, the anti-HCV screening immunoassay is recommended, and if positive, supplemental testing using RIBA or HCV RNA (Table 63-5). With RIBA, the serologic assay can be performed on the same serum or plasma sample collected for the screening anti-HCV assay. The detection of HCV RNA requires that serum or plasma samples be collected and handled in a manner suitable for NAT and that testing be performed in a laboratory with appropriate facilities established for NAT testing *(260)*. In certain situations, the HCV RNA results can be negative in persons with active infection. As the titer of anti-HCV increases during acute infection, the titer of HCV RNA declines *(262,263)*. Thus, HCV RNA is not detectable in certain persons during the acute phase of their infection, but this finding can be transient and chronic infection can develop *(264)*. In addition, absence of HCV RNA positivity has been observed among patients with chronic HCV infection *(265–267)*. Therefore, the significance of a single negative HCV RNA result is unknown, and the need for further investigation or follow-up is determined by verifying anti-HCV status. Although, in rare instances, detection of HCV RNA might be the only evidence of HCV infection, a study conducted among almost 3,000 hemodialysis patients in the United States found that only 0.07% were HCV RNA positive but antibody negative (CDC, unpublished data).

TABLE 63-5

Interpretation of Test Results for Hepatitis C Virus Infection

Anti-HCV[a] Positive

- An anti-HCV positive result is defined as anti-HCV screening test positive and recombinant immunoblot assay (RIBA) positive or nucleic acid test (NAT) positive or signal-to-cutoff (s/co) ratio level indicative of a true positive antibody result; or anti-HCV screening test positive, NAT negative, RIBA positive (http://www.cdc.gov/hepatitis/HCV/LabTesting.htm) *(258)*.
- An anti-HCV positive result indicates past or current HCV infection.
- An HCV RNA-positive result indicates current (active) infection, but significance of single HCV RNA negative result is unknown; it does not differentiate intermittent viremia from resolved infection.
- All anti-HCV positive persons should receive counseling and undergo medical evaluation, including additional testing for the presence of virus and liver disease.
- Anti-HCV testing generally does not need to be repeated, once a positive anti-HCV result has been confirmed.

Anti-HCV Negative

- Anti-HCV negative result is defined as an anti-HCV screening test negative[b]; or anti-HCV screening test positive, RIBA negative; or anti-HCV screening test positive, NAT negative, RIBA negative.
- An anti-HCV negative individual is considered uninfected.
- No further evaluation or follow-up for HCV is required, unless recent infection is suspected or other evidence exists to indicate HCV infection (e.g., abnormal liver enzyme levels in immunocompromised persons or persons with other etiology for their liver disease).

Anti-HCV Indeterminate

- An indeterminate anti-HCV result is defined as anti-HCV screening test positive, RIBA indeterminate; or anti-HCV screening test positive, NAT negative, RIBA indeterminate.
- An indeterminate anti-HCV screening test result indicates that the HCV antibody status cannot be determined.
- Can indicate a false-positive anti-HCV screening test result, the most likely interpretation in those at low risk for HCV infection; such persons are HCV RNA negative.
- Can occur as a transient finding in recently infected individuals who are in the process of seroconversion; such individuals usually are HCV RNA positive.
- Can be a persistent finding in an individual chronically infected with HCV; such persons are usually HCV RNA positive.
- If NAT is not performed, another sample should be collected for repeat anti-HCV testing (≥1 mo later).

[a]Anti-HCV, antibody to hepatitis C virus.
[b]Interpretation of screening immunoassay test results based on criteria provided by the manufacturer *(259)*.

HEPATITIS DELTA VIRUS

Delta hepatitis is caused by the hepatitis delta virus (HDV), a relatively small defective virus that causes infection only in persons with active HBV infection. The prevalence of HDV infection is low in the United States, with rates <1% among HBsAg-positive persons in the general population and >10% among HBsAg-positive persons with repeated percutaneous exposures (e.g., injecting drug users, persons with hemophilia) *(268)*. Areas of the world with high endemic rates of HDV infection include southern Italy, parts of Africa, and the Amazon basin *(269–273)*.

Few data exist on the prevalence of HDV infection among chronic hemodialysis patients, and a few studies have reported nonexistent to low prevalence among

hemodialysis patients *(273,274)*. In endemic areas, prevalence rates may be relatively high among hemodialysis patients who are HBsAg positive *(275–278)*. Only one transmission of HDV during hemodialysis has been reported in the United States *(274)*. In this episode, transmission occurred from a patient who was chronically infected with HBV and HDV to an HBsAg-positive patient after a massive bleeding incident; both patients received dialysis at the same station.

HDV infection may occur as either coinfection with HBV or as a superinfection in a person with chronic HBV infection. High mortality rates are associated with both types of dual infection. A serologic test that measures total antibody to HDV is commercially available.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

During 1985 to 2002, the percentage of US hemodialysis centers that reported providing chronic hemodialysis for patients with HIV infection increased from 11% to 39%, and the proportion of patients with known HIV infection increased from 0.3% to 1.5% (59). Although the proportion of patients with HIV infection has remained fairly stable during the past decade, the number of infected patients has increased, as has the number of centers treating patients with HIV infection. HIV is transmitted by blood and other body fluids. No patient-to-patient transmission of HIV has been reported in a US hemodialysis center. However, there have been reports of transmission of HIV among patients in other countries. All of these outbreaks have been attributed to several breaks in infection control: (a) reuse of access needles and inadequately disinfected equipment, (b) sharing of syringes among patients, and (c) and sharing of dialyzers among different patients *(279–283)*. HIV infection is usually diagnosed with assays that measure antibody to HIV, and a repeatedly positive EIA test should be confirmed by Western blot or other confirmatory test.

PREVENTING INFECTIONS AMONG CHRONIC HEMODIALYSIS PATIENTS

Preventing transmission of blood-borne viruses and pathogenic bacteria from both recognized and unrecognized sources among chronic hemodialysis patients requires implementation of a comprehensive infection control program. The components of such a program include infection control practices specifically designed for the hemodialysis setting, including routine serologic testing and immunization, surveillance, and training and education. CDC has published recommendations describing these components in detail (171).

The infection control practices recommended for hemodialysis units (Table 63-6) will reduce opportunities for patient-to-patient transmission of infectious agents, directly or indirectly via contaminated devices, equipment and supplies, environmental surfaces, or hands of personnel. These practices should be carried out routinely for all patients in the chronic hemodialysis setting because of the increased potential for blood contamination during hemodialysis and because many patients are colonized or infected with pathogenic bacteria.

Such practices include additional measures to prevent HBV transmission because of the high titer of HBV and its ability to persist in an infectious state on environmental surfaces (Table 63-6). It is the potential for environmentally mediated transmission of HBV, rather than internal contamination of dialysis machines, that is the focus of infection control strategies for preventing HBV transmission in dialysis centers. For patients at increased risk for transmission of pathogenic bacteria, including antimicrobial-resistant strains, additional precautions also might be necessary in some circumstances. Furthermore, surveillance for infections and other adverse events is required to monitor the effectiveness of infection control practices, as are training and education of both staff members and patients to ensure that appropriate infection control behaviors and techniques are carried out.

In each maintenance hemodialysis unit or facility, policies and practices should be reviewed and updated to ensure that infection control practices recommended for hemodialysis units are implemented and rigorously followed. Intensive efforts must be made to educate new staff members and reeducate existing staff members regarding these practices. Readers should consult CDC recommendations for details on these practices (171). The following is a summary of the selected issues.

Routine Testing

All chronic hemodialysis patients should be routinely tested for HBV and HCV infection, and the results promptly reviewed to ensure that patients are managed appropriately based on their test results. Test results (positive and negative) must be communicated to other units or hospitals when patients are transferred for care. Positive test results should be reported to the appropriate public health department, as required by state notifiable disease reporting mandates. Routine testing for HDV or HIV infection for purposes of infection control is not recommended in populations with low endemicity (e.g., the United States).

Before admission to the hemodialysis unit, the HBV serologic status (i.e., HBsAg, total anti-HBc, and anti-HBs) of all patients should be known. For patients transferred from another unit, test results should be obtained before the patient transfer. If a patient's HBV serologic status is not known at the time of admission, testing should be completed within 7 days. The hemodialysis unit should ensure that the laboratory performing the testing for anti-HBs can define a 10-mIU/mL concentration to determine protective levels of antibody.

Routine HCV testing should include use of both a screening immunoassay to test for anti-HCV and supplemental or confirmatory testing with an additional, more specific assay. The use of an HCV RNA test as the primary test for routine screening is not recommended, because few HCV infections will be identified in anti-HCV negative patients. However, if ALT levels are persistently abnormal in anti-HCV negative patients in the absence of another etiology, testing for HCV RNA should be considered. Blood samples collected for HCV RNA testing should not contain heparin, which interferes with the accurate performance of this assay.

TABLE 63-6

Recommended Infection Control Practices for Hemodialysis Units

Infection Control Precautions for All Patients

- Wear disposable gloves when caring for the patient or touching the patient's equipment at the dialysis station; remove gloves and perform hand hygiene (if hands are visibly soiled wash with soap and water) between each patient or station.
- Items taken into the dialysis station should be disposed of, dedicated for use only on a single patient, or cleaned and disinfected before taken to a common clean area or used on another patient.
  - Nondisposable items that cannot be cleaned or disinfected (e.g., adhesive tape, cloth covered blood pressure cuffs) should be dedicated for use only on a single patient then discarded.
  - Unused medications (including multidose vials) or supplies (syringes, alcohol swabs, etc.) taken to the patient's station should be used only for that patient and should not be returned to a common clean area or used on other patients.
- When multidose medication vials are used (including vials containing diluents), prepare individual patient doses in a clean (centralized) area away from dialysis stations and deliver separately to each patient. Do not carry multidose medication vials from station to station.
- Do not use common medication carts to deliver medications to patients. Do not carry medication vials, syringes, alcohol swabs, or supplies in pockets.
- Clean areas should be clearly designated for the preparation, handling, and storage of medications and unused supplies and equipment. Clean areas should be clearly separated from contaminated areas where used supplies and equipment are handled. Do not handle and store medications or clean supplies in the same or adjacent area to where used equipment or blood samples are handled.
- Use external transducer protectors (venous or arterial) for each patient treatment to prevent blood contamination of the dialysis machine's pressure-monitoring equipment. Change these external transducer protectors between each patient treatment and when they become wetted[a], and do not reuse them. The redundant internal transducer protectors do not need to be changed routinely between patients. If the external transducer protectors are contaminated with blood, the internal transducer protector should be checked before dialyzing the next patient.[a]
- Clean and disinfect the dialysis station (chairs, beds, tables, machines, etc.) between patients.
  - Give special attention to cleaning control panels on the dialysis machine and other surfaces that are frequently touched and potentially contaminated with patient's blood.
  - Discard all fluid and clean and disinfect all surfaces and containers associated with the prime waste (including buckets attached to the machines).

For dialyzers and blood tubing that will be reprocessed, cap dialyzer ports and clamp tubing. Place all used dialyzers and tubing in a leak-proof container for transport from station to reprocessing or disposal area.

Schedule for Routine Testing for Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Infections

Patient Status	*On Admission,*[b]	*Monthly*	*Semi-Annual*	*Annual*
All patients	HBsAg, Anti-HBc (total), Anti-HBs, Anti-HCV, ALT			
HBV susceptible, including vaccine nonresponders		HBsAg		
Anti-HBs positive (≥10 mIU/mL), anti-HBc negative				Anti-HBs
Anti-HBs and Anti-HBc positive		No additional testing is needed		
Anti-HCV negative		ALT	Anti-HCV	

[a]Results of HBV testing should be known before patient begins dialysis.
HBsAg, hepatitis B surface antigen; Anti-HBc, antibody to hepatitis B core antigen; Anti-HBs, antibody to surface antigen; Anti-HCV, antibody to hepatitis C virus; ALT, alanine aminotransferase.

Hepatitis B Vaccination

- Vaccinate all susceptible patients against hepatitis B
- Test for anti-HBs 1–2 mo after the last dose
  - If anti-HBs is <10 mIU/mL, consider patient susceptible, revaccinate with an additional three doses, and retest for anti-HBs
  - If anti-HBs is >10 mIU/mL, consider immune and retest annually
    - Give booster dose of vaccine if anti-HBs declines to <10 mIU/mL and continue to retest annually

Management of HBsAg-Positive Patients

- Follow infection control practices for hemodialysis units for all patients.
- Dialyze HBsAg-positive patients in a separate room using separate machines, equipment, instruments, and supplies.
- Staff members caring for HBsAg-positive patients should not care for HBV-susceptible patients at the same time (e.g., during the same shift or during patient change over).

[b]FDA Safety Alert: Potential Cross-Contamination Linked to Hemodialysis Treatment (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062283); (Adapted from CDC. Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR Morb Mortal Wkly Rep* 2001;50(RR5):1–43.)

Hepatitis B vaccination is an essential component of prevention in the hemodialysis setting. All susceptible patients and staff should receive hepatitis B vaccine. Susceptible patients who have not yet received hepatitis B vaccine, are in the process of being vaccinated, or have not adequately responded to vaccination should continue to be tested regularly for HBsAg. Detailed recommendations for vaccination and follow-up of hemodialysis patients have been published elsewhere (171).

Management of Infected Patients

Hepatitis B Virus HBsAg-positive patients should undergo hemodialysis in a separate room designated only for HBsAg-positive patients. They should use dedicated machines, equipment, and supplies, and most importantly staff members should not care for both HBsAg-positive and susceptible patients during the same shift or while the HBsAg-positive patient is in the treatment area. Dialyzers should not be reused on HBsAg-positive patients because HBV is efficiently transmitted through occupational exposure to blood; reprocessing dialyzers from HBsAg-positive patients might place HBV-susceptible staff members at increased risk for infection.

HBV chronically infected patients (i.e., those who are HBsAg-positive, total anti-HBc positive, and IgM anti-HBc negative) are infectious to others and are at risk for chronic liver disease. They should be counseled on how to prevent transmission to others, especially for those who are their household and sexual partners. Household contacts and sexual partners should be advised to receive hepatitis B vaccine. The HBsAg-positive patient should also be evaluated according to current medical practice guidelines (by consultation or referral, if appropriate) for possible treatment and for the presence or development of chronic liver disease. It is recommended that individuals with chronic liver disease be vaccinated against the hepatitis A virus (HAV), if susceptible, to prevent any additional injury to the liver.

HBV chronically infected patients do not require any routine follow-up testing for purposes of infection control. However, annual testing for HBsAg is reasonable to detect the small percentage of HBV-infected patients who might lose their HBsAg.

Hepatitis C Virus HCV-positive patients do not have to be isolated from other patients or dialyzed separately on dedicated machines. The purpose of routine testing is to detect potential transmission within centers and ensure that appropriate practices are being properly and consistently used. Furthermore, HCV-positive patients can participate in dialyzer reuse programs. Unlike HBV, HCV is not transmitted efficiently through occupational exposures. Thus, reprocessing dialyzers from HCV-positive patients should not place staff members at increased risk for infection (59,*88*).

All HCV-positive persons should be evaluated according to current medical practice guidelines (by consultation or referral, if appropriate) for possible treatment and the presence or development of chronic liver disease. They also should receive information concerning how they can prevent further harm to their liver and prevent transmitting HCV to others *(284,285)*. Persons with chronic liver disease should be vaccinated against hepatitis A, if susceptible.

Hepatitis Delta Virus Because HDV depends on an HBV-infected host for replication, prevention of HBV infection will prevent HDV infection in a person susceptible to HBV. Patients known to be infected with HDV should be isolated from all other dialysis patients, especially those who are HBsAg positive and HDV susceptible.

Human Immunodeficiency Virus Infection control precautions recommended for all hemodialysis patients are sufficient to prevent HIV transmission between patients. HIV-infected patients do not have to be isolated from other patients or dialyzed separately on dedicated machines. In addition, they can participate in dialyzer reuse programs, because HIV is not transmitted efficiently through occupational exposures. Reprocessing dialyzers from HIV-positive patients should not place staff members at increased risk for infection.

Bacterial/Fungal Contact transmission can be prevented by hand hygiene *(286)*, proper glove use, and disinfection of environmental surfaces. Infection control precautions recommended for all hemodialysis patients are adequate to prevent transmission from most patients infected or colonized with pathogenic bacteria, including antimicrobial-resistant strains. However, additional precautions should be considered for treatment of patients who might be at increased risk for transmitting pathogenic bacteria. Such patients include those with either an infected skin wound with drainage that is not contained by dressings (the drainage does not have to be culture positive for MRSA or VRE or any specific pathogen) or fecal incontinence or diarrhea uncontrolled with personal hygiene measures. For these patients, the following additional precautions apply (171):

1. Staff members treating the patient should wear a separate gown over their usual clothing and remove the gown when finished caring for the patient.
2. Dialyze the patient at a station away from the main flow of traffic and with as few adjacent stations as possible (e.g., at the end or corner of the unit).

Vancomycin is used commonly in dialysis patients, in part because vancomycin can be conveniently administered to patients when they come in for hemodialysis treatments. Prudent antimicrobial use is an important component of CDC recommendations for preventing the spread of vancomycin resistance *(287)*. Vancomycin is not indicated for therapy (chosen for dosing convenience) of infections due to ß-lactam–susceptible gram-positive microorganisms in patients with renal failure (148,*287*,*288*). Depending on the situation, alternative antimicrobials (e.g., cephalosporins) with dosing intervals greater than 48 hours, which would allow postdialytic dosing, could be used. Recent studies suggest that cefazolin given three times a week in the dialysis unit provides adequate blood levels and could be used to treat many infections in hemodialysis patients *(289,290)*.

Disinfection, Sterilization, and Environmental Cleaning

Good cleaning, disinfection, and sterilization procedures are important components of the infection control program in the hemodialysis center. The procedures do not differ from those recommended for other healthcare settings

(291,292), but the high potential for blood contamination makes the hemodialysis setting unique. Additionally, the need for routine aseptic access of the patient's vascular system makes the hemodialysis unit more akin to a surgical suite than to a standard hospital room. Medical items are categorized as critical (e.g., needles and catheters), which are introduced directly into the bloodstream or normally sterile areas of the body; semicritical (e.g., fiberoptic endoscopes), which come in contact with intact mucous membranes; and noncritical (e.g., blood pressure cuffs), which touch only intact skin *(292,293)*.

Cleaning and housekeeping in the dialysis center have two goals: to remove soil and waste on a regular basis, thereby preventing the accumulation of potentially infectious material, and to maintain an environment that is conducive to good patient care *(293)*. Crowding of patients and overtaxing of staff members may increase the likelihood of microbial transmission. Adequate cleaning may be difficult if there are multiple wires, tubes, and hoses in a small area. There should be enough space to move completely around each patient's dialysis station without interfering with the neighboring stations. Where space is limited, elimination of unneeded items; orderly arrangement of required items; and removal of excess lengths of tubes, hoses, and wires from the floor can improve accessibility for cleaning. Because of the special requirements for cleaning in the dialysis center, staff should be specially trained in this task.

After each patient treatment, frequently touched environmental surfaces, including external surfaces of the dialysis machine and the dialysis chair, should be cleaned (with a detergent/detergent germicide) and disinfected (with a hospital-grade disinfectant germicide) in a two-step process. A recent study in the Netherlands where the investigators used luminol to detect nonvisible blood contamination demonstrated the importance of environmental cleaning *(294)*. It is the cleaning step that is most important for interrupting the cross-contamination transmission routes *(295,296)*. Antiseptics, such as formulations with povidone iodine, hexachlorophene, or chlorhexidine, should not be used for environmental cleaning, because these are formulated for use on skin and are not designed for use on hard surfaces.

There is no evidence to suggest that medical waste is more infectious than residential waste or has caused disease in the community *(297)*. However, wastes from a hemodialysis center that are actually or potentially contaminated with blood should be considered infectious and handled accordingly. Eventually, these items of solid waste should be disposed of properly in an incinerator or sanitary landfill, depending on state or local laws.

Standard protocols for sterilization and disinfection are adequate for processing any items or devices contaminated with blood. Historically, there has been a tendency to use "over kill" strategies for instrument sterilization or disinfection and housekeeping protocols. This is not necessary. The floors in a dialysis center are routinely contaminated with blood, but the protocol for floor cleaning is the same as for floors in other healthcare settings. Usually, this involves the use of a good detergent germicide; the formulation can contain a low- or intermediate-level disinfectant.

Blood-borne viruses, such as HBV and HIV, are inactivated by any standard sterilization systems such as standard steam autoclave cycles of 121°C (249.8°F) for 15 minutes, ethylene oxide gas *(296)*, and low-temperature hydrogen peroxide gas plasma *(298)*. Large blood spills should be cleaned to remove visible material; the presence of organic soil can interfere with the activity of the disinfectant. Once the visible soil has been removed, the area should receive low- to intermediate-level disinfection following the label directions of the germicide manufacturer.

Blood and other specimens, such as peritoneal fluid, from all patients should be handled with care. Peritoneal fluid can contain high levels of HBV and should be handled in the same manner as the patient's blood *(299)*. Consequently, if the center performs inpatient peritoneal dialysis, the same criteria for separating HBsAg-positive patients who are undergoing hemodialysis apply to those undergoing peritoneal dialysis.

Blood contamination of venous pressure monitors has been implicated in HBV transmission *(300)*. Therefore, external pressure transducer filters should be used for each patient treatment; these filters should not be reused.

In single-pass artificial kidney machines, the internal fluid pathways are not subject to contamination with blood. Although the fluid pathways that exhaust dialysis fluid from the dialyzer may become contaminated with blood in the event of a dialyzer leak, it is unlikely that this blood contamination will reach a subsequent patient. Therefore, disinfection and rinsing procedures should be designed to control contamination with bacterial rather than blood-borne pathogens.

For dialysis machines that use a dialysate recirculating system (such as some ultrafiltration control machines and those that regenerate the dialysate), a blood leak in a dialyzer, especially a massive leak, can result in contamination of a number of surfaces that will contact the dialysis fluid of subsequent patients. However, the procedures that are normally practiced after each use of a recirculating machine—draining of the dialysis fluid, subsequent rinsing, and disinfection—will reduce the level of contamination to below infectious levels. In addition, an intact dialyzer membrane will not allow passage of bacteria or viruses. Consequently, if a blood leak does occur with either type of dialysis machine, the standard disinfection procedure used for machines in the dialysis center to control bacterial contamination will also prevent transmission of blood-borne pathogens.

Future Directions Infection control strategies that prevent and control HBV infection among hemodialysis patients have been well established. Areas that need further research include determining the ideal hepatitis B vaccine dosage regimen for predialysis and postdialysis pediatric patients and for predialysis adult patients, as well as the optimal timing for follow-up testing and administration of booster doses among vaccine responders. With regard to HCV infection, further studies are needed to clarify the specific factors responsible for transmission of HCV among hemodialysis patients and to evaluate the effect of the current recommendations on prevention and control of HCV infection in this setting.

Many areas related to the occurrence of bacterial and fungal infections in maintenance hemodialysis patients

need additional information. Studies are needed on the prevalence and epidemiology of these infections among chronic hemodialysis patients and the patient-care practices (e.g., those related to vascular access care and cannulation) that would be most useful in preventing infections. Since dialysis patients play a prominent role in the epidemic of antimicrobial resistance, more research regarding optimal strategies to ensure judicious use of antimicrobials in these patients should be conducted. Additional research topics would also include determining the frequency of transmission of pathogens within the dialysis unit and whether additional precautions are necessary to prevent such transmission.

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CHAPTER 64

Infections Associated with Peritoneal Dialysis

John J. Szela and Jeffrey D. Band

HISTORICAL PERSPECTIVES

Although peritoneal dialysis has been used to treat acute renal failure for many years, it has only been over the past 25 to 30 years that peritoneal dialysis has become an alternative to hemodialysis for treatment of chronic renal failure. In 2007, more than 26,000 patients in the United States were maintained on chronic peritoneal dialysis (1). Six percent of the United States dialysis population is undergoing peritoneal dialysis as a form of dialytic therapy.

Two factors have largely contributed to the initial growth of peritoneal dialysis in the treatment of chronic renal failure. First, the introduction of an implantable, cuffed, indwelling silicone catheter by Tenckhoff and Schecter *(2)* in 1968 permitted secure and safe access to the peritoneal cavity. Prolonged continuous or intermittent dialysis was now possible. Second, a continuous, portable, and relatively simple dialysis technique was introduced by Popovich et al. *(3)* in 1976, called continuous ambulatory peritoneal dialysis (CAPD). Modification and simplification of this technique by Oreopoulos et al. *(4)* in 1978 resulted in fewer interruptions, increased portability, and reduced costs, leading to its popularity and acceptance.

However, peritonitis and, less commonly, catheter exit-site or tunnel infections initially led to cautious growth of this new form of chronic dialytic therapy. Rates of peritonitis as high as two to five episodes per patient year were reported in the past *(5–7)*. Better patient selection, improved education, and important changes in delivery systems and connectors designed to prevent touch contamination during bag exchanges have significantly reduced rates of peritonitis *(8–10)*. However, the major limitation of chronic peritoneal dialysis is peritonitis and its sequelae. Peritonitis is the most common reason for hospitalization *(11)* and for discontinuation of this form of dialysis *(12)*. Fortunately, hospitalization rates have declined for peritoneal dialysis patients secondary to decreased peritonitis rates and use of intraperitoneal (as opposed to intravenous) antimicrobics when needed.

Infections in patients on peritoneal dialysis are largely preventable. Knowledge of the epidemiology and pathogenesis of these infections and sources of infecting microbes is essential to design effective prevention and control strategies.

METHODS OF PERITONEAL DIALYSIS

Peritoneal dialysis may be performed in various settings and with a number of techniques. It involves infusing a dialysis solution composed of balanced salts and various concentrations of glucose into the peritoneal cavity by means of a catheter and achieving ultrafiltration by hyperosmolality; retained metabolites traverse the peritoneum from the bloodstream to the solution.

Acute Peritoneal Dialysis

Acute peritoneal dialysis is generally limited to the patient with newly diagnosed acute renal failure or to other circumstances in which dialysis is anticipated for only a few days. It has now largely been replaced by continuous renal replacement therapy. Its origins date back to the 1920s *(8)*. A rigid catheter is inserted into the peritoneal cavity at the bedside after making a small incision, and manual exchanges are performed every 1 to 3 hours as necessary *(13)*. The procedure confers a significant risk of complications, including bowel perforation. Infection is common, especially in cannulations persisting for more than a few days. Some reasons include same location of entry and exit site, lack of an implanted cuff barrier to bacterial migration, migration of the catheter with resultant serosal injury, and the need for frequent exchanges; each poses a risk of contamination.

Chronic Peritoneal Dialysis

Patients with chronic renal failure require maintenance peritoneal dialysis to alleviate symptoms of uremia and correct other metabolic abnormalities. Chronic peritoneal dialysis did not become an acceptable therapeutic alternative to hemodialysis until the mid-1960s, when a semipermanent implantable silastic catheter was developed by Palmer et al. *(14)* and modified by Tenckhoff et al. *(2,5)*. The Tenckhoff catheter is still the most frequently used peritoneal dialysis catheter today (15). Repeated insertions of a peritoneal catheter were no longer necessary to deliver dialysate. The catheter, composed of pliable silicone and usually containing two extraperitoneal Dacron cuffs, is inserted through one incision and tunneled through a subcutaneous tract until the outer end emerges from a new exit site. The Dacron cuffs initiate an inflammatory response

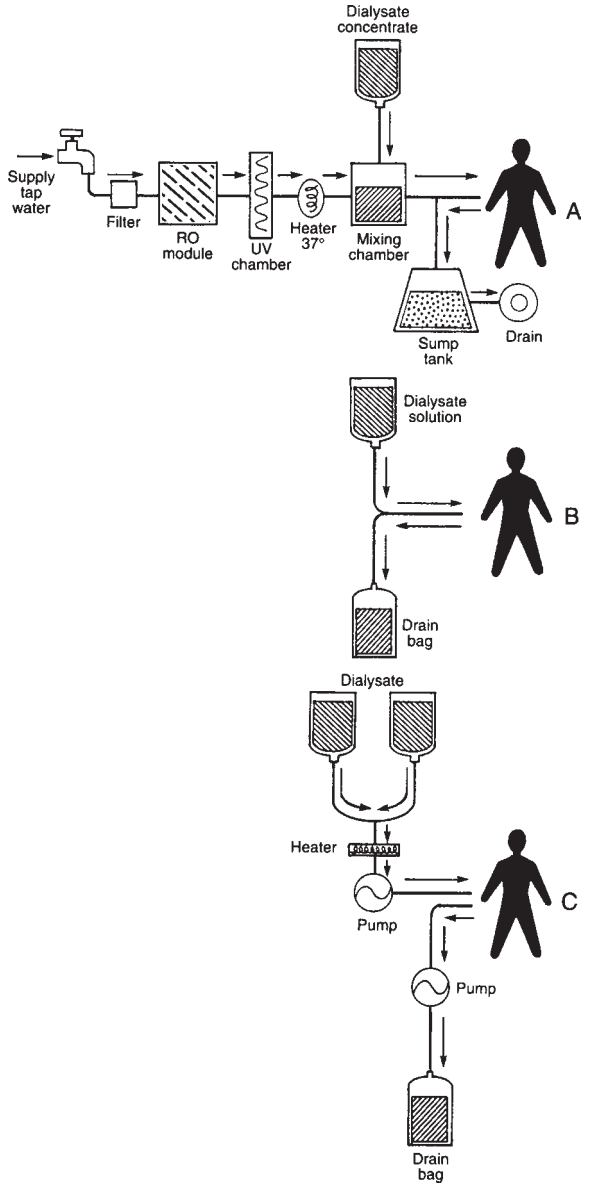

FIGURE 64-1 Schematic diagrams of peritoneal dialysis systems. **A:** Chronic intermittent peritoneal dialysis (CIPD) by automated machine. **B:** Continuous ambulatory peritoneal dialysis (CAPD). **C:** Continuous cycling peritoneal dialysis (CCPD) by roller pumps.

in the subcutaneous tissue near the exit site and deep in the abdominal wall, helping to seal the catheter in place, prevent fluid leaks, and limit bacterial migration around the catheter. Chronic peritoneal dialysis can be performed either intermittently or, as is common today, continuously (Fig. 64-1).

Chronic Intermittent Peritoneal Dialysis

Chronic intermittent peritoneal dialysis (CIPD) uses prolonged periods in which continuous dialysis is performed, thus permitting at least 48 hours of freedom from dialysis. To perform dialysis, a closed automated dialysis system is used to deliver dialysate to the patient *(5–7)*. To simplify the process and to reduce costs, an automated peritoneal dialysis system was developed that used reverse osmosis (RO) capable of producing sterile pyrogen-free water from tap water, which is then mixed with dialysis concentrate *(7)*. These machines gained widespread popularity in the mid-1970s. Although RO proved to be effective in removing bacterial counts by as much as four logs *(16)*, additional backup systems using heat or ultraviolet (UV) irradiation were added to ensure sterile water. Rates of peritonitis were reduced with these closed systems; however, the machines were found to be quite demanding in terms of maintenance, care, monitoring, and disinfection and may themselves provide a reservoir for pathogens *(17)*. With the meteoric rise of simpler procedures (described later), these machines have largely been replaced.

Continuous Ambulatory Peritoneal Dialysis

CAPD is a form of closed-system continuous dialysis that is machine free. Patients on CAPD manually exchange dialysate, usually four times daily, by using dialysate delivered by gravity into the peritoneal cavity. Empty bags, connected to the catheter by extension tubing, collect the effluent, also by gravity, at the end of the dwell time. Fluid from the last exchange of the day dwells overnight in the peritoneal cavity. The technique was pioneered by Popovich et al. *(3)* in 1976 but initially suffered from high rates of peritonitis and patient inconveniences because of bottled dialysate. Oreopoulos et al. *(4)* modified the process and replaced the bottled dialysate with plastic dialysate bags, improving convenience, reducing manipulations, and lowering rates of infectious complications. CAPD is, thus, performed without the necessity of machines, is portable, and is simple to learn and perform *(10,18–21)*.

Continuous Cycling Peritoneal Dialysis

A variant of CAPD, continuous cycling peritoneal dialysis (CCPD) combines the principles of continuous automated dialysis during the night with those of prolonged dwell time dialysis during the day by use of a machine cycler allowing for frequent exchanges *(22)*. CCPD has many advantages, including eliminating active dialysis during the day, reducing the number of exchanges, and possibly reducing rates of peritonitis. However, CCPD may be associated with a faster rate of first-episode peritonitis than CAPD (23). Other disadvantages include cost, machine dependency, and lack of portability. Simpler cyclers will make CCPD an increasingly popular technique. CCPD became more prevalent than CAPD in 2001 and, as of 2007, is approaching twice the prevalence of CAPD (1).

DEFINITIONS

There are a number of infections associated with peritoneal dialysis. By definition, *peritonitis* signifies inflammation of the peritoneal membranes as a result of infection or other insult. For clinical purposes, the definition proposed by Vas *(22)*, consisting of any two of the following three criteria, is often used to establish a diagnosis of peritonitis: cloudy peritoneal effluent containing more than 100 neutrophils/mm^3, abdominal pain or tenderness, and microorganisms in the peritoneal fluid.

Exit-site infections are usually characterized by the presence of pain, erythema, tenderness, or induration of the

catheter site often accompanied by purulent discharge. Infection, when present, is commonly limited to the area between the cutaneous surface (exit site) and the superficial Dacron cuff embedded in the subcutaneous tissue near the skin.

With *tunnel infections,* in which the area between the two Dacron cuffs is commonly referred to as the *tunnel* (the other cuff is embedded deep in the abdominal wall near the peritoneum), signs of infection include induration, tenderness, or redness of the overlying tissues with or without overt abscess formation.

EPIDEMIOLOGY AND RISK FACTORS ASSOCIATED WITH INFECTION

Regardless of the method of dialysis, infection, especially peritonitis, remains a serious threat to the patient. The incidence of peritonitis associated with an acute dialysis is high, approaching 0.5% to 4% *(24)*. The incidence of peritonitis in patients receiving chronic dialytic therapy varies from center to center and depends on the method of chronic dialysis. However, no study has actually randomized patients with chronic renal failure to receive treatment by the three different methods of chronic dialytic therapy.

Over the years, the incidence of peritonitis associated with CAPD has continued to decrease from early observations of six episodes per patient year reported in the late 1970s *(25,26)* to 0.35 episodes per patient year documented by 2004 (27). The initially precipitous drop in infections was largely attributable to enhanced center experience and training *(26)*, substituting plastic dialysis bags for glass bottles, reducing the number of connect–disconnect times *(4)*, incorporating titanium connectors to connect tubing to catheters *(28)*, and developing other methods to reduce touch contamination during bag exchanges *(28–30)*. Currently, the peritonitis rate is down to an average of one infection per 25 patient months of dialysis (31).

Clearly, the risk of developing peritonitis on CAPD increases with time. The period of greatest risk is the first few months of therapy. By the end of 6 months of treatment, the probability of developing at least one episode of peritonitis is at least 30% *(32)*. This risk increases to 50% by the end of 1 year of treatment, 70% by 2 years, and approaches 80% by 3 years of uninterrupted therapy *(26)*. More than half of all episodes of peritonitis occur in only 25% of all patients on CAPD. Twenty percent of patients develop three or more infections each year, whereas others remain free of infection for 3 or more years *(10,33,34)*.

Several factors place a patient at increased risk for infection, especially peritonitis. These factors have been best studied in patients receiving CAPD. Although age or gender *(35)* does not appear to be important risk factors [rates may be higher in young children who perform their own therapy as opposed to children who obtain assistance from another family member *(36)*], underlying disease states may be important. For example, diabetic patients have been found to have higher rates of both peritonitis and exit-site infections *(37)*. Lack of compliance with asepsis, lapses in technique, low patient motivation, depression, lack of social support, fewer years of education, and lower socioeconomic status all have been found to be contributing factors to infection (38). Both African Americans *(39)* and Native Americans *(40)* are at increased risk. The type of catheter design and operator do not appreciably influence rates of peritonitis *(41)*. Antibiotic prophylaxis at time of catheter placement may decrease infection risk *(42,43)*. Vancomycin use in this setting appears superior to cephalosporin use in prevention of early peritonitis *(42)*. However, routine use of vancomycin is discouraged for fear of VRE development (15). Downward direction of the exit site also lowers rates of peritonitis *(44)*. Data have demonstrated that catheters containing both a superficial and a deep Dacron cuff (double-cuffed catheters) were associated with significantly lower rates of peritonitis than single-cuffed catheters *(41)* and may be associated with longer catheter survival and fewer exit-site complications *(45)*. However, another study found that single-cuffed catheters were not inferior if the single cuff was placed in the deep position *(46)*. Studies have also confirmed that both the type and the method of connection used between the dialysis bag and the indwelling peritoneal catheter can influence rates of peritonitis. Patients using connection devices permitting flush before fill systems such as Y-sets *(30)* or using disconnect systems that sterilize the connection, such as UV radiation *(47)*, had rates of peritonitis significantly lower than those of patients using standard spike connectors *(29)*. Manual spiking of dialysis bags is a discouraged procedure (48). Finally, patients who were prescribed intraperitoneal medications and added these medications themselves had higher rates of peritonitis *(29)*.

Intermittent peritoneal dialysis appears to result in lower rates of peritonitis when compared with CAPD. Perhaps much of this reduction can be attributed to the need for less frequent manipulations. In fact, patients on CIPD perform only 156 to 208 connect–disconnect procedures per year, as opposed to the more than 1,400 required for CAPD. Likewise, patients on CCPD appear to become infected at rates between those described for CIPD and for CAPD *(18)*; these patients perform approximately 700 connect–disconnect procedures annually.

Exit-site or tunnel infections occur more commonly in individuals with concomitant peritonitis. Studies have also demonstrated that nasal carriers of *Staphylococcus aureus* are at increased risk for infection *(49–54)*. Persistent carriage of *S. aureus* at the catheter exit site or the anterior nares is associated with a threefold increase of CAPD infections than compared with intermittent carriers (55). Another study found that frequent and comprehensive washing (ablution) combined with intranasal mupirocin significantly decreased *S. aureus* carriage and CAPD-related *S. aureus* peritonitis *(56)*. Diabetics may also be at increased risk for infection, although this observation may be confounded by the observation of high carriage rates of *S. aureus* in these patients *(57)*. The overall risk of an exit-site or tunnel infection in a patient receiving CAPD approaches 0.2 to 0.7 episodes per patient year *(51,58)*. Half of patients on CAPD do not develop exit-site infections within 2 years of catheter placement.

Epidemics of peritonitis in patients receiving chronic dialysis have been observed, especially in patients receiving CIPD via machines that use RO to sterilize water that then mixes with a dialysate concentrate *(17,59,60)*. Outbreaks

have also occurred as a result of delivering contaminated dialysate to the patient, either directly *(61,62)* or indirectly by use of water baths to heat the dialysate before infusion *(63–65)*. Contaminated disinfectants used to clean exit sites and tubing ports have also resulted in outbreaks of infection *(66)*.

PATHOGENESIS

Routes of Infection

The four major pathways resulting in peritonitis in patients on dialysis are schematically represented in Figure 64-2. These include intraluminal transmission of microorganisms (microorganisms gaining entry through the infusion system); periluminal infections (infection of the catheter site with resultant local infection and, at times, spread into the peritoneum); transmural infections (peritonitis as a result of intestinal injury, perforation, or transmigration of microorganisms); and hematogenous spread, usually from a site of infection elsewhere. Exit-site or tunnel infections almost always result from a periluminal infection, although peritonitis can cause infection at the deep Dacron cuff of the silastic catheter with resultant tunnel infection or abscess formation.

Few studies have examined the most common means by which peritonitis develops in patients receiving acute dialytic therapy. Clearly, infection of the catheter site with resultant spread into the peritoneum is a major route of infection. Unlike the situation with chronic dialysis, the cannula is usually inserted directly into the peritoneum after a stab wound is made. A protective tunnel with stabilization by Dacron cuffs is not usually made for short-term acute dialysis. Another important means by which peritonitis may develop in these patients is inadvertent perforation of the bowel during blind catheter placement or as a result of perforation from migration of the rigid catheter during dialysis with injury to the bowel wall. Microorganisms can also be introduced in the lumen during bag or tubing changes.

Contrast this scenario with what is observed in patients on chronic forms of peritoneal dialysis. It appears from inferential and intervention studies that the most important route of infection in these patients is intraluminal. Intraluminal contamination can occur during the numerous connect–disconnect manipulations by means of loose-fitting connectors or malfunctioning clamps, through defects in the plastic tubing or bags, or from the dialysis fluid itself. First, peritonitis occurs at least twice as often as exit-site infections in patients on chronic dialysis (27), suggesting that microorganisms are instilled into the peritoneal cavity. Second, the most common microorganisms causing peritonitis are coagulase-negative staphylococci rather than *S. aureus,* a microorganism found more frequently as a cause of periluminal infections *(67)*. Third, studies have found that a major cause of peritonitis in patients on chronic dialysis is poor technique or observed breaks in technique resulting in intraluminal contamination *(68)*. Fourth, CIPD or CCPD, methods associated with fewer manipulations, have consistently been associated with fewer infections *(18)*. Finally, incorporating devices or procedures to reduce touch contamination have resulted in fewer infections *(29,30)*.

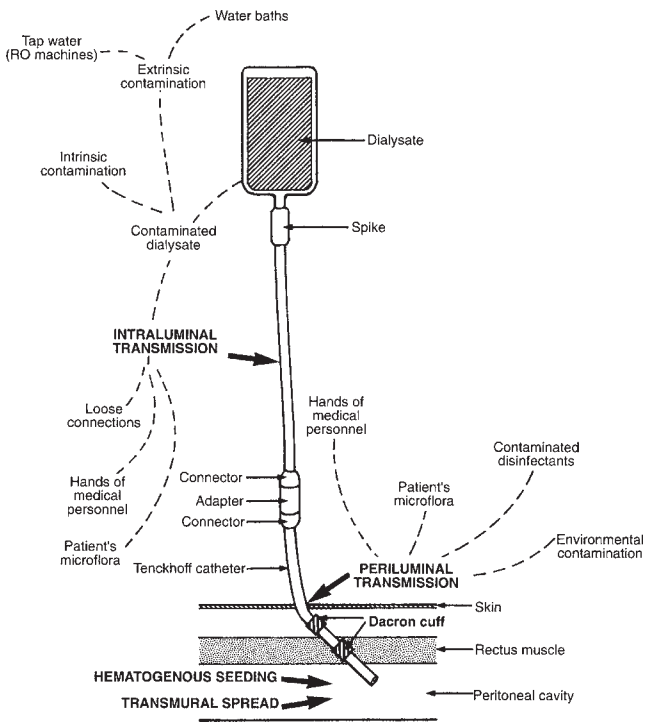

FIGURE 64-2 Sources of peritonitis and exit-site and tunnel infections in dialysis patients.

Contaminated Dialysate

Intrinsic contamination of dialysate has been reported infrequently and may result in infective peritonitis *(61)* or a sterile peritonitis resulting from delivery of endotoxin *(62)*. In-use or extrinsic contamination may occur during bag exchanges. Fortunately, commercially available dialysate does not support the growth of staphylococci, the most common pathogen responsible for infection, although some gram-negative microorganisms proliferate readily if introduced *(69,70)*. Water-adapted microorganisms such as *Mycobacterium chelonae*–like microorganisms and *Pseudomonas* species have caused outbreaks of peritonitis in patients on CIPD *(17,60)*. Microorganisms such as *M. chelonae*–like organisms not only can live in chlorinated water but also may survive exposure to high concentrations of disinfectants such as formaldehyde *(71)*.

Infection of the catheter site is the second most common cause of peritonitis and the leading cause of exit-site infections in patients on chronic peritoneal dialysis. The implanted catheter never forms a complete sealed junction with the skin; thus, microorganisms are present within the exit site and can result in infection. Although the superficial embedded Dacron cuff is a reasonable barrier, limiting the migration of microorganisms deeper into the abdominal wall or to the peritoneum, its efficacy is clearly not 100% *(72)*. Up to 17% of patients who develop an exit-site infection also have peritonitis *(67)*. *S. aureus* carriers are at high risk for developing an exit-site infection *(50–54,57)* as are diabetics *(73)*.

Transmural infections occur as a result of abdominal perforation or injury, inflammation of the serosal surfaces,

or transmural migration *(74)*. Rates of peritonitis resulting from intestinal microorganisms are higher in patients with preexisting diverticular disease *(75)*. Infection of the peritoneum or exit site by the hematogenous route is uncommon.

Host Defense Mechanisms

For peritonitis to develop, the patient's host defenses must not be able to contain, destroy, and remove the invading pathogens. Peritoneal fluid normally contains up to 200 cells/mm^3, of which more than 80% are mononuclear cells predominately macrophages *(76–78)*. These cells represent the primary cellular barrier against infection *(79)*; patients prone to infection may have fewer macrophages available to combat infection *(80)*. Many microorganisms causing peritonitis require opsonization by heat-stable substances, such as immunoglobulin G (IgG) and other specific antibodies, or heat-labile components, including complement for efficient removal. Deficiency in IgG or C3 may also predispose patients to infection, as would neutropenia *(81)*.

It is well known that the delivery of dialysate into the peritoneal cavity has a direct adverse effect on host defense mechanisms because of the effects of the low pH and hyperosmolarity of the dialysate. Both acidity and hyperosmolarity reduce the ability of macrophages and polymorphonuclear leukocytes to phagocytize and kill microorganisms *(82–84)*. Also, the presence of extra liters of fluid in the peritoneal cavity during dialysis results in a marked dilutional effect on both cellular and humoral protective factors, resulting in fewer leukocytes per milliliter and a relative opsonic deficiency *(81,85)*.

Obviously, an indwelling peritoneal catheter has adverse effects on the host. A conduit between the outside environment and the peritoneum now exists. The catheter may act as a foreign body, initiating inflammatory changes that predispose to infection, and can serve as a substrate on which colonization may be established. Although silastic catheters appear to be less thrombogenic than polyurethane catheters *(86)*, all catheters eventually become coated with a fibrin sheath *(87)*. Microorganisms can become embedded in this sheath or in the biofilm produced by many microorganisms, resulting in proliferation with resultant infection. This protective environment may be responsible for the difficulty in eradicating infection by seemingly appropriate antibiotics or for relapses of infection *(88)*.

Finally, patients with end-stage renal failure often have defects in cellular immune functions and are more susceptible to infection in general *(89–91)*.

TABLE 64-1

Prevalence of Microorganisms Isolated from Patients with Peritonitis and Catheter (Exit-Site and Tunnel) Infections

		Catheter
Microorganisms	***Peritonitis (%)***	***Infections (%)***
Gram-positive aerobic bacteria		
Coagulase-negative staphylococci	40–65	15–20
S. aureus	10–25	25–35
Streptococcal species	8–15	2–5
Enterococci	3–7	2–5
Corynebacterium or *Bacillus* species	1–4	2–5
Gram-negative aerobic bacteria		
Escherichia coli	7–12	5–10
Klebsiella species	2–4	2–5
Other Enterobacteriaceae	1–7	1–5
Pseudomonas species	5–9	10–15
Miscellaneous	1–5	1–5
Multiple microorganisms	2–6	25–35
Anaerobes	<5	<1
Fungi	4–8	4–6
Miscellaneous	2–5	3–5

(Data from references *22,33,34,51,67,73,92*.)

ETIOLOGIC AGENTS

Causative Microorganisms of Peritonitis

Although numerous microorganisms have been isolated from infected patients on peritoneal dialysis, most of these microorganisms are skin commensals such as coagulase-negative staphylococci (Table 64-1) *(22,33,34,51,67,73,92)*. At least two thirds of all episodes are caused by gram-positive microorganisms; *Staphylococcus epidermidis* is isolated most frequently. The second most common microorganism is *S. aureus,* followed by various streptococcal species. Gram-negative bacteria account for 20% to 30% of all episodes, with *E. coli* and other members of the family Enterobacteriaceae most prevalent. Fewer than 10% of episodes of peritonitis are due to *Pseudomonas aeruginosa* or related microorganisms. Anaerobes are uncommon. When anaerobes are present, the possibility of peritonitis from bowel perforation increases, especially if polymicrobic peritonitis is found.

Peritonitis resulting from fungal microorganisms has been reported to occur in as many as 8% of episodes. The most commonly isolated fungus is *Candida albicans,* followed by other *Candida* species *(93,94)*. Less commonly isolated microorganisms include *Mycobacterium* species and related pathogens. Viral microorganisms and parasites are exceedingly uncommon causes of peritonitis in patients on peritoneal dialysis.

Aseptic peritonitis is a well-described entity. Although the frequency of culture-negative peritonitis has decreased with improved culture techniques (95), 10% of episodes of peritonitis yield no growth of pathogens on culture. Clearly, some of these episodes represent failure to isolate an infecting microorganism because of the lack of sensitivity of culture techniques *(96)*. Others may be due to a foreign body reaction to the implanted catheter *(97)*, chemical peritonitis *(17,98)*, or delivery of endotoxin into the peritoneum *(61)*. Culture-negative peritonitis rates >20% should prompt a program's review of culture methods (48).

Causative Microorganisms of Exit-Site or Tunnel Infections

The microbiology of exit-site or tunnel infections differs somewhat from that observed in patients with peritonitis (Table 64-1). Mixed infections, rare in dialysis-associated peritonitis, may be found in up to 30% of these catheter infections *(67)*. The most commonly isolated pathogen is *S. aureus,* accounting for 25% to 35% of all episodes, followed by *S. epidermidis* in 10% to 20% of cases. *Pseudomonas* species are also more frequently recovered from device-related infections than from peritoneal fluid in patients with peritonitis.

Piraino et al. *(67)* found that 17% of all catheter infections occurred simultaneously with or were followed shortly thereafter by an episode of peritonitis resulting from the same microorganism, supporting the conclusion that exit-site infections can result in peritonitis. Peritonitis and exit-site infections caused by *S. aureus* and *P. aeruginosa* require catheter removal more often than when these same infections are caused by *S. epidermidis* (38). Others have found high rates of treatment failure when infection was due to fungi *(93,94,99)*. Piraino et al. (38,*67*) also found that peritonitis episodes resulting from *S. epidermidis* infrequently had associated exit-site infections, whereas peritonitis caused by *S. aureus* or *Pseudomonas* species were frequently associated with a catheter infection.

Comments on Specific Pathogens

Coagulase-Negative Staphylococci Eighty percent of coagulase-negative staphylococci belong to the species *S. epidermidis (100,101)*; coagulase-negative staphylococci are an important component of the cutaneous flora. Although adherence factors and slime production are thought to be important in pathogenesis of infection, studies have not confirmed this hypothesis. Strains capable of producing slime were not more frequently isolated from episodes of peritonitis (95); in one study, peritonitis-causing strains lacking adherence and slime productivity were more frequently associated with complications *(102)*. Infections resulting from *S. epidermidis* tend to be milder and more responsive to therapy than infections resulting from *S. aureus*. These infections are generally felt to be a consequence of touch contamination (see also Chapters 30 and 31).

Staphylococcus aureus Several studies have found that nasal carriers of *S. aureus* are at higher risk for exit-site infections and peritonitis than noncarriers *(49–54,103)*. Epidemiologic typing has confirmed a high concordance between strains of *S. aureus* isolated from infections and those isolated from the nares *(54,103,104)*. More recently, strains of staphylococci with reduced susceptibilities to glycopeptide antibiotics including vancomycin have been described *(105–107)*, as well as isolates possessing absolute resistance *(108,109)* (see also Chapters 28 and 29). *S. aureus* peritonitis may be a consequence of touch contamination but is more often associated with catheter infection.

Enterococci Although an infrequent cause of initial peritonitis in patients on peritoneal dialysis, enterococci, including vancomycin-resistant strains, have been found in increasing frequency, especially among patients with heavy exposure to antimicrobics. Guidelines for preventing the emergence and spread of vancomycin-resistant enterococci have been published *(110)* (see also Chapter 33).

Enterobacteriaceae Although the precise origin of these microorganisms as a source of exit-site infections and peritonitis is not known, hand and cutaneous carriage seems more plausible than transmural migration. Ill patients and those with chronic medical problems often are colonized with these microorganisms *(111–113)*. Also, dialysate readily supports the growth of microorganisms such as *E. coli*, as opposed to staphylococcal species; a high index of suspicion for contamination by these microorganisms should be maintained *(69,70)*.

Pseudomonas Species These microorganisms also colonize the skin of chronically debilitated patients *(111–113)*. Their repeated isolation should also prompt investigation of products, including disinfectants, that might be contaminated *(66,114)* or exposure to water sources, including pool water or even potable water *(115)*.

Fungi The source of most yeast is the patient's skin, mucous membranes, or the bowel; less comes from the environment. Fungal peritonitis is rarely caused by exit-site infections but rather by touch contamination from individuals colonized by yeast (116). Established predisposing factors include recently treated bacterial peritonitis, use of broad-spectrum antibiotics, and healthcare-associated acquisition *(94)*. Infections usually respond poorly to therapy without removal of the peritoneal catheter. Filamentous fungal infections usually arise from environmental contamination. Of these, *Fusarium* species is most common *(117)*.

Mycobacteria Environmental contamination, especially from water, predisposes to mycobacterial infections resulting from *M. chelonae* and related microorganisms *(118)*. Several outbreaks have been reported in patients receiving intermittent peritoneal dialysis by automated machines *(17)*.

Miscellaneous Microorganisms Infections resulting from other human flora (e.g., *Haemophilus* species, *Neisseria* species, *Branhamella* species, and *Gardnerella* species) have been reported, as have infections caused by diverse microorganisms, including *Campylobacter* species, *Pasteurella* species, *Listeria* species, and vibrios. Even episodes of peritonitis caused by *Prototheca wickerhamii* have been reported *(119)*.

DIAGNOSTIC CONSIDERATIONS

Clinical Manifestations of Peritonitis and Exit-Site Infections

Most patients who develop peritoneal dialysis–associated peritonitis usually have some complaints of abdominal pain and notice a change in their dialysis effluent from a clear to somewhat cloudy fluid. Onset may be abrupt or relatively indolent depending on the bacterial load and nature of the infecting pathogen. For example, patients who develop peritonitis from *S. aureus* or *P. aeruginosa*

TABLE 64-2

Symptoms and Signs Associated with Dialysis-Associated Peritonitis

Clinical Manifestations	*Percentage of Patients (Range)*
Symptoms	
Abdominal pain	73–95
Nausea, vomiting	25–35
Chills	18–23
Diarrhea	6–9
Signs	
Cloudy effluent	86–98
Abdominal tenderness	
Fever (=38°C)	24–34
Drainage problems	10–15

(Data from references *10,67,121–123.*)

have a more aggressive course than patients who have *S. epidermidis* peritonitis *(64,67,73,120)*. Obviously, if peritonitis occurs as a result of bowel perforation, patients usually develop signs of an acute abdomen.

Table 64-2 lists the common manifestations of dialysis-associated peritonitis *(10,67,121–123)*. Of particular importance is the relative infrequency of constitutional manifestations. In general, less than one third of infected patients have fever. However, patients can develop acute illness rapidly. Incubation periods range from a few hours to several days.

Exit-site or tunnel infections usually present with pain accompanied by serous or seropurulent drainage. Unless peritonitis is also present, systemic signs or symptoms occur rarely.

Examination of the Peritoneal Fluid

More than 90% of patients with peritonitis have cloudy effluent because of the elevated number of peritoneal leukocytes. Normally, the peritoneal fluid contains <60 white blood cells/mm^3; most are mononuclear cells. Infection rapidly results in an increase in the number of white blood cells in the peritoneal fluid and a shift from mononuclear cells to polymorphonuclear leukocytes *(76–78,124)*.

Most patients develop cell counts ranging from a few hundred to several thousand *(20,124,125)*; more than 50% of the cellular component is composed of polymorphonuclear leukocytes *(126)*. Polymorphonuclear leukocyte counts >100/mm^3 in the peritoneal fluid correlate strongly with infection. Occasionally, in some infections, a mononuclear cellular response is found, such as with tuberculous peritonitis. However, most microorganisms associated with dialysis-induced infection result in neutrophilia.

Peritoneal neutrophilia can also be seen in noninfectious inflammatory conditions affecting the peritoneum, including peritonitis caused by chemical irritants or endotoxin, an intraperitoneal bleed, serositis resulting from systemic vasculitis, or primary gastrointestinal disease. Occasionally, peritoneal eosinophilia is observed. Its presence suggests a foreign body (catheter) reaction or an allergy to a catheter component or other product. It is generally a self-limiting process *(127)*.

Gram Staining of Peritoneal Fluid or Drainage from Exit Sites

For cases of suspected peritonitis, preparation of a gram-stained smear (or other special stains for acid-fast or fungal microorganisms, as appropriate) of the sediment from a centrifuged sample of effluent is important. If the stain is positive, more specific therapy can be instituted, and purely empiric therapy can be avoided. Unfortunately, studies have found a positive Gram stain in only 9% to 35% of cases of peritonitis *(128)*. If purulent drainage is present from an exit-site infection, the Gram stain may prove quite useful in guiding initial therapy.

Culture Methods

Peritoneal dialysate effluent should be cultured as soon as possible in any patient with suspected peritonitis. If this is not feasible, the bag should be stored in a refrigerator and transported to the laboratory within 6 hours.

The optimal method for culturing peritoneal effluent is a matter of considerable controversy. Because the inoculum is usually quite low *(20,129)*, large-volume sampling has resulted in a higher yield. Effluent should generally be concentrated by centrifugation or filtration or inoculated into an enrichment medium *(20,22)*. Use of filters, however, is technically demanding and may result in contamination *(130)*. von Graevenitz and Amsterdam's review (95) of the various microbiologic techniques available is excellent. These authors reviewed studies published before 1987 and found significant problems in comparing various culture methods because of problems in study design and the use of inadequate volumes for direct culturing. They concluded that a minimum of 10 mL of effluent should be cultured, using an enrichment broth with antiphagocytic and lytic properties.

More recently, additional studies have demonstrated that, in addition to concentrating specimens, direct sampling of dialysate into an isolator tube with subsequent inoculation or direct inoculation into semiautomated blood culture systems such as Bactec bottles has been associated with high yields *(131–133)*. An Ad Hoc Advisory Committee on Peritonitis Management (chaired by W.F. Keane, M.D.) recently released a consensus on techniques for sampling and culturing peritoneal dialysis effluent and exit sites (134). Their recommendations are as follows:

1. Peritoneal dialysate effluent should be analyzed as promptly as possible after peritonitis is suspected.
2. An aliquot of 10 to 50 mL should be centrifuged, and the sediment should be examined by Gram stain.
3. Specimens should be cultured by using either concentration methods such as centrifugation (resuspension in nutrient broth or sterile saline with subsequent inoculation of blood and MacConkey agar plates; if a perforated viscus is suspected, anaerobic cultures can also be done; lytic substances such as Triton X can be added to the effluent before centrifugation and may increase the yield of positive cultures) or Millipore filtration. A semiautomated blood culture system for culturing peritoneal dialysis effluents appears to be suitable as well.

4. Using media with antiphagocytic substances and antibiotic binding resins may also result in higher yield.
5. A Calgi swab should be used to culture purulent exudate obtained from an exit site.

COURSE AND PROGNOSIS

Although most patients are not acutely ill, some patients initially develop high-grade toxicity with onset of infection. Blood cultures occasionally are positive. Peritoneal infection also results in impaired ultrafiltration, increased glucose absorption, and tremendous protein losses *(135)*. Infection can result in pulmonary complications resulting from bowel distention with displacement of the diaphragm and pulmonary edema from inadequate volume removal. The inflammatory reaction itself produces a fibrinogen-rich exudate with fibrin clot formation and impaired drainage. Repeated episodes can cause scarring with loss of the peritoneal membrane for further ultrafiltration.

Most cases of peritonitis respond promptly to appropriate antimicrobic therapy. However, as discussed previously, certain microorganisms tend to be more difficult to treat or do not respond well to antimicrobial therapy unless the implanted catheter is removed *(67,93,94,99)*. Patients who relapse after seemingly appropriate therapy also usually require catheter replacement. However, this can often be done as a simultaneous procedure often obviating the need for "bridge" hemodialysis (38).

Most exit-site infections can be managed conservatively. However, the presence of a tunnel abscess almost always necessitates replacement of the implanted catheter, which can often be done as well by a simultaneous procedure (38).

PREVENTION AND CONTROL

Despite major advances since the acceptance of chronic peritoneal dialysis as a method of chronic dialytic therapy, infection and catheter-related complications continue to cause significant morbidity. Table 64-3 summarizes important recommendations for prevention.

It is strongly suggested that each center monitor all peritoneal dialysis–associated infections by type, cause, microorganism, etc. as part of its quality assurance programs. The recent 2005 ISPD Recommendations offer several monitoring methodologies for this purpose (48).

Prevention largely depends on three factors: proper selection and training of patients, strict adherence to aseptic techniques in all aspects of dialysis, and use of intervention strategies for special at-risk populations.

Patient Selection and Training

Few medical conditions make chronic peritoneal dialysis the method of choice for chronic dialytic therapy. Its ease of performance, ability to be done in the home setting, lower cost when compared with hemodialysis, and, as in the case of CAPD, machine independence have led to greater patient acceptance. Rates of complications are reduced in the highly motivated patient who has received thorough training with continued supervision *(136,137)*. Although peritoneal dialysis training nurses experience would be expected to lower infection rates, one study showed the opposite effect, at least for gram-positive infections *(138)*. This suggests that more "active learning" and continuing trainer education may be more reliable than lengthier experience times. Periodic patient retraining, use of infection control programs, and continuous infection review can aid in lowering infection rates (139).

TABLE 64-3

Prevention of Infection in Patients on Chronic Peritoneal Dialysis

- Select well-motivated patients and thoroughly instruct them in sterile techniques.
- Place the implantable silicone catheter using sterile technique. Double-cuffed catheters may be preferred.
- Anchor the catheter site firmly.
- Wash hands before all manipulations and avoid touch contamination of tubing connections.
- Consider special catheter connectors such as Y-sets using the "flush before fill" concept, patient-assist devices, or connecting devices using ultraviolet sterilization.
- Reduce manipulations to a minimum.
- Perform daily site care with at least soap and water (possibly chlorhexidine) and inspect site for signs of early infection.
- Consider antibiotic prophylaxis (topical, such as mupirocin vs. systemic) only in very limited circumstances (e.g., staphylococcal carriers with frequent exit-site infections).
- If using an automated machine using reverse osmosis to "sterilize" tap water, clean, and disinfect it regularly.
- Treat other sites of infection early to reduce chances of hematogenous or transmural spread to the peritoneum.
- Optimize host defenses by good nutrition and care of other medical problems.

Type of Catheter and Insertion Techniques

Although studies have not established that the precise type of catheter inserted has definitely affected rates of infection, Silastic catheters containing both a superficial and a deep Dacron cuff may lower rates of infection when compared with single-cuffed catheters *(45,46)*. Because silicone can be degraded by iodine or povidone-iodine over time and does not resist biofilm formation (134), newer catheter materials are needed. Bonding of antimicrobic agents to indwelling devices may reduce risks for device-associated infections *(140)*. Studies have not shown definitive advantages for any single method of placement (blind vs. surgical vs. peritoneoscopic insertion) or for placement performed in an operating room suite as opposed to elsewhere; strict attention to asepsis is always important (15,*46*,139). Downward direction of the catheter exit has been suggested (139). A recent Cochrane review also failed to find any catheter-related intervention that had any impact on peritoneal dialysis–associated peritonitis or exit-site infection (141). Antimicrobial prophylaxis appears to be warranted immediately before surgical placement

of the catheter (*42*,139,*142*). Likewise, preoperative skin cleansing with chlorhexidine-alcohol appears to be more protective against infection than povidone-iodine for surgical-site antisepsis (143).

Asepsis during Peritoneal Dialysis

Most episodes or peritonitis are due to inadvertent contamination of the dialysis fluid or peritoneal catheter during exchanges (intraluminal contamination). Strict adherence to aseptic practices is essential and can reduce infection rates *(68,144)*. Good hand washing practices using an alcoholic gel rub or antimicrobial soap *(145)*, performing dialysis in a clean and safe environment, and inspecting all supplies for defects before use are important. Numerous connectors and connecting devices have been developed to reduce the possibility of accidental contamination during bag exchanges. These include such items as the titanium adapter *(28,146)*, use of added tubing to permit flush before fill as the Y-connector *(30)*, mechanical patient assist devices *(146)*, connecting devices with in-line bacteriologic filters *(130)*, and devices designed to clean the connections with disinfectants *(147,148)*, UV radiation *(47)*, or heat *(149)*. Studies on the efficacy of these devices have produced contradictory results but definitely show added costs. It does appear that both the UV and the Y-connectors have promise; a study of 3,366 CAPD patients who started dialysis at home for the first time between January 1, 1989, and June 30, 1989, demonstrated a relative risk of first peritonitis significantly lower for the Y-set (relative risk: 0.6; $p < .01$) and UV set (relative risk: 0.75; $p < .01$) when compared with the standard spike connecting set *(29)*. The difference in relative risk between the Y- and the UV sets was also statistically significant ($p < .01$). The benefits of the Y-systems on reducing rates of peritonitis was confirmed in another recent study with rates of one episode per 40 months, compared with one episode per 16 months for other systems *(150)*. In Europe, Y-sets containing disinfectants have resulted in fewer episodes of peritonitis when compared with standard connection systems. However, because of fear of accidental chemical peritonitis during use, these modified systems are not popular in the United States. More recently, Y-sets, in which both the dialysis solution and the drain bags were preattached, appear to have reduced peritonitis rates further *(151)*. A recent randomized control trial review showed that the only catheter-related intervention that was effective at preventing peritonitis was use of twin bag and Y set disconnect systems (152). Of two common twin bag systems, Ultrabag and Andy-Disc, the Ultrabag System has trended toward a lower peritonitis risk (153). The use of standard spike systems is strongly discouraged.

Systems that permit fewer connections and disconnections have also been associated with reduced rates of peritonitis. Some patients can tolerate three exchanges per day rather than four. Use of the CCPD machine reduces manipulations to twice daily with lower rates of peritonitis *(18)*. Automated intermittent peritoneal dialysis permits even fewer interruptions but may be associated with outbreaks when used at centers or with endemic disease because of problems with disinfection and sterilization *(17,59,60)*. Formal recommendations for the care of these machines have been published *(154)*.

Use of disinfectants can also reduce rates of peritonitis. With the popular twin bag system came disposable peritoneal dialysis tubing that does not require disinfection. However, disinfectants are still used to maintain sterility of transfer set tips and peritoneal dialysis catheters. Either povidone-iodine or sodium hypochlorite (each with pros and cons) can be used. This topic has been reviewed recently *(155)*.

Site Care and Special Considerations

Daily inspection and care of the exit site is also important, although some controversy exists as to whether such care should include daily showering with soap or additional use of antiseptics on the exit site. One study suggested that rates of exit-site infection can be reduced by using a protective nonocclusive dressing and povidone-iodine cleansing *(44,51)*; others have not confirmed this observation (134), whereas another small study suggested chlorhexidine to be superior to povidone-iodine *(156)* for site care. An excellent summary of exit-site practices has recently been updated (15). However, optimal site care procedures are largely undetermined secondary to lack of controlled studies. Infection must be detected and treated early to reduce progression to a tunnel abscess or peritonitis.

S. aureus carriers are anywhere from two- to sixfold at higher risk for peritonitis than noncarriers *(157)*. *S. aureus* nasal carriers seem to have benefited from attempts to eliminate carriage by use of various antimicrobic prophylactic agents in some, but not all, studies *(49,52)*. Agents used have included rifampin, trimethoprim-sulfamethoxazole, intranasal bacitracin or mupirocin, or topical mupirocin applied to the exit site *(57,158)*. A multicenter study involving 267 staphylococcal carriers suggested that monthly application of intranasal mupirocin for 5 days results in a reduction of exit-site infections due to *S. aureus* *(159)*. A meta-analysis involving 14 studies and a total of 1,450 patients showed that topical mupirocin decreased rates of peritonitis and exit-site infections by *S. aureus* by 70% (160). However, a recent Cochrane review did not show an overall decrease in peritonitis (only exit-site infections) (161), and this was corroborated earlier in another study *(162)*. Widespread usage of mupirocin applied topically to the nares or exit site may result in significant development of resistance *(163)*, may cause catheter rupture *(164)*, and may not be cost-effective *(165)*. However, another study documented low mupirocin resistance rates even after 7 years of exit-site use *(166)*. Unfortunately, more serious infections such as tunnel infections and peritonitis resulting from *S. aureus* were also unaffected by this regimen. However, the epidemiology of infections in staphylococcal carriers is not completely understood, and many chronic carriers do not develop exit-site infections. It might be prudent to restrict such intervention to proven carriers with repeated infections. The device should best be removed after successful renal transplantation (within 4–6 weeks after surgery). The use of mupirocin appears to decrease *S. aureus* peritoneal dialysis infections but does not decrease pseudomonas or other gram-negative infections. Use of topical gentamicin at the exit site was shown to decrease gram-negative infections (including pseudomonas) at the exit site and gram-negative peritonitis. It may also be as effective as mupirocin at preventing

S. aureus infections at least in one randomized, double-blind study (116). Whether or not regular showering with chlorhexidine at home will reduce exit-site infections or peritonitis, especially due to gram-positive microorganisms including coagulase-negative staphylococci and *S. aureus* is uncertain. If studies demonstrate benefit, as suggested in recent papers in other settings, rates of infection due to gram-positives may fall further (167,168).

Antibiotic Prophylaxis to Reduce Episodes of Peritonitis

Preoperative intravenous antimicrobial prophylaxis appears to reduce early rates of peritonitis but does not alter rates of exit-site or tunnel infections (161,*162*) nor does it result in a reduction of peritonitis in the long term *(169,170)*. An uncontrolled and nonrandomized study suggested that oral prophylaxis with nystatin administered at the time of bacterial peritonitis may reduce subsequent episodes of fungal peritonitis *(171)*. More recent studies also suggested that oral nystatin reduced antibiotic-related fungal peritonitis *(171,172)*. A recent Cochrane review also corroborated this finding (161) but found no conclusive evidence to support use of topical disinfectant, oral prophylactic antibiotics, connection device germicidal chambers, or staphylococcal vaccines.

FUTURE CONSIDERATIONS

Improved catheter materials designed to minimize foreign body reactions, adherence of microorganisms, and biofilm formation; improved techniques of catheter placement and site sealing; newer delivery systems resulting in fewer episodes of contamination; and improved methods of skin cleansing are needed. Enhancing both local and systemic host defense systems may also lead to lower rates of infections in patients on chronic peritoneal dialysis therapy. Trials of a *S. aureus* conjugate vaccine in patients receiving hemodialysis appear promising in preventing systemic infection resulting from *S. aureus (173)*, and investigations using modified hyperimmune globulin to *S. aureus* are also being investigated for patients with recurrent staphylococcal infections.

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CHAPTER 65

Infections that Complicate the Insertion of Prosthetic Devices

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The insertion of implants and medical devices is now a common procedure that benefits patients, often in a lifesaving way, who are suffering from a variety of exogenous-acquired (trauma, endocarditis, rheumatic fever, hydrocephalus) or degenerative diseases (arthrosis or arthrosclerosis). A fundamental feature of foreign bodies is their exquisite susceptibility to infection. The inoculum of bacteria necessary to induce such postsurgical infections is extremely low when compared with surgery in the absence of a foreign body *(1,2)*. In addition, bacteria that are often nonpathogenic and normally present as skin commensals (i.e., coagulase-negative staphylococci or *Propionibacterium* species) are able to cause infections under these conditions *(2)*.

The impact of such infections is profound, because they often result in tissue destruction, serious dysfunction of the prosthetic device, and sometimes systemic dissemination of the pathogen. These infections are very difficult to cure with antimicrobial agents alone and most often necessitate the removal of the device or surgical debridement. In this chapter, we take as paradigms the four most frequent surgical implants: orthopedic implants, vascular devices, cerebrospinal shunts, and breast implants. By analogy, the knowledge of infections associated with these four foreign bodies includes the current knowledge for most surgical implant infections. In the first part, we provide insights into their general pathogenesis, incidence (Table 65-1), microbiology, and prevention. In the second part, we discuss individual aspects of the different implants including clinical presentation, pathogenesis, microbiology, and prevention.

PATHOPHYSIOLOGY

To understand the difficulties underlying foreign body infections, it is necessary to characterize four different problems: (i) biofilms, (ii) local neutrophil dysfunction, (iii) small colony variants (SCV) of staphylococci, and (iv) multiresistant staphylococci.

Biofilms

The biofilm concept is extensively discussed in Chapter 31 and only the most important aspects are summarized here. Fundamental differences exist between surface-adherent bacteria and bacteria present in the fluid (planktonic) phase. It has been suggested that biofilm-enclosed microorganisms escape antibiotic killing because the extracellular material prevents diffusion and bacterial uptake of antimicrobial agents *(2,3)* (Fig. 65-1). Moreover, microorganisms attached to foreign material and exposed to bactericidal concentrations of antibiotics develop tolerance (i.e., the bacteria become resistant to the lethal effect of the antibiotic) *(2,3)*. In an *in vitro* model of surface-adherent *Staphylococcus aureus* growing onto polymethylmethacrylate, it was possible to demonstrate a decreased susceptibility to antimicrobial agents within 4 hours after adherence *(3)*.

Altered Host Defense in the Vicinity of Foreign Material: Neutrophil Dysfunction

Data from a study investigating neutrophils from animals with experimental foreign body infection revealed that cells recovered from the vicinity of the implant produced only a weak respiratory burst and had poor bactericidal activity compared with those collected from the blood of the same animals. This deficiency was due to prior activation of the neutrophils by the foreign material. This phagocytic defect may explain the high susceptibility of foreign bod-

TABLE 65-1

Frequency of Foreign Body Infections

Device	*Infection Incidence*[a]
Cardiovascular Implants	
Prosthetic heart valves	~4%
Pacemakers	1–3%
Cardioverter-defibrillators	~4%
Left ventricular assist devices	10–30%
Vascular grafts	~1.5%
Neurosurgical Shunts	
Cerebrospinal fluid shunts	1–10%
Orthopedic Implants	
Primary hip arthroplasties	<1.5%
Primary knee arthroplasties	<1.5%
Primary shoulder arthroplasties	~4%
Fracture implants (plates, nails)	3–4%
External fixation PINs	2–11%

[a]Adapted from reference *(27)*.

ies to infection *(4)*. A foreign body reduces the inoculum of *S. aureus* required to induce infection from more than 100,000 to as few as 100 colony-forming units *(5)*. Additionally, the extracellular slime substance produced by adherent staphylococci has potent immunomodulatory properties *(6)*. Several neutrophil functions appear to be affected. Chemotactic responsiveness is diminished and degranulation of specific granule content is increased. Finally, total joint prostheses may shed ultrahigh molecular weight polyethylene particles, thus impairing the phagocytic abilities of the neutrophil *(7)*.

Staphylococcal Small Colony Variants

Staphylococci are responsible for most infections associated with implants *(8)*. Staphylococcal SCV phenotypes are often found in foreign body infections *(9,10)*. They constitute a subpopulation of bacteria and have atypical colony morphology and unusual biochemical characteristics, thus making them a challenge for clinical microbiologists to identify. Clinically, SCV persist in mammalian cells and are less susceptible to antibiotics, especially aminoglycosides, than their wild-type counterparts and are a cause of recurrent infections (*3*,11,*12*). SCV of *S. epidermidis*, a phenomenon well known in *S. aureus (9,10)*, also exist and can emerge during glycopeptide therapy *(13)*.

Multiresistant Staphylococci

Since implants are particularly prone to infections due to staphylococci, resistance to current antibiotics among these pathogens adds to the heavy burden of disease. The ever-increasing incidence of implant infections due to methicillin-resistant *S. aureus* (MRSA) *(14)* and methicillin-resistant *S. epidermidis* (MRSE) *(15,16)* is a serious challenge. MRSE is already the most commonly encountered variant of *S. epidermidis* in many healthcare institutions *(16,17)*. With coagulase-negative staphylococci, polyclonal implant infections may occur, and this may be one of the explanations for treatment failure as laboratories do not always perform antibiotic susceptibility testing for all isolates *(2)*. So far, it remains unknown when patients become colonized with MRSE upon hospital admission, but it is probable that it occurs very fast. In a Swedish study, most patients on an orthopedic ward were colonized with MRSE at day 14 of admission *(18)*.

MRSA is usually resistant to many clinically important non–beta-lactam drugs, such as fluoroquinolones and clindamycin that have excellent bone and joint penetration *(19)*. Vancomycin, which is mostly used to treat MRSA infections, has slow bactericidal activity. In this setting, treatment of these infections can be problematic, particularly in the presence of multiple drug intolerance or allergy.

MRSA-related orthopedic implant infections (even with hospital-acquired MRSA) yield a high risk of treatment failure, independent of the clonal microbiological properties and genetic characterization of the isolates. In a recent study including different orthopedic implant material, treatment failure was reported as 35% *(20)*. Failure was nine times more frequent in patients with prosthetic joint infections due to hospital-acquired MRSA than in patients with methicillin-susceptible *S. aureus* (MSSA) infection (21). However, this remains a controversial issue, and while some reports do not attribute an increased treatment failure *(22)*, others report higher failures in resistant staphylococcal infection *(23)*. Of note, known MRSA skin colonization poorly predicts the pathogen of underlying implant infection due to *Staphylococcus* species *(24)*.

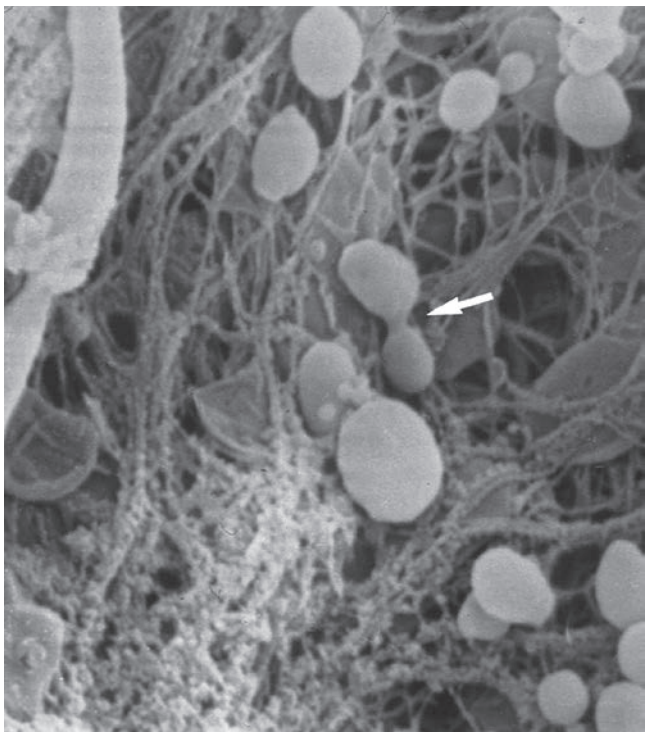

FIGURE 65-1 Biofilm in prosthetic infection. Scanning electron micrograph from infected total hip prosthesis. Cocci-shaped bacteria are shown, partly surrounded by extensive biofilm, amorphous material, and fibrinous elements. In the middle (*arrow*), the bacterium is dividing. *Staphylococcus epidermidis* was isolated (*2*).

ORIGIN AND MICROBIOLOGY OF PROSTHETIC INFECTIONS

Surgical site infections (SSI) are discussed in detail in Chapter 21 and only key salient points are provided here. Prostheses become infected by three different routes: (i) through the introduction of microorganisms during the operative procedure *(25);* (ii) by hematogenous seeding *(26)* or (iii) by lymphatic spread in the case of adjacent erysipelas. Most SSIs are believed to be acquired during surgery *(25)*, and this is supported by the success of prevention measures targeted on activities inside the operating room and a few reports demonstrating matching strains of pathogens from the surgeon's fingers and postoperative infection *(27)*. At present, the proportion of SSI really acquired in the operating room versus postoperatively on the ward remains unknown. Similarly, within the subgroup of SSI acquired during surgery, the proportion attributable to the patient himself or herself versus that transmitted by the surgical staff or the operating room environment is also unknown *(27)*. Freshly implanted biomaterial is probably more susceptible to infection. In addition, any factor or

event that delays surgical site healing increases the risk of infection, and ischemic necrosis, infected hematomas, and suture abscesses are common preceding events for joint sepsis *(28)*.

Apart from the setting of cardiac implants, hematogenous seeding probably occurs rarely compared to inoculation during surgery and early postoperative care. The estimated incidence of hematogenous infection among all arthroplasty infections ranges from a low 5.6% *(29)* to 9% to 10% *(27,30)*. However, in absolute terms, the incidence is quite low. Ainscow et al. *(31)* detected only three cases of prosthetic joint infections among 1,112 prostheses (2.7 per 1,000) that developed a hematogenous infection. In their prospective arthroplasty cohort, the authors of this chapter detected only seven hematogenous infections among 6,100 arthroplasties (1.1 per 1,000) performed during 1996 to 2008. Arthroplasty patients hospitalized for severe remote infections developed only one hematogenous arthroplasty infection compared with 88 remote infections *(27)*. Any bacteremia can induce an implant infection by hematogenous seeding *(27)*, although there appears to be a higher risk for prosthetic joint infection in the setting of *S. aureus* bacteremia *(32–34)*. The skin is reported to be the most frequent source of infection *(25)* followed by the genitourinary, respiratory, and gastrointestinal tracts *(27)*. However, this ranking is not fixed and depending on the setting, a gastrointestinal origin can be predominant *(27)*.

Staphylococci (*S. aureus* and coagulase-negative staphylococci) account for at least 60% of all implant infections (*8*,*35*,36) (Table 65-2). Aerobic gram-negative bacteria *(37)*, streptococci, enterococci, and anaerobes cause infection in <25% of cases. Culture-negative arthroplasty infection may occur in 15% of cases *(38)*. Polymicrobial infection is commonly seen as a complication of poor postoperative wound healing *(39)*. Certain comorbidities increase the risk of infection with specific microorganisms. For instance, patients with rheumatoid arthritis are at increased risk for *S. aureus* infection *(40)*, and *Propionibacterium acnes* is more commonly encountered in patients with an infected total shoulder arthroplasty *(41,42)*.

PREVENTION OF PROSTHETIC INFECTIONS

Prevention remains the cornerstone of infection control. It is efficacious and certainly more cost-effective than any form of therapy. SSI and preventive measures in general are discussed in detail in Chapter 21. In this section, we highlight special issues regarding the prevention of surgical prostheses infections.

Well-established, modifiable risk factors for SSI are reported in the literature. These include preoperative hair shaving instead of clipping (43), intraoperative hypothermia *(44)* or hyperglycemia *(45)*, lack of compliance with hand hygiene and surgical antisepsis (46), and suboptimal timing of perioperative antibiotic prophylaxis *(47)*. However, it is probable that no single measure is superior to others in preventing SSI of exogenous origin. This highlights the need for a multimodal approach involving active postdischarge surveillance and measures at every step of patient care: from the operating room to nonnegligent postoperative care *(27)*. An active surveillance program is important for the detection of implant infections *(27)* and should comprise a minimum length of 1-year follow-up *(48)*. Programs without active postdischarge surveillance readily miss half of all prosthetic infections *(27)*. Multicenter or supranational intervention programs based on guidelines, "bundles," or safety checklists are likely to be beneficial on a global scale *(27)*.

Antimicrobial Prophylaxis

The benefit of the administration of preoperative antimicrobial agents is largely undisputed. In orthopedic implant surgery, prophylaxis helps to reduce infection rates from 4% to 8% without antibiotics to 1% to 3% according to several trials performed in the 1970s to 1980s *(27)*. Administration of prophylactic antibiotic agents follows some rules. (a) A single intravenous dose of first- or second-generation cephalosporins is sufficient for most types of surgery *(47–51)*, and an additional benefit of antibiotics in irrigation fluid *(47)* has not been proven. (b) Timing is of

TABLE 65-2

Predominant Microorganisms Isolated in Prosthetic Joint Infection

	References		
	Steckelberg et al.*[a] *(1994) (35) (n = 578) (%)	***Fitzgerald and Jones*[b] *(1985) (84) (n = 131) (%)***	***Mayo Clinic cohort*[c] *(1969–1991) (35) (n = 1033) (%)***
Staphylococcus aureus	23	29	23
Coagulase-negative staphylococci	30	35	25
Other gram-positive microorganisms	12	7	11
Gram-negative aerobes	6	15	11
Anaerobes	4	7	6
Mixed	12	—	14

[a]Includes polymicrobial infections *(35)*.
[b]Includes polymicrobial infections *(84)*.
[c]Mayo Clinic cohort *(35)*.

utmost importance (*47*,52,*53*) and prophylaxis should be entirely administered within 1 hour before incision. (c) One dose is sufficient. For operating procedures longer than 4 hours or with significant blood loss, redosing might be justified (*47*,52). (d) When a tourniquet is used, the entire dose should be administered prior to its inflation *(54)*.

A single dose of vancomycin (1 g) is the prophylactic antibiotic of choice for all procedures requiring prophylaxis in patients colonized with MRSA *(48,55)*. Concerning MRSE, a switch to glycopeptide prophylaxis for implant surgery patients is sometimes suggested in the literature. A review of four randomized trials comparing prophylactic teicoplanin versus prophylactic cephalosporin in settings with a high MRSE prevalence identified the same infection rates in both groups (56). This has been confirmed also in a meta-analysis of seven randomized trials for cardiac surgery *(57)*, even though single trials in favor of a general switch to vancomycin prophylaxis in cardiac surgery exist *(58)*. A recent systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery in endemic MRSA settings failed to show increased efficacy in preventing SSI due to methicillin-resistant strains *(59)*. Even for MRSA, there is insufficient evidence to determine whether there is a threshold prevalence to justify a switch to general glycopeptide prophylaxis *(59)*.

Antibiotic prophylaxis before a dental intervention in implant patients is contested, apart from those with artificial cardiac valves (*60*,61), cardioverter-defibrillators, and left ventricular assist devices. This topic is further expanded upon in the corresponding subchapter.

Other Prevention Measures

MRSA has the capacity to colonize patients' skin for several months *(62)* if not years. These infections represent a failure in quality of care, are costly, and may ultimately compromise patient safety. Prevention is of the utmost importance and the introduction of universal MRSA screening upon hospital admission is seriously debated for this patient population (63,*64*). However, the results of several outstanding prospective trials in recent years are inconclusive. While some before–after studies *(65–67)* report a benefit, other randomized, crossover design trials (63,*68*) failed to show a reduction in infection rates (or at least in SSI rates due to MRSA). The debate is not closed. The screening for MSSA nasal colonization and consequent decolonization is equally debated *(27)*. Very recently, a multicenter, double-blind, prospective trial assessing *S. aureus* carriage at admission by PCR and subsequent nasal and total body decolonization during 5 days showed a significant reduction of hospital-acquired *S. aureus*. The authors concluded that the number of hospital-acquired surgical site *S. aureus* infections can be reduced by this strategy. However, results for SSI due to non–*S. aureus* were not reported *(69)*.

Vaccines provide an attractive conceptual alternative to preventing bacterial infections. A preliminary study with an antistaphylococcal vaccine in hemodialysis patients failed to reduce sepsis due to *S. aureus* in the first year following vaccination (relative risk reduction: 26%; $p = .23$) *(70)*, but further research is necessary to explore this possibility.

Aggressive treatment of infection present elsewhere in the body is required before any implant replacement, and all patients need to be informed about this potential complication. Infections should be treated without any delay to allow surgery to be performed. Asymptomatic bacteriuria is probably no risk for subsequent implant infection *(26,71)*.

Many hospitals in resource-rich countries are equipped with relatively expensive vertical or horizontal laminar airflow systems in operating rooms that reduce the bacterial burden in the air *(72,73)*. However, in 2008, a retrospective analysis of the German national nosocomial infection surveillance system showed no benefit of ventilation with laminar airflow and suggested that it was even associated with a significantly higher risk for severe SSI after hip prosthesis *(74)*. Of note, this study has some flaws, such as a lack of data on individual antibiotic prophylaxis, obesity, normothermia, etc., and these findings need confirmation in large-scale studies *(75)*.

INFECTED ORTHOPEDIC PROSTHESES

Orthopedic surgery encompasses most implant-associated surgery. Joint replacement has become one of the most common prosthetic surgical procedures over the past decades because of its success in restoring function to disabled arthritic individuals (*76*,77). The overall number of prostheses is rising steadily due to the increasing number of replacements in an aging population. Thus, the number of arthroplasty infections will equally continue to increase, and it is projected that approximately four million hip and knee arthroplasties will be performed annually in the United States alone by the year 2030 *(78)*. Second to loosening, infection is the most common complication of arthroplasty surgery.

Presentation of Arthroplasty Infections

There is no standard definition of what constitutes an arthroplasty infection and thus, interpretation of the literature related to the treatment of these infections is difficult (77,*79*). Arthroplasty infection is obvious when multiple cultures from specimens surrounding the prosthesis yield identical microorganisms, when purulence and microorganism are detected surrounding the prosthesis, or when a sinus tract that communicates with the prosthetic device is present. To enhance specificity of diagnosis, five or six periprosthetic intraoperative samples should be obtained for aerobic and anaerobic culture (77,*80*). Submitting a smaller number of specimens leads to a decrease in sensitivity of the submitted cultures. When possible, withholding antimicrobial therapy for at least 2 weeks prior to collecting the specimens increases the yield of recovering a microorganism (77,*80*).

The absence of an obvious mechanical reason for a painful prosthesis in the first few years following implantation, a history of prior wound healing problems, or superficial or deep infection, should raise the suspicion of arthroplasty infection. The pattern of clinical presentation is determined largely by the nature of the infecting microorganism (i.e., the symptoms may be more prominent in *S. aureus* infections and less with coagulase-negative staphylococci). Constant joint pain suggests infection, whereas mechanical loosening commonly causes pain only with motion and weight bearing *(76)*.

Epidemiology of Arthroplasty Infections

Improved infection control practices and the standardization of antimicrobial prophylaxis have decreased the incidence of infection over the last 30 years *(76)*. Currently, the infection rate for hip and knee surgery is generally <1.5%, but it may be higher for other joints *(27)* (Table 65-1). Infections have been categorized by the postoperative period in which they occur *(81,82)*. Acute infection is defined as identified within 12 weeks of surgery (up to 40% of total infections). Subacute infection occurs within 2 years of operation (up to 45% of infections). In this setting, the patient usually develops articular pain after several months of symptom-free ambulation. Late infection (15% of infections) develops after 2 years of pain-free mobility and may be hematogenous in origin. However, this classification is artificial and flawed: for example, hematogenous infections can produce a fulminant presentation resembling early infection despite their late onset. Moreover, the absence of positive blood cultures does not exclude an occult bacteremia. In practice, blood cultures are not regularly obtained if patients do not have chills or fever, signs frequently absent in the elderly population undergoing joint replacement surgery *(26)*.

Prevention of Orthopedic Implant Infections

There is a wide range of risk factors for arthroplasty and other orthopedic implant infections, such as incorrect antibiotic prophylaxis (*47*,*48*,*50*,77), obesity, long operating times *(26)* revision arthroplasty *(83)*, or immunosuppression *(84)*. These are usually the same for every SSI, but arthroplasty-specific issues are also to be considered. Antibiotic-containing cement can be used both for prophylactic *(85)* and therapeutic indications (86,*87*). The choice of antibiotics is limited to those that are water soluble and thermostable as the polymerization of cement is an exothermic reaction that generates a substantial amount of heat (86). The most commonly used agents are tobramycin (e.g., 4.8 g of tobramycin per 40 g of cement), gentamicin, vancomycin (2 g per 40 g of cement), and cephalosporins to a lesser extent (86). Higher antibiotic doses substantially weaken the consistency of the cement. Implantation in sheep showed an antibiotic concentration in the bone cortex four times the minimal inhibitory concentration (MIC) 6 months after implantation. Human pharmacokinetics during total hip replacement showed concentrations 20 times the MIC in drainage fluids *(85)*, and local levels of antibiotics remained effective up to 4 months following surgery *(88)*. Many trials assess the use of antibiotic-loaded cements with systemic perioperative antibiotic prophylaxis. McQueen et al. *(89)* performed a prospective, randomized trial including 295 arthroplasties of the hip and knee. The cement group received 1.5 g of cefuroxime in 40 g of cement powder and the parenteral antibiotic group received 1.5 g of cefuroxime intravenously at the induction of anesthesia and two additional doses of 750 mg at 6 and 12 hours later. The observed frequency of deep surgical site infection was 0.7% in the cement group and 1.3% in the parenteral antibiotic group. Espehaug et al. *(90)* reviewed 10,905 primary cemented total hip replacements and concluded that systemic antibiotics combined with antibiotic-containing bone cement led to a lower number of infections. In another analysis of the same arthroplasty register, antibiotic-containing cement reduced infection frequency from 0.7% (with 24 hour intravenous prophylaxis) to 0.4% (24 hour intravenous treatment plus antibiotic-containing cement) *(91)*. The use of antibiotic-impregnated cement is usually only one of a series of determinant variables in clinical studies, and a lowering of the infection rate is often difficult to attribute to its use alone. It is also worth noting that tobramycin and gentamicin, the most widely used compounds, are not the ideal agents to prevent staphylococcal infections and may lead to local development of *S. aureus* SCVs *(9,10,76)*.

Antibiotic Prophylaxis before Dental Procedures The prevention of hematogenous infections in prosthetic joint infections with regard to dental procedures is not evidence-based (61) for several reasons: (a) the usual prosthetic joint infection pathogens are not of oral origin; (b) even if administered, systemic antibiotics do not completely suppress occult bacteremia occurring during dental intervention; (c) humans may have up to 12 daily episodes of occult bacteremia of dental origin. Routine antibiotic prophylaxis should be clearly distinguished from antibiotic treatment required in the case of established oral cavity infection (61). A computer simulation model *(92)* assessed the risks and efficacy of no prophylaxis, oral penicillin prophylaxis, and oral cephalexin prophylaxis among dental patients at risk for prosthetic joint infection. The analysis suggested a lower risk of infection than the risk of death-associated anaphylactic reaction to an antibiotic. Recently, a prospective cohort study conducted at the Mayo Clinic failed to show any protective effect of prophylactic antibiotics prior to dental procedures for subsequent hip or knee prostheses infections *(93)*.

In conclusion, we discourage the use of prophylactic antimicrobial agents before a dental intervention for patients with joint prostheses. Instead, patients with orthopedic prostheses should be carefully instructed about the risk of infection and carry this information with them at all times. However, any minor infections should be treated aggressively. Finally, a constant optimal oral and dental hygiene is more important in terms of prevention and should be routinely recommended (61).

INFECTIONS OF CARDIOVASCULAR SURGICAL IMPLANTS

Prosthetic Heart Valve Endocarditis

In a series assessing 5,671 recipients of prosthetic heart valves, 220 patients developed prosthetic valve endocarditis (PVE). Estimates of cumulative risks varied from 1.5% to 4.1% at 12 months and from 3.2% to 5.7% at 60 months *(94)*. Agnihotri et al. *(95)* reviewed risk factors in 2,433 patients who underwent valve replacement; endocarditis occurred in 3.7%. Both studies defined a higher risk period during the initial 12 months after surgery and a lower risk period thereafter. Although no difference has been reported between patients with mitral or aortic prostheses, a difference appears to emerge among mechanical valve recipients as compared with patients with bioprostheses. Calderwood et al. *(96)* found an enhanced risk for PVE among recipients

of multiple prostheses compared with recipients of a single valve. Ivert et al. *(97)* noted an increased risk of PVE with a longer cardiopulmonary bypass time.

Pathogenesis Specific to Prosthetic Valve Endocarditis: Early Versus Late Infection Early infection occurs within 12 months after surgery and most authors consider these as healthcare-associated and acquired during surgery. The bacteriology of late PVE suggests that these infections have been acquired outside the hospital. Incidental infections (e.g., urinary tract infections and furunculosis) and trauma to mucosal surfaces (e.g., genitourinary tract or pneumonia) may be identified as predisposing events for 50% of patients with late-onset PVE. The recovery of fastidious gram-negative bacilli (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*, so-called HACEK) months and often years after surgery suggests that late-onset PVE is primarily acquired through incidental nonnosocomial infection and bacteremia.

In the past, fungi have not only accounted for significant numbers of early cases, but were also associated with high fatality rates. *Candida* species are the most common fungi causing PVE. Patients with PVE caused by *Legionella* species, mycobacteria, and fungi other than *Candida* species commonly present with negative blood cultures when routine techniques are used. Similarly, for *Coxiella burnetii* (the etiologic agent for Q fever), *Bartonella, Brucella* species, or *Treponema whippelii*, blood cultures are usually negative.

Clinical Features of Prosthetic Valve Endocarditis With the exception of more frequent signs of valve dysfunction and myocardial invasion, the clinical features of PVE are similar to those of native valve endocarditis. Most patients present with new murmurs, congestive heart failure, and septic embolism, for example, cerebrovascular complications. A small proportion of patients present with acute fulminant disease with severe hypotension or septic shock associated with infection resulting from *S. aureus* or *S. pyogenes*.

Prevention Placebo-controlled trials demonstrated a significant reduction in SSI by antibiotic prophylaxis *(50)*. Based on a literature review, Kaiser *(50)* recommends cefazolin (1 g intravenously). For patients unable to tolerate beta-lactam antibiotics, vancomycin (1 g intravenously) is suggested. In hospitals with a high prevalence of MRSA or MRSE, general cardiac surgical prophylaxis with vancomycin is appealing, but has not shown to be superior to prophylaxis with a cephalosporin *(60)*.

Patients must also be protected against late-onset PVE. Existing problems likely to give rise to transient bacteremia in the future (e.g., existing dental and gingival disease) should be addressed before an elective valve replacement is performed. For dental interventions, the regimen in the guidelines of the American Heart Association should be followed whenever possible *(60)* as the presence of prosthetic valves is a recognized indication for antibiotic prophylaxis before this type of intervention (Table 65-3). Peroral amoxicillin is the preferred choice, because it is well absorbed in the gastrointestinal tract and provides high and sustained serum concentration, although a substantial part of the *Streptococcus viridans* group may be resistant to it *(98)*. For patients with (pseudo)allergy to penicillins, the use of oral cephalosporins, clindamycin, or macrolides is recommended, although again, a minority of oral streptococci might be resistant to clindamycin *(99)*. Cephalosporin use should be avoided for patients with a history of anaphylaxis to penicillins due to possible cross-reactions.

The official recommendations for an intrabuccal procedure partly apply to bronchoscopies for which prophylaxis might be warranted when involving incision of the mucosa *(60)*. For invasive procedures related to the urogenital or gastrointestinal tract, antibiotic prophylaxis can be applied, thereby covering enterococci that are practically the sole pathogens known to provoke endocarditis. Again, no published data demonstrate a conclusive link between the gastrointestinal or urogenital tract procedures and the development of endocarditis and, to our knowledge, there are no studies demonstrating that the administration of antibiotic prophylaxis really prevents endocarditis in these settings *(60)*.

Prosthetic cardiac valve sewing rings impregnated with antimicrobial agents showed promising results *in vitro* but were marketed without definitive outcome-based randomized studies in humans *(100)*.

Infections Associated with Pacemakers and Cardioverter-Defibrillators

The estimated number of functioning pacemakers worldwide was more than three million in 2006, and approximately 200,000 for cardioverter-defibrillators *(101)*. The risk for pacemaker and cardioverter-defibrillator infections with antibiotic prophylaxis upon insertion is low. According to a recent prospective randomized trial in Brazil, this risk is 0.63% compared to the placebo arm of 3.28% *(102)*. The incidence of age- and gender-standardized pacemaker infections is estimated as 550 cases/million pacemaker recipients per year *(103)* or 1.9 infections per 1,000 pacemaker years (104).

As for other implant infections, gram-positive pathogens (staphylococci, followed by streptococci and enterococci) predominate over *Klebsiella* and other species (*103*,104). Apart from a lack of antibiotic prophylaxis, known risk factors in multivariate analysis are postoperative hematoma *(102)*, advanced age, diabetes mellitus *(103)*, and bacteremia of remote origin (*101*,104). In a large retrospective, population-based cohort study among 1,524 patients with pacemakers or cardioverter devices, Uslan et al. (104) found 45% to 54% infections with remote bacteremia due to *S. aureus* versus 12% in case of remote gram-negative bacteremia. The stratified risk was higher for patients with defibrillators compared to those with pacemakers. Early bacteremia (defined as <1 year after insertion) is more likely to reflect subsequent pacemaker infection *(105)*. Endothelization of implanted leads could be a key factor in the prevention of late infection and is usually complete within 1 to 3 months of insertion *(101)*. Prompt treatment of remote infections, by analogy to the antibiotic prophylaxis of endocarditis before dental procedures *(60)*, and general issues regarding SSI are the cornerstones of prevention (see also Chapter 61).

Infections Associated with Left Ventricular Assist Devices

Cardiac transplantation is a potentially lifesaving intervention for terminal heart failure. Ventricular assist devices provide temporary support until myocardial recovery

TABLE 65-3

Antibiotic Prophylaxis for Patients with Mechanical Heart Valves before Dental Procedures

		Regimen: Single Dose 30–60 min Before Procedure	
Situation	***Agent***	***Adults***	***Children***
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral	Cephalexin[a,b]	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone[b]	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

These recommendations are valid also for cardioverter-defibrillator and ventricular-assist devices.
[a]Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
[b]Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.
IM, intramuscular; IV, intravenous.
(Reprinted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis. *Circulation* 2007;116:1736–1754. ©2007 American Heart Association, Inc, with permission.)

occurs or a donor heart becomes available. They reduce the risk of death and improve quality of life *(100)*. One part of the device is inside the patient's blood system and the other part is connected outside with a permanent highway for bacteria to colonize and ultimately infect through connecting drivelines. The incidence of infection is extremely high and ranges between 18% and 59% *(106–108)*, even if rates might be decreasing in recent years *(106)*. Infection generally enhances the mortality risk in this patient population to 33% *(109)* and is frequently more prevalent than other complications such as thromboembolism (30%), bleeding (30%), hemolysis (10%), neurologic events (25–30%), tamponade (25%), or right ventricular failure (20–30%) *(106,107)*. In general, driveline infection is the most common *(106)* and half of all infections include multiple sites. The risk for sepsis peaks generally between 20 and 30 days postoperatively. After 90 days, the incidence is around 5% *(110)*.

As for other implants, staphylococci predominate among infecting microorganisms, but gram-negative pathogens (e.g., *Pseudomonas* sp.) or fungi are also encountered, especially in the case of selection by previous antibiotic treatment. Fungemia has the highest hazard ratio for death, followed by gram-negative and then gram-positive bacteremia *(106)*.

Prevention of Infections Associated with Ventricular Assist Devices The prevention of ventricular assist device infections is similar to other SSI in general. There are no specific randomized trials in this particular field. Numerous strategies have been used *(111)*, but their efficacy is difficult to assess in the absence of data resulting from clinical trials *(108)*. Tunneling of the driveline contralateral to the pump pocket is recommended to increase the length of the subcutaneous course, thus potentially delaying ascension of the pathogens to the pump pocket *(108,112)*. The exit sites of the driveline should be kept mechanically stable and dressing changes should be performed on a daily basis. Indications for antibiotic prophylaxis are the same as those recommended for patients with an artificial heart valve *(60,108)*. A prolonged antibiotic prophylaxis or a preemptive antibiotic treatment upon positive swab cultures of driveline exit sites is not evidence-based and should be avoided.

Infections Associated with Vascular Grafts

Infections of vascular prostheses are associated with substantial morbidity and mortality *(113)*. The incidence of graft infections ranges from <1% to more than 6%; however, it varies markedly depending on the anatomic site of the prosthesis. The highest incidence has been observed in grafts crossing the inguinal area.

Pathogenesis and Risk Factors As for many other implant-related infections, most arterial prosthetic infections are thought to arise from contamination at the time of implantation. Only a few late-onset infections appear to be due to hematogenous spread from other body sites. The high incidence of graft infections in the groin may be due to the superficial location of the graft that favors cutaneous contamination and SSI occurring at this site, which may secondarily contaminate the prosthesis. Independent risk factors for infection include surgery on lower extremities, delayed surgery, diabetes mellitus, past history of vascular surgery, and short-course antimicrobial prophylaxis *(114)*.

Microbial Etiology Staphylococci are the most common microorganisms isolated from vascular prosthetic infections *(113)* followed by *E. coli* (13.4%), *Streptococcus* species (8.5%), *Pseudomonas* species (6.1%), *Klebsiella* species (5.4%), *Proteus* species (4.8%), and coagulase-negative staphylococci (3.6%). As for other implants, the prevalence of MRSA infections in these patients is increasing. Infection of aortic grafts with MRSA appears to be fatal and lower graft infection is associated with high limb loss *(115)*.

Prevention Infection prevention is no different from general SSI prevention. Potential sites of bacteremic seeding (urinary tract infection, dental abscess, etc.) and local infections of ischemic extremities should be eradicated before placement of a bypass graft. Because of their vascular location, these prostheses are more exposed to bacteremia. Paradoxically, the incidence of graft infections induced by bacteremia is quite low. Data are inadequate to determine the necessity for antimicrobial prophylaxis in patients with arterial prostheses undergoing dental and surgical procedures. Prevention is, thus, analogous to the prophylaxis recommended to prevent infective endocarditis in patients with prosthetic heart valves, particularly during the first postoperative months when experimental data indicate that the graft is most susceptible to bacteremic seeding. If prophylaxis is chosen, the regimens suggested by the American Heart Association are applicable *(60)*.

INFECTIONS OF CENTRAL NERVOUS SYSTEM SHUNTS

Incidence and Risk Factors

Neurosurgeons increasingly use prosthetic devices within the central nervous system for a variety of clinical indications, such as hydrocephalus or continuous monitoring of intracranial pressure in posttraumatic patients. Shunt infection is a serious complication causing persisting intellectual, cognitive, and neurological deficits *(116)* and may even be life threatening. The costs of managing these complications have been estimated as high as US$ 30,000 per patient *(117)*. The incidence of infection varies greatly (between 0.3% and 13%) *(116)* depending on the nature of the intracerebral device. Risk factors are elderly patients *(102,103)*, infants and premature births *(116–120)*, immunosuppression, intracranial pressure of ≥ 20 mm Hg, impaired consciousness, ventricular catheterization for ≥5 days, duration of shunt use, duration of surgery, hematomas *(119)*, and overcrowding of operating rooms *(116)*. However, the highest risk by multivariate analysis is associated with the presence of a former shunt infection (odds ratio, 5.0: 95% confidence interval, 1.6–16) *(116)*. As a general conclusion, reported risk factors for infections are no different from those for other implant-related infections.

Microbial Etiology and Clinical Presentation

Leading pathogens of shunt infections are staphylococci and MRSE (or coagulase-negative staphylococci in general) with *Propionibacterium* species reported to be more prevalent than *S. aureus (116,120)*. The most common presentation of shunt infection is nonspecific, consisting of fever, nausea, altered sensorium, vomiting, malaise, or signs of increased intracranial pressure. The latter suggests malfunction. In most cases, these symptoms appear within a few weeks to months after insertion. Obvious SSI may be evident in the immediate postoperative period. Classic signs of meningeal irritation are present in roughly one-third of shunt infections. Inflammatory exudates may lead to inoculation of cerebrospinal fluid, resulting in the formation of a peritoneal cyst. These cysts are often palpable in infants and can be visualized by radiological imaging. At times, patients infected with microorganisms representative of normal skin flora, such as coagulase-negative staphylococci and *Propionibacterium* species, may pursue an extremely indolent clinical course and exhibit only intermittent low-grade fever and malaise with little or no change in spinal fluid cell count, glucose, or protein.

Prevention

As for other types of infections associated with foreign materials, there has been a marked decrease in the incidence of infections associated with the insertion of indwelling central nervous system prosthetic devices, partly because of the use of antibiotic prophylaxis and improvements in technique and materials. In 2005, Choksey and Malik reported only one shunt infection among a total of 176 procedures performed in 126 patients with hydrocephalus due to strictly adhering to the following surgical principles: asepsis; appropriate and timely antimicrobial prophylaxis; and avoidance of hematomas *(121)*. To our knowledge, no one has yet reported a better result with shunt-related surgery over a prolonged period *(27)*.

Several placebo-controlled studies justify the use of perioperative antibiotic prophylaxis during implantation. Langley et al. (122) conducted a meta-analysis to determine the value of antimicrobial prophylaxis in shunt placement. Twelve randomized controlled studies were selected representing 1,359 patients. Combining the results of the 12 trials showed that prophylaxis was associated with a significant reduction in subsequent infection (Mantel-Haenszel weighted risk ratio = 0.52), corresponding to a 48% risk reduction. This was confirmed in a Cochrane meta-analysis involving 17 trials with a total of 2,134 participants *(123)*. Again, the use of systemic antibiotic prophylaxis for the first 24 hour postoperatively decreased shunt infections by half, although the benefit beyond 24 hour remained uncertain.

An unresolved issue is the ideal dosing of antibiotics for the prevention of intracranial or ventricular infections.

While enhanced doses for the treatment of these infections are commonly accepted among infectious disease physicians, antibiotics are administered often at the same dose as for example, arthroplasty surgery. At least in cases of hydrocephalus, shunted patients might require higher than usual doses of vancomycin *(124)*.

Continuous prophylactic antibiotics are widely used for patients with external ventricular drains (EVDs) despite the lack of evidence. Alleyne et al. *(125)* reported the results of a retrospective cohort study in two groups of patients who received cefuroxime (1.5 g/8 hour) for the entire duration of EVD, that is, an average of 9.2 days compared with cefuroxime given periprocedural only (maximum three doses). The overall rate of ventriculitis (3.9%) was similar in the two groups. Because long-term use of antimicrobials may select for resistant microorganisms (126), we recommend periprocedural antibiotics only.

The use of ventricular catheters impregnated with antimicrobial agents failed to show any benefit in terms of intra- or extracranial infections in a recent prospective randomized trial from Hong Kong *(127)*. This lack of benefit was confirmed in a retrospective Cochrane meta-analysis *(123)* and in a prospective observational study *(116)*.

INFECTION IN BREAST IMPLANTS

Mammary implants are used in breast augmentation and reconstruction after mastectomy. Approximately 50,000 procedures are performed annually in the United States alone *(128)*. They may be placed above the muscle and under the gland (subglandular) or under the muscle (submuscular) (129) and consist often of silicone gel contained within a silicone rubber envelope (Fig. 65-2).

Incidence

In a worldwide survey of complications among 10,941 patients undergoing breast augmentation, infections were observed in 2.5% of all procedures (incidence, 1.7% and 0.8% for acute and late infections, respectively) *(130)*. Other large epidemiologic retrospective cohort studies with long-term follow-up confirmed similar incidences ranging from 1.7% to 2.5% (129,*131*,*132*). The incidence of postsurgical implant infections correlates with the complexity of the surgical condition. Acute postsurgical infection has been encountered in 0% to 4% of cases *(130,133)*. Most infections occur during the first month after implantation, but neither the type of implant nor the surgical procedure appear to have a significant influence on the timing of infection *(133)*. Late infection usually results from a secondary bacteremia, infection at another site, or an invasive procedure *(130,133)*.

Risk Factors

Risk factors for breast implant-associated infection have not been carefully assessed in prospective studies and almost all studies are retrospective. The risk factors for breast implant infections are similar to other implants or SSI in general. Olsen et al. *(134)* retrospectively assessed 325 patients and revealed the following variables as independent risk factors in multivariate analysis: suboptimal antibiotic prophylaxis, blood transfusion, smoking, a high American Society of Anesthesiologists score, underlying cancer, and high glycemia during surgery. In particular, breast reconstruction after mastectomy and radiotherapy for cancer is associated with a higher risk for infection and other complications after surgery (129,*134*). Other possible predisposing factors include skin-penetrating accidents, nipple piercing *(135)*, pyoderma gangrenosum, preceding infectious processes, breast trauma, breast skin irritation *(133)*, and reconstruction. Infection was less likely in a two-stage procedure in another series *(136)*. One hypothesis is that there is no time for host defense mechanisms to cleanse the tissue of bacteria before the insertion of the prosthesis in immediate reconstruction. With delayed reconstruction, there has been time for bacteria to have been removed from the tissue.

Microbiology of the Breast

The human breast is not a sterile anatomic structure. Multiple breast ducts provide a passage from the skin surface to deep within the breast tissue. Coagulase-negative staphylococci were isolated from 53% of specimens in

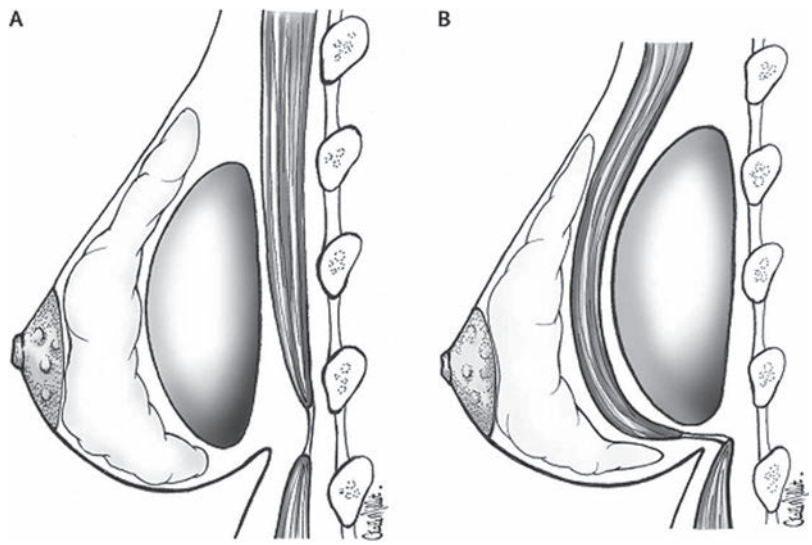

FIGURE 65-2 Anatomical position of breast implants. **A**: Breast prosthesis in the subglandular position. **B**: Breast prosthesis in the submuscular position. (Redrawn from the Pittet B, Montandon D, Pittet D. Infection in breast implants. *Lancet Infect Dis* 2005;5:94–106©, with permission from Elsevier.)

TABLE 65-4

Microbiology of Infections Associated with Breast Implants

Organism	*n*	*%*
Breast SSI (n = 43)[a]		
Methicillin-sensitive *S. aureus* (± other organisms)	18	41.9
Methicillin-resistant *S. aureus* (± other organisms)	7	16.3
Coagulase-negative *S.* only	3	7.0
Streptococcus viridans group (+ other organisms)	2	4.7
Pseudomonas aeruginosa (± other organisms)	8	18.6
Proteus mirabilis	1	2.3
Serratia marcescens	2	4.7
Mixed flora	7	16.3
No growth[b]	4	9.3
Donor-site SSI (n = 8)[c]		
Methicillin-resistant *S. aureus* (± other organisms)	1	
Coagulase-negative *S.* only	1	
Pseudomonas aeruginosa (± other organisms)	3	
Proteus mirabilis	1	
Mixed flora	4	
No growth	1	

[a]Cultures not performed for 14 patients with breast SSI. Percentages calculated based on number cultured ($n = 43$).
[b]Two of the four cultures that had no growth had organisms while on Gram stain.
[c]Cultures not performed for two patients with donor-site SSI.
SSI, surgical site infection.
(Reprinted from the Olsen MA, Lefta M, Dietz JR, et al. Risk factors for surgical site infection after major breast operation. *J Am Coll Surg* 2008;207:326–334, with permission from Elsevier.)

women undergoing breast surgery *(137)*. Microorganisms were lactobacilli (9%), *Bacillus* species (5%), and alpha-hemolytic streptococci (3%). Anaerobic microorganisms were mostly *P. acnes*. Cultures of material milked from the nipples before breast augmentation grows mainly *S. epidermidis* (67%), but also *B. subtilis* (24%) and diphtheroids (see also Table 65-4.)

Capsular Contracture and Locally Instilled Antibiotic Prophylaxis

Capsular contracture is the most common and frustrating complication in women who have undergone breast implantation (*128*,129). Contracture of the scar around a soft deformable implant will lead to a hard spherical mass; this type of envelope is referred to as a capsule. Factors thought to be associated with capsular contracture include infection *(128)*, hematoma, silicone bleed, and individual predisposition for hypertrophic scarring. Implant filler material (silicone, saline), placement (submuscular, subglandular, subcutaneous), and surface texture might also affect the risk of capsular contracture *(138)*.

Cultures performed at the time of surgical capsulotomy are often positive, predominantly growing *S. epidermidis* and *P. acnes (128,139)*. Based on this finding, Burckhardt et al. *(139)* used local antibiotics leading to a decreased incidence of capsular contracture. The practice of breast pocket irrigation with various antimicrobial solutions and povidone-iodine is supported by some data and extensive clinical practice among most plastic surgeons (129,*140*,*141*). However, in 2000, the U.S. Food and Drug Administration prohibited the use of povidone-iodine for breast implant surgery (129) as it may be associated with deflation of saline-filled prostheses in a small proportion of patients. Similarly, minocycline and rifampin-impregnated, saline-filled silicone implants were less likely to be colonized and cause *S. aureus* infection than unimpregnated implants when inserted subcutaneously in a rabbit model *(142)*. Further studies are required on the clinical effectiveness and the potential for resistance development before widespread use can be recommended.

Systemic Prophylactic Antibiotics

The need for prophylaxis in breast surgery is controversial. Although most experts do not recommend prophylaxis routinely for breast procedures, they do recommend prophylaxis in cases of implant placement. Systemic antibiotic prophylaxis at the time of surgery was associated with a significant reduction of the infection rate (0.42% vs. 0.87%) in a large study of 39,455 patients undergoing breast augmentation (129). Some authors advocate antibiotic prophylaxis prior to any dental procedure in patients with breast implants, but there is no scientific evidence to support this recommendation.

CONCLUSIONS

The increasing need for prosthetic materials and indwelling medical devices has markedly improved both materials used and surgical implantation techniques. Overall, three major strategies have been developed to prevent infectious complications: a sterile environment; better operating procedures; and the appropriate use of prophylactic antibacterial agents. Only the latter lends itself to a well-controlled, randomized, double-blind clinical trial. Thus, many improvements in the setting of medical device complications seem to reflect improved medical or surgical practice without proof based on randomized studies. Sterile environment and the different quality of surgical procedures can hardly be randomized.

So far, systemic antibiotic prophylaxis has proven efficacy for prosthetic heart valve replacement, and orthopedic and vascular prostheses. To extrapolate from these results to other procedures, several factors have to be taken into account. These encompass timing of administration, dosage, pharmacokinetics and tissue penetration, and type of infecting microorganism. With these simple concepts, new clinical and experimental studies can be conceived regarding prosthetic infections.

Changes in surface characteristics, such as surface charge and adhesive properties for host proteins and/or bacteria, may be another means to decrease infection rates. Incorporation of antibacterial substances, such as silver,

must be explored further. Clearly, this will continue to be an area for high priority not only for the field of infectious diseases and infection control, but also for biotechnology.

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CHAPTER 66

Healthcare-Associated Infections Related to Respiratory Therapy

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The most representative data on the incidence of healthcare-associated infections have been provided by the Centers for Disease Control and Prevention (CDC) via the National Healthcare Safety Network (NHSN, formerly NNIS) system. According to the NHSN system data, healthcare-associated pneumonia (HAP) is the third leading cause of device-related healthcare-associated infection (HAI) and second leading cause of HAI overall, accounting for approximately 16% of all HAIs and 24% to 27% of all infections acquired in medical intensive care and coronary care units (1,*2–4*,5). The frequency (episodes per 100 hospitalizations) of HAP is 0.2 to 0.94, the lower rates being reported from small private hospitals and the higher rates from large academic hospitals *(2,6)*. The pooled mean rate of ventilator-related HAP (per 1,000 days ventilated) in intensive care units (ICU) range from 1.3 (medical pediatric ICU) to 5.5 (burn ICU) (7). The frequency of HAP is reportedly higher in selected patient populations, ranging from 0.66 to 1.47 in the elderly (*8*,9), 1.7 to 7.2 among newborn ICU patients *(6,10)*, and 2.0 to 21.6 among adult ICU residents (*11–14,*15,*16*). A point prevalence study of ICUs in 17 Western European countries revealed that 20.6% of all patients had an ICU-acquired infection; pneumonia accounted for 46.9% and lower respiratory tract infections other than pneumonia accounted for 17.8% of all ICU-acquired infections *(17)*. A more recent point prevalence study conducted in May 2007 included 14,414 patients in 1,265 ICUs from 75 countries revealed that 51% of patients were infected and that among infected patients 64% had a respiratory tract infection (18).

More than 50% of the antibiotics prescribed in ICUs are for the treatment of HAP, and over 90% of HAPs in ICUs are ventilator-associated pneumonias (VAPs) (5). HAP increases hospital stay by an average of 7 to 9 days per patient and has been reported to produce an excess cost of more than $40,000 per patient (5). The crude mortality rate for HAP may be as high as 30% to 70%, and the HAP-related attributable mortality is estimated to range from 33% to 50% (5,*19*). It is often difficult to define the exact incidence of HAP and VAP, because there are frequently overlaps with other lower respiratory tract infections, such as tracheobronchitis, especially in mechanically ventilated patients (5).

Multiple risk factors for HAP have been identified by univariate analysis: abdominal or thoracic surgery *(14,20,21)*, advanced age *(14,21)*, altered mental status (*8*,9,15,*21*), prior episodes of large-volume aspiration (*8*,9,*12*,*20*,*22*), H_2 blocker therapy (9,*22*,*23*), steroid therapy *(22)*, ICU residence (9,*20*), nasogastric intubation (*8*,9,*14*,*20*), previous antibiotic use (9,*20*,*24*,*25*), rapidly or ultimately fatal disease *(12,14)*, trauma (15,*16*), neurologic disease *(16)*, underlying chronic lung disease *(20)*, and intubation with mechanical ventilation (9,*12*,15,*20*). The risk factors for ICU-acquired pneumonia have been reviewed *(26,27)*. Most (9,*12*,*20*,*22*,*28*) but not all *(14)* multivariable analyses have shown that mechanical ventilation is a major risk factor for HAP, with odds ratios ranging from 1.3 to 12.1 (for positive studies). The exact incidence of pneumonia is considered 6- to 20-fold greater than in nonventilated patients (5). Few investigators have included variables related to type of respiratory care procedures in their multivariable risk factor analyses. Joshi et al. *(14)* found a 2.95-fold increased risk of HAP associated with recent bronchoscopy in ICU patients. Reintubations are additional risk factors for VAP (5).

This chapter focuses on healthcare-associated infections associated with respiratory therapy. The epidemiology of HAP in general has been reviewed by others (see Chapter 22). Several reviews have focused on the prevention of HAP, especially VAP (5,29,*30*,31,*32*).

PATHOGENESIS OF HEALTHCARE-ASSOCIATED PNEUMONIA AND ROLE OF RESPIRATORY CARE EQUIPMENT

HAP may occur by four major routes: (a) aspiration of oropharyngeal flora; (b) inhalation of infectious aerosols; (c) contiguous spread adjacent site; and (d) hematogenous spread from a distant focus of infection. Colonization of the oropharynx and gastrointestinal tract by pathogenic gram-positive and gram-negative bacilli, followed by aspiration in the setting of impaired host defenses, is the major cause of HAP. Exposure to invasive respiratory devices and equipment is important in the pathogenesis of HAP and VAP (5).

Contaminated respiratory care equipment may lead to HAP by two routes. First, respiratory care equipment may serve as a reservoir for microorganisms, especially

gram-negative bacilli. Fluid-containing devices such as nebulizers and humidifiers may become heavily contaminated by bacteria capable of multiplying in water. Pathogens may then be spread to the patient by hospital personnel or by aerosolization into room air. Second, contaminated equipment may lead to direct airway inoculation of microorganisms if it is directly linked to a ventilatory system or if contaminated medications are instilled by aerosolization. The role of inhalation and respiratory care equipment in HAP has been reviewed several times in the era of medical/surgical intensive care (15,*26*,*27*,29,*32–35*,36,*37–44*,45–*47*). Multiple reports exist in the scientific literature regarding outbreaks associated with the use of equipment introduced into the respiratory system, ranging from tongue depressors to bronchoscopes *(48)*.

Fluid-containing respiratory devices are the major environment-associated reservoirs for HAP; however, most or all phases of respiratory support have been linked to healthcare-associated respiratory infections or suggested as potential environmental reservoirs. These include mechanical ventilation bags (MVBs), ventilators, aerosolized medications, bronchoscopy, suction catheters, suction regulators devices, and respiratory support personnel. Evidence suggests that alterations in infection control practices during the 1960s decreased the number of cases of HAP from environmental sources *(49)*.

INFECTIONS ASSOCIATED WITH INTUBATION AND MECHANICAL VENTILATION

Pathophysiology of Infection

Intubation for respiratory support increases the patient's risk of HAP. Nasotracheal or orotracheal intubation predisposes patients to bacterial colonization and HAP by the following pathophysiologic alterations (5,*50–52*): (a) it causes sinusitis and trauma to the nasopharynx (nasotracheal tube); (b) it impairs swallowing of secretions; (c) it acts as a reservoir for bacterial proliferation; (d) it increases bacterial adherence and colonization of airways; (e) it requires the presence of a foreign body that traumatizes the oropharyngeal epithelium; (f) it causes ischemia secondary to cuff pressure; (g) it impairs ciliary clearance and cough; (h) it can cause leakage of secretions around the cuff; and (i) it requires suctioning to remove secretions. Mechanical ventilation also exposes the patient to fluid-filled devices, such as in-line nebulizers and humidifiers, which are used to provide humidification or medications.

Incidence of Respiratory Infections

Multiple studies have demonstrated that mechanical ventilation is a major predisposing factor for HAP (5,*22*,*26*,*28*,*53–61*). Direct comparisons of the various studies require caution because of important differences in study design, including patient population, period of study, criteria for entry into the study, and diagnostic criteria for pneumonia. However, the following generalizations can be made: between 15% and 40% of patients who undergo mechanical ventilation for more than 48 hours develop HAP, and the case-fatality rate is exceedingly high.

INFECTIONS ASSOCIATED WITH COMPONENTS OF MECHANICAL VENTILATION

Ventilators

The internal machinery of mechanical ventilators is not considered an important source of bacterial contamination of inhaled air *(62)*. In the 1960s, the use of a high-efficiency bacterial filter interposed between the machinery and the main breathing circuit was advocated to eliminate contaminants from the driving gas and to prevent retrograde contamination of the machine by patients *(63)*. The filters were shown, however, to alter the function of the ventilators by impeding high gas flows. Later studies have not shown that a filter placed between the inspiratory phase circuit and the patient prevents infection *(64,65)*.

Placement of a filter or condensate trap on the expiratory limb of the mechanical-ventilator circuit may help prevent cross-contamination of the ventilated patient's immediate environment *(66)*, but the importance of such filters in preventing HAP has not been demonstrated (29,*67*).

Periodic sterilization or high-level disinfection of the internal ventilator machinery is unnecessary; however, ventilator circuits should be sterilized or subjected to high-level disinfection between patient uses (68). Failure to properly clean and sterilize ventilator circuits between patients has led to outbreaks with *Pseudomonas aeruginosa (69)*, *Bacillus cereus (70)*, and *Acinetobacter* species *(71)*. The failure to properly disinfect ventilator temperature probes between patients has led to outbreaks of *Burkholderia cepacia* pneumonia *(72)*.

Nebulizer Equipment

Nebulizers have been a significant source of HAP. Nebulizers with large-volume (>500 mL) reservoirs, including those used in intermittent positive-pressure breathing (IPPB) machines and ultrasonic or spinning-disk room-air "humidifiers," pose the greatest risk of pneumonia to patients, probably because of the total amount of aerosol they generate (73). Other types of nebulizers include small-volume nebulizers for administration of medications, most commonly bronchodilators. Such small-volume nebulizers may be placed in the inspiratory circuit of mechanical ventilators or handheld.

Nebulizers used in association with mechanical ventilators may be inserted into the inspiratory phase tubing of the mechanical ventilator circuit for the administration of medications or used to provide humidification of air. In-line medication nebulizers may become contaminated by reflux of tubing condensate *(74)* or use of contaminated solutions *(75)*. Contaminated nebulizers may then lead to HAP via direct instillation of pathogenic bacteria into the lung *(76,77)*. Botman and de Krieger *(78)* demonstrated that small-volume nebulizers frequently become colonized with pathogenic bacteria, and that nebulizers are associated with an increased risk of respiratory colonization of patients. The risk of pneumonia is related to the production of contaminated bacterial droplets <4 μm in diameter *(50)*. Particles larger than 10 μm are trapped in the nasopharynx or trachea, whereas particles smaller

than 4 μm may be delivered into the patient's terminal bronchioles and alveoli. Craven et al. *(50)* emphasized that the risk of pneumonia is related to the size and number of the aerosol particles, the concentration of pathogenic bacteria, and whether aerosol particles are delivered directly into the endotracheal tube or into the oropharynx. The temperature of the reservoir fluid is also critically important, because most healthcare-associated pathogens cannot survive for long periods in distilled water or saline at temperatures above 50°C. Decreases in the frequency of nebulizer contamination were shown to relate to decreases in the occurrence of necrotizing pneumonia *(49)*.

In addition to the previously mentioned mechanisms of contamination, in-line, fine-particle nebulizers used to humidify air mixed with oxygen from a wall oxygen outlet may become contaminated when ambient air contains bacteria *(79)*.

Contaminated nebulizers have been responsible for several outbreaks. Four cases of *Legionella pneumophila* pneumonia resulted when contaminated tap water was used in jet nebulizers to humidify oxygen administered by face mask *(80)*. Failure to disinfect nebulizers between patients led to an outbreak of *Serratia marcescens* pneumonia *(75)*. Use of contaminated ultrasonic nebulizers in IPPB machines has led to infections with *S. marcescens (81,82)* and *P. aeruginosa (83)*. Use of contaminated inhaled budesonide with sulbutamol through nebulizers led to seven cases of *B. cepacia* bacteremia in a pediatric ICU *(77)*. In 2005, six pediatric cases of *Ralstonia* spp. infections were related to the use of a particular brand of oxygen delivery device *(84)*.

Mechanical Ventilation with Humidification

Humidification of inspiratory air is an important aspect of ventilator management. Humidification may be achieved by bubble-through humidifiers, which produce minimal aerosols, or wick humidifiers, which produce no aerosols *(85)*. Bubble-through humidifiers are usually heated to temperatures that reduce or eliminate bacterial pathogens *(86)*. For these reasons, current humidification practices are not believed to pose a significant risk of pneumonia to ventilated patients (73). However, one study that purposely used contaminated water found that although colony counts in bubble-through humidifiers decreased with time, viable microorganisms remained throughout the study *(86)*. Further, when bubble-through humidifiers were heated, both condensate and effluent gas rapidly became contaminated. Additional studies are required of actual ventilators in use to assess the importance of humidification as a risk factor for HAP *(87)*. It is currently recommended that sterile water be used to fill these humidifiers (29) because tap or distilled water may harbor relatively heat-resistant pathogens *(80,85,88–91)*.

A potential risk factor for pneumonia in patients using mechanical ventilation with humidification is the condensate that forms in the inspiratory-phase tubing of the ventilator circuit. This condensate forms as a result of the difference in the temperatures of the inspiratory-phase gas and ambient air. Condensate formation is increased if the tubing is unheated compared to the use of heated bubble-through humidifiers. Both the ventilator tubing and condensate rapidly become colonized by gram-negative and gram-positive bacteria during use. The colonizing pathogens originate from the patient, and thus, the highest levels of bacteria are closest to the endotracheal tube, with lower levels near the humidifier reservoir. Craven et al. *(88)* demonstrated that 33% of inspiratory circuits became colonized by oropharyngeal flora from the patient within 2 hours of use, and 80% were colonized within 24 hours of use. They hypothesized that spillage of this contaminated fluid into the patient's respiratory tract, as might occur during procedures such as patient suctioning or transportation for clinical studies, might lead to HAP. Contaminated condensate can also serve as a reservoir for respiratory pathogens, which can be transmitted person to person via the hands of medical personnel if staff members fail to wash their hands following ventilator manipulation.

The frequency of ventilator tubing changes and its relationship to the incidence of HAP has been investigated by several research groups (Table 66-1). In a landmark study, Craven et al. *(99)* reported that ventilator tubing could be safely changed every 48 hours as opposed to the then-recommended 24-hour changes. After many years and multiple investigations (Table 66-1), current data indicate that breathing circuits, including all its variable components, should not be changed on a routine basis, and individual components should be replaced only when they malfunction or become visibly contaminated (68,*100*).

Filling the in-line humidifier with contaminated water has led to an outbreak of *Pseudomonas fluorescens* infections *(101)*. The reuse of inadequately disinfected ventilator circuits has led to outbreaks with *Acinetobacter* species *(71,102)* and *Pseudomonas* species *(103)*. Reusable ventilator tubing should be thoroughly cleaned and dried after patient use and then sterilized with ethylene oxide gas, subjected to high-level disinfection with a Food and Drug Administration (FDA)-cleared chemical sterilant, or pasteurized (see Chapters 80 and 81). Only sterile water should be used in humidifiers and nebulizers.

Condensate formation can be eliminated by the use of a heat-moisture exchanger (HME) or a hygroscopic condenser humidifier (also known as an "artificial nose") *(104,105)*. The HME eliminates the need for a humidifier by recycling heat and moisture exhaled by the patient. Because a humidifier is not used, no condensate forms in the inspiratory tubing of the ventilator circuit. Thus, bacterial colonization of the tubing is avoided. Some authorities still advocate to routinely change the HME every 5 to 7 days or as clinically indicated *(100)*. Potential problems with HMEs include increased dead space and resistance to breathing, and leakage around the endotracheal tube with drying of sputum and blockage of the tracheobronchial tree *(106)*. Several investigators have reported on the use of an HME *(107–118)*. Prospective studies demonstrate that changing HMEs every 48 to 72 hours rather than every 24 hours did not affect their efficacy or the incidence of HAP *(115,119–121)*. In addition, randomized studies found no difference in the infection rates of patients assigned to a hydrophobic HME or a hygroscopic HME *(113,118,119,122,123)*. Multiple randomized trials have compared the rates of VAP in patients in whom an in-line HME was used compared to patients managed with a conventional heated-wire humidifier

TABLE 66-1

Rates of Ventilator-Associated Pneumonia and Frequency for Change of Tubing Circuits for Mechanical Ventilation

Reference	*Year*	*Study Design*	*Humidifier*	*Circuit*	*Interval for Circuit Changes (No. of Days)*	*No. of Patients with Pneumonia*	*% of Patients with Pneumonia*	*Incidence (VAP/1,000 Ventilator Days)*	*p Value*
Dreyfuss et al. *(59)*	1991	Randomized	Wick/ Bubble	Standard	2	35	31	24.6	NS
					None	28	29	28.6	
Boher et al. *(92)*	1992	Before/After	NA	NA	2	1,172	NA	18	NA
					7	518	NA	13	
Mermel et al. *(93)*	1994	Randomized	NA	Standard Heated Wire	2–3	60	7	25	NS
					7	56	2	7	
Hess et al. *(94)*	1995	Before/After	Bubble	Standard	2	1,708	5.5	9.6	NA
					7	1,715	4.6	8.6	
Kollef et al. *(95)*	1995	Randomized	Wick	Standard	7	153	29	17.4	NS
					None	147	24	16.4	
Long et al. *(96)*	1996	Randomized	Wick	Heated Wire	2–3	213	13	9	NS
					7	234	11	10	
Kotilainen et al. *(97)*	1997	Before/After	NA	Heated Wire	3	88	9.1	12.9	NS
					7	146	6.2	7.4	
Fink et al. *(98)*	1998	Before/After	Wick	Standard	2	343	NA	11.3	0.0004[a]
					7	137	NA	3.2	
				Heated Wire	30	157	NA	6.6	

NA, not available; NS not statistically significant.
[a]2-day interval compared with 7-day and 30-day intervals (7-day vs. 30-day difference not significant $p = .27$).

(109,112–114,116,117,124). The rates of pneumonia were lower with use of the HME (range of relative risks (RRs), 0.35–0.85); one study reached statistical significance *(117)*. Use of the HME was speculated to be cost-effective and reduces the rate of late-onset, ventilator-related HAP *(117,125)*, but recent guidelines state that despite the fact that HME reduces colonization, the role of HME in VAP prevention is not clear and remains questionable (5,*100*,*126*).

Manual Ventilation Bags

Manual ventilation bags are used for urgent ventilation, during routine suctioning of the intubated patient, during transport of the intubated patient, and to ventilate patients during chest physiotherapy. The exterior surface and connecting port of manual ventilation bags are routinely contaminated during use. Secretions left in the bag may be aerosolized and/or sprayed into the lower respiratory tract of patients. Further, the exterior surface may serve as a reservoir for pathogens transmitted person to person on the hands of healthcare personnel. Contaminated manual ventilation bags have been linked to epidemics of HAP and VAP related to specific microorganisms *(102,127–129)*. Thompson et al. *(130)* demonstrated that, in patients with gram-negative bacteria in their sputum, 71% of the manual ventilation bag valves and 29% of the air samples taken from the exhalation valve assemblies were culture positive for the same microorganisms. Weber et al. *(131)* cultured the interior and exterior surfaces of manual ventilation bags used on 14 ICU patients whose respiratory tracts were colonized or infected. Overall, 51 simultaneous cultures of manual ventilation bag components resulted in the following findings: (a) the manual ventilation bag exterior surface was culture positive 100% of the time; (b) the manual ventilation bag exhalation port was culture positive 96% of the time; and (c) the manual ventilation bag interior surfaces were culture positive only 12% of the time. In three instances (6%), the manual ventilation bag port became colonized with a pathogen prior to its appearance in the patient's respiratory tract, suggesting that the manual ventilation bag was the source for the colonizing pathogen.

Contaminated manual ventilation bags may serve as a source for healthcare-associated infection by colonizing the hands of medical personnel who then may cross-transmit such pathogens directly to other patients or to respiratory or other medical equipment, and by introducing pathogens into patients. The following guidelines have been suggested

for the prevention of healthcare-associated respiratory tract infections associated with manual ventilation bags *(131)*. First, all medical personnel should wash their hands before and immediately after any contact with patients or potentially contaminated equipment such as manual ventilation bags. Second, manual ventilation bags should be sterilized or subjected to high-level disinfection between patients (68). Third, the manual ventilation bag should be cleaned of visible secretions daily and then disinfected with alcohol (68). Both the exterior surface and the manual ventilation bag exhalation valve should be disinfected. The interior surface does not need to be disinfected during routine use. When reprocessed in an appropriate area of the ICU or in central processing, if tenacious sputum cannot be removed from the exhalation port, the port should be disassembled, cleaned, and sterilized or subjected to high-level disinfection.

Prevention of Healthcare-Associated Pneumonia

Several authors have summarized measures that may reduce the incidence of VAP (5,29,*30*,31,45,73,*100*,*132–135*,136,*137–139*,140,*141–150*,151,*152*). These measures include (a) preference to the orotracheal (as opposed to nasotracheal) route when intubation is necessary; (b) use of aseptic technique for respiratory tract manipulation; (c) use of mouth washes with oral antiseptics for intubated patients (e.g., chlorhexidine); (d) proper disinfection and maintenance of respiratory equipment; (e) use of a new ventilator circuit each time a new patient is placed on a ventilator, but no routine change of circuits for a single patient unless visibly soiled or mechanically malfunctioning; (f) new HME for each patient, and change of HME as clinically indicated (some still recommend routine changes every 5 to 7 days *(100)*); (g) hand hygiene before and after contact with mucous membranes or contaminated equipment, whether or not gloves are worn; (h) elevation of the head of the bed to 45 degrees (when it is not possible to elevate this high, then attempts should be made to raise the head of the bed as much as possible *(100)*); (i) continuous subglottic suctioning, particularly in patients expected to be mechanically ventilated for >72 hours *(100)*; and (j) noninvasive ventilation to avoid risks associated with endotracheal intubation and mechanical ventilation *(153)*. Additional measures include (a) identification and elimination of environmental reservoirs for pathogens; (b) use of barrier precautions for colonized and infected patients; (c) extubation and removal of nasogastric tubes as soon as clinically possible; (d) avoidance of oversedation and paralytics; (e) use of proper endotracheal suctioning techniques; (f) maintaining adequate endotracheal cuff pressures; and (g) control of antibiotic use. Table 66-2 summarizes the current and the past CDC guidelines relevant to this chapter for the prevention of HAP.

More recent guidelines, from various professional societies, (*100*,151,*152*) address issues and data related to VAP prevention that were not fully covered in the 2004 CDC guidelines (29). These are as follows: (a) subglottic drainage of secretions. Although this was mentioned in CDC's 2004 guidelines as being helpful in preventing VAP *(154)*, more recent guidelines have more strongly supported the use of subglottic suctioning (5,*100*,151,*152*). (b) Silver-coated endotracheal tubes. In a large prospective study, involving 54 institutions and 2003 patients, the use of silver-coated endotracheal tubes reduced the incidence of VAP by 36%, though no differences in mortality, length of ICU stay, and duration of mechanical ventilation were noted (140). (c) Polyurethane cuffed endotracheal tubes. So far, this device, which is designed to prevent leakage and aspiration of subglottic secretions around the endotracheal cuff, has only been tested in a pilot study design and only in postoperative cardiac surgery patients *(155)*. (d) Selective oral decontamination (SOD) and selective digestive decontamination (SDD). One randomized trial *(156)* demonstrated a favorable impact of SOD and SDD on mortality of mechanically ventilated patients; and one meta-analysis *(157)* reported a reduction in VAP rates associated with SOD and SDD, but reported conflicting results regarding reduction in overall mortality. Emergence of antimicrobial resistance is a concern pertaining to this practice. (e) Oral care with chlorhexidine. Most guidelines recommend routine care with antiseptics (most commonly chlorhexidine), despite publication of few negative trials *(158–160)*. (f) Daily assessment of readiness to wean and following weaning protocols reduces VAP prevalence and improves patient outcomes (151,*161*). (g) Stress ulcer prophylaxis. The bulk of recent data (although mostly retrospective) suggest that avoiding use of antacids, when possible, might reduce risk for VAP (151,*162*,*163*). (h) Implementing VAP prevention bundles are cost-effective and are associated with reduced incidence of VAP (*133*,151,*164–166*).

Studies evaluating airway management of mechanically ventilated patients have been reviewed *(167)*. The following conclusions are justified by the current scientific literature. First, ventilator circuits should not be routinely changed (68,*100*). Second, the type of endotracheal suction system does not appear to influence the rate of VAP, but results from various studies have conflicted. Two trials comparing open and closed suctioning systems showed no significant difference; range of RRs, 0.84 to 0.91 *(168,169)*; but in a later study, use of a closed suctioning system was associated with a significantly decreased risk for VAP (adjusted RR 0.29, $p = .05$) *(170)*. Additional studies are needed to determine the impact of closed suctioning on reduction of risk for VAP. Recent Canadian guidelines recommended the use of closed system over open ones *(100)*. Third, lower rates of VAP and decreased hospital costs may correspond with the avoidance of heated humidifiers and use of HMEs *(114,167)*. Fourth, as mentioned previously, the use of endotracheal tubes that allow continuous aspiration of subglottic secretions has been associated with a reduced risk of pneumonia (5,*100*,*152*). Lower rates of pneumonia with use of kinetic versus conventional beds have been demonstrated in several studies, but significant reductions have not been demonstrated consistently *(100,152)*. In addition, complicating factors relating to patient discomfort and problems maintaining IV access occurred in several of the studies and may limit the use of kinetic beds. For this reason, routine use of kinetic beds has not been recommended by the CDC (29). Finally, noninvasive positive-pressure ventilation can be used in certain patient populations as an alternative to endotracheal intubation and mechanical ventilation *(153)*

TABLE 66-2

Recommendations for the Prevention of Healthcare-Associated Pneumonia Involving Respiratory Care Equipment

Prevention Strategy	*CDC 1994 (73)*	*Kollef 1999 (31)*	*CDC 2002 (29)*
Decontaminate hands with soap and water if hands are visibly soiled or contaminated with blood or body fluids, or with a waterless antiseptic agent after contact with mucous membranes, respiratory secretions, or objects contaminated with respiratory secretions, whether or not gloves are worn	IA	B	IA
Thoroughly clean all equipment and devices to be sterilized	—	—	IA
Whenever possible, use steam sterilization or high-level disinfection by wet heat pasteurization for reprocessing semicritical equipment or devices	IB	—	IA
When rinsing is necessary after chemical disinfection of semicritical equipment or devices used on the respiratory tract, use sterile or pasteurized water if feasible. If not feasible, rinse with isopropyl alcohol or use a drying cabinet	IB	—	IB
Do not routinely sterilize or disinfect the internal machinery of mechanical ventilators	**IA**	—	IB
Do not change routinely, on the basis of duration of use, the ventilatory circuit that is in use on an individual patient. Change the circuit when it is visibly soiled or mechanically malfunctioning	Change ≥48 h, IA	A	IA
Sterilize reusable breathing circuits and bubbling wick humidifiers, or subject them to high-level disinfection between uses on different patients	IB	—	IB
Periodically drain and discard any condensate that collects in the tubing of a mechanical ventilator, taking precautions not to allow condensate to drain toward the patient.	IB	C	IA
Placement of a filter at the distal end of the expiratory-phase tubing of the breathing circuit to collect condensate	U	—	U
Do not place bacterial filters between the humidifier reservoir and the inspiratory-phase tubing of the breaking circuit of a mechanical ventilator	IB	—	II
Use sterile or pasteurized water to fill bubbling humidifiers	II	—	IB
Preferential use of a closed, continuous-feed humidification system	U	—	U
Use a HME to prevent pneumonia in a patient receiving mechanical ventilation	U	A	U
Change an HME that is in use on a patient when it malfunctions mechanically or becomes visibly soiled	IB	—	IB
Do not change routinely more frequently than every 48 h, an HME that is in use on a patient	No routine change, IB	—	IB
Daily change of HME	—	A	—
Do not change routinely (in the absence of gross contamination or malfunction) the breathing circuit attached to an HME while it is in use on a patient	IB	—	II
Follow manufacturers' instructions for use and maintenance of wall oxygen humidifiers unless data show that modifying the instructions poses no threat to the patient and is cost-effective	IB	—	IB
Between patients, change the tubing, including any nasal prongs or mask, used to deliver oxygen from a wall outlet	IB	—	IB
Use only sterile or pasteurized fluid for nebulization and dispense the fluid into the nebulizer aseptically	IA	—	IA
Do not routinely sterilize or disinfect the internal machinery of anesthesia equipment	IA	—	IB
Do not routinely sterilize or disinfect the internal machinery of pulmonary-function testing machines between uses on different patients	II	—	II
Unless there is a filter between the mouthpiece and tubing of pulmonary-function testing equipment, sterilize or subject to high-level disinfection or pasteurization reusable mouthpieces and tubing or connectors between uses on different patients	IB	—	IB
Do not use large-volume room-air humidifiers that create aerosols unless they can be sterilized or subjected to high-level disinfection at least daily and filled with sterile or pasteurized water	IA	—	IB
Use of either the multiuse closed-system suction catheter or the single-use open-suction catheter	U	—	U

(*Continued*)

TABLE 66-2

Recommendations for the Prevention of Healthcare-Associated Pneumonia Involving Respiratory Care Equipment (*Continued*)

Prevention Strategy	*CDC 1994 (73)*	*Kollef 1999 (31)*	*CDC 2002 (29)*
If the open-system suction is employed, use a sterile single-use catheter	II	—	II
Use only sterile or pasteurized fluid to remove secretions from the suction catheter if the catheter is to be used for reentry into the patient's lower respiratory tract	IB	—	IB
Remove devices such as endotracheal tubes from patients as the clinical indications are resolved	IB	C	IB
When feasible and no medical contraindications, use noninvasive positive-pressure ventilation delivered continuously by facial or nasal mask, instead of performing endotracheal intubation, in patients with hypoxemia or acute respiratory failure	—	C	II
Use an endotracheal tube with a dorsal lumen about the endotracheal cuff to allow drainage (by continuous suctioning) of tracheal secretions that accumulate in the patient's subglottic area	U	A	IB
If there is no medical contraindication, elevate at an angle of 30–45° the head of the a patient at high risk of aspiration pneumonia	IB	B	IB
Routine use of "kinetic" beds or continuous lateral rotational therapy for prevention of healthcare-associated pneumonia in critically ill and/or immobilized patients	—	—	U

CDC Classification: IA, strongly recommended for all hospitals and strongly supported by well-designed experimental or epidemiologic studies; IB, strongly recommended for all hospitals and viewed as effective by experts in the field and a consensus of HICPAC based on strong rationale and suggestive evidence, even though definitive studies may not have been done; II, suggested for implementation in many hospitals – recommendations may be supported by suggestive clinical or epidemiologic studies, a strong theoretical rationale, or definitive studies applicable to some but not all hospitals; U (unresolved issue), practices for which insufficient evidence regarding efficacy exists.
Kollef Classification: A, supported by at least two randomized, controlled investigations; B, supported by at least one randomized, controlled investigation; C, supported by nonrandomized, concurrent-cohort investigations, historical-cohort investigations, or case series; D, supported by randomized, controlled investigations of other healthcare-associated infections; U, undetermined or net yet studied in clinical investigations.

and has been shown to significantly decrease the risk for pneumonia in a randomized trial (RR, 0.13) *(171)*.

INFECTIONS ASSOCIATED WITH OTHER RESPIRATORY CARE PROCEDURES

Bronchoscopy

Infection Risks Flexible fiberoptic bronchoscopy is widely used as a diagnostic and therapeutic modality to procure pulmonary specimens for microbial identification via special stains and cultures to obtain specimens for cytologic and histopathologic examination, to aid in intubation, to provide pulmonary toilet, and to remove foreign bodies *(172–174)*. Overall, flexible bronchoscopy has proven to be an invaluable and safe diagnostic procedure *(174)*. A mail survey of more than 24,000 bronchoscopies by Credle et al. *(175)* revealed a rate of major complications of 0.08% and only two cases of pneumonia. A later survey by Suratt et al. *(176)* that included information on approximately 48,000 bronchoscopies did not mention infections complications. A prospective study of 100 patients undergoing flexible bronchoscopy detected temperatures >101°F and/or a new or more extensive pulmonary infiltrate on chest radiography in 16 patients *(177)*. These findings resolved without antimicrobial therapy in all but one patient, and bacteremia was not demonstrated in any patient. However, in a similar study involving 43 consecutive bronchoscopies, Kane et al. *(178)* reported no instances of postprocedure fever or bacteremia. A survey of 51 European centers that performed a total of 7,446 pediatric bronchoscopies reported the following incidence of fever (not defined): rigid bronchoscopy <5% of cases—22 centers, 5% to 10% of cases—four centers, and more than 10% of cases—one center; fiberoptic bronchoscopy <5% of cases—30 centers, 5% to 10% of cases—five centers, and more than 10% of cases—three centers *(179)*. The significance of the fever was not analyzed. A recent review of complications of bronchoscopy did not even report infections or fevers as notable complications *(174)*.

Mechanism of Healthcare-Associated Infections Bronchoscopes routinely become contaminated with a patient's respiratory flora during use. Because many hospitalized patients are colonized with gram-negative bacilli, contamination with these microorganisms is likely. Bronchoscopes may also become contaminated with environmental flora via airborne spread, rinses with nonsterile tap water, contact with contaminated transport cases, healthcare workers' hands, or use of nonsterile brushes. The major environmental agents of concern are bacteria that survive in water (e.g., *Pseudomonas,* nontuberculous mycobacteria). Mycobacteria are of particular concern, because they are relatively resistant to disinfectants. In the setting of impaired host defenses, use of contaminated bronchoscopes may lead to

colonization or infection of the patient. Use of contaminated scopes may also result in pseudoepidemics in which cultures obtained at the time of bronchoscopy represent colonization of the scope as opposed to colonization or infection of the patient. Although the patient is not infected, such false-positive cultures may have serious consequences, leading to inappropriate therapy of the patient with the risk of drug toxicity and/or an inappropriate diagnosis, which may lead to failure to consider other explanations of the patient's original symptoms and signs (see also Chapter 9).

Healthcare-Associated Outbreaks Healthcare-associated outbreaks due to flexible bronchoscopy have been reviewed *(180,181)* (Table 66-3). Contaminated equipment has resulted in cross-transmission leading to infection and pseudoepidemics *(183–217,219,222–224,226,228–236,238,240,242–244)* (see also Chapter 9). These outbreaks highlight the critical importance of proper cleaning and disinfection. Problems uncovered by these outbreaks include failure to properly remove debris from scope channels by brushing *(188,205,211)*, use of inadequate disinfectants *(188,193,184,192,210)*, use of contaminated tap water *(200,192,206,210,232)*, and failure to dismantle all equipment *(185,199,198)*. Detection of outbreaks *(209,210,216–218,220222,226,228,229,)* and determination of the environmental reservoir *(209,210,222,226)* have been aided by molecular typing of outbreak pathogens. Several specific issues in proper cleaning and disinfection of bronchoscopes warrant further elaboration. First, all scope components (e.g., suction valves) must be dismantled and appropriately cleaned and disinfected (68). Second, terminal rinses to remove residual glutaraldehyde must be done with sterile water. Third, damaged scopes leading to protected foci for microorganisms may lead to cross-transmission despite use of adequate cleaning and disinfectants *(194,229,230)*. Finally, properly cleaned bronchoscopes must be sterilized with ethylene oxide or peracetic acid, or disinfected with an appropriate high-level disinfectant such as 2% glutaraldehyde or 0.55% orthophthalaldehyde. Outbreaks have occurred when the disinfectant used was 70% alcohol *(184)*, povidone-iodine *(188)*, alcohol plus povidone-iodine *(193)*, cetrimide plus chlorhexidine *(192)*, or 0.13% glutaraldehyde-phenate *(210)*. Further, the disinfectant must be in contact with all surfaces for the correct exposure time and at the appropriate temperature *(194,201,203)*. Exposure times for glutaraldehyde of <20 minutes do not reliably inactivate mycobacteria. Preventing healthcare-associated transmission of microorganisms by bronchoscopy requires meticulous attention to hand washing and proper cleaning and disinfection of the bronchoscopes. Appropriate care must also be taken by bronchoscopy personnel not to contact pathogens from the patient via airborne transmission (see also Chapters 38, 39, and 80).

Guidelines for Disinfection of Bronchoscopes General guidelines for the disinfection of medical equipment are available (68) (see also Chapter 62). Bronchoscopes should be sterilized or high-level disinfected between patients; however, because of the pressures of time, most scopes are subjected to high-level disinfection. By definition, high-level disinfection will inactivate all microbes with the exception of high numbers of bacterial spores. The microorganisms most resistant to inactivation are bacterial endospores and mycobacteria. Diluted glutaraldehyde preparations (<2%) do not reliably inactivate mycobacteria with a 20-minute exposure time *(245)*. Of concern, many hospitals employ either inadequate exposure times or inappropriate disinfectants *(246)*. US guidelines differ from those practiced in other parts of the world, and current practice in the United States should be based on the most recent US guidelines (68).

Spirometry

Spirometry is a basic function test that allows the measurement of forced vital capacity and time-related indicators of dynamic pulmonary function *(247)*. Data obtained from the forced expiration maneuver can be used to generate flow–volume and volume–time curves. Such measures are widely used in diagnosing pulmonary disorders, evaluating the risks associated with intra-abdominal surgery, and assessing the response to bronchodilators. Much attention has been paid in the past to standardizing spirometry equipment and methods *(248)*. Several outbreaks have been linked to the use of contaminated spirometers *(249,250)*. Contaminated spirometers have been linked to cross-transmission of *Stenotrophomonas maltophilia (172)*, *Haemophilus influenzae (251)*, and *Acinetobacter* species *(249)*. Hazaleus et al. *(250)* reported transmission of *Mycobacterium tuberculosis* infection to 1 of 22 patients who underwent pulmonary-function testing using a dry-seal spirometer within 12 days of its use for a patient with active pulmonary tuberculosis. Few studies have carefully evaluated the potential of spirometers as vehicles for cross-transmission of microorganisms. Rutala et al. *(252)* prospectively examined the extent of microbial contamination of two commonly marketed dry-rolling spirometers following use for patients with a heavily colonized or infected respiratory tract. The investigation revealed that the mouthpieces became contaminated with the patients' oral flora and with the associated respiratory pathogen; 14% of tubing samples after patient testing contained the respiratory pathogen. All other equipment samples (e.g., interior surface of the machine) were negative for the respiratory pathogen. These data suggest that changing the mouthpieces and tubing between patients will eliminate the possibility of cross-transmission, and that it is unnecessary to routinely clean the interior surfaces of the machine. Burgos et al. *(253)* found frequent colonization of the proximal tubing, distal tubing, water, and water-bell of a water-sealed spirometer; however, no transmission of potentially pathogenic microorganisms from equipment to patients or vice versa was demonstrated.

Room Humidifiers

Cool-mist humidifiers have been linked to healthcare-associated epidemics of sepsis or pneumonia caused by *Acinetobacter* species *(254,255)*, *P. aeruginosa (256)*, and *Legionella pneumophila (80,257)*. Experiments using tap water contaminated with *L. pneumophila* have demonstrated that cool-mist humidifiers can readily generate aerosols of *Legionella* that disseminate throughout a two-bed patient room *(258)*. Nonaerosol humidifiers used

TABLE 66-3

Pseudoepidemics and Infections Transmitted by Flexible Bronchoscopes

Reference	Publication Year	Microorganism	Isolates	Infections	Deaths	Source of Contamination
Webb and Vall-Spinosa *(182)*	1975	*Serratia marcescens*	3	3	1	Biopsy channel; disinfection failure
Surratt et al. *(183)*[a]	1977	*Pseudomonas aeruginosa*	82	—	—	Data not provided
Weinstein et al. *(184)*[a]	1977	*Proteus* spp.	8	—	—	Disinfection failure
Hussain *(185)*	1978	*P. aeruginosa*	1	1	0	Biopsy suction value
Markovitz *(186)*	1979	*P. pseudomallei*	1	1	0	Data not provided
Steere et al. *(187)*[a]	1979	*Mycobacterium gordonae*	52	—	—	Contaminated green dye added to cocaine for tropical anesthesia
Leers *(188)*	1980	*M. tuberculosis*	1	0	0	Improper cleaning/disinfection
Schleupner and Hamilton *(189)*[a]	1980	*Trichosporon cutaneum, Penicillium* sp.	8	—	—	Contaminated cocaine solution used for tropical anesthesia
Martone et al. *(190)*[a]	1981	*B. cepacia*	21	—	—	Contaminated lidocaine and normal saline setups, inadequate disinfectant
Sammartino et al. *(191)*	1982	*P. aeruginosa*	11	1	0	Inner channel
Dawson et al. *(192)*	1982	*M. intracellulare*	2	—	—	Plastic tubing; disinfection failure
Nelson et al. *(193)*	1983	*M. tuberculosis*	2	1	0	Disinfection failure
Pappas et al. *(194)*	1983	*M. chelonae*	72	2	1	Punctured suction channels
Siegman-Igra et al. *(195)*[a]	1985	*S. marcescens*	4	—	—	Terminal rinse with tap water
Goldstein and Abrutyn *(196)*[a]	1985	*Bacillus sp.*	14	—	—	Automated suction valve
Stine et al. *(197)*[a]	1987	*M. gordonae*	8	—	—	Terminal tap water rinse?
Prigogine et al. *(198)*[a]	1988	*M. tuberculosis*	8	—	—	Automatic aspiratory adapter
Wheeler et al. *(199)*[a]	1989	*M. avium*	2	—	—	Suction valve
Wheeler et al. *(199)*	1989	*M. tuberculosis*	3	1	0	Suction valve
Hoffmann et al. *(200)*[a]	1989	*Rhodotorula rubra*	30	—	—	Tub water, cleaning brushes
Jackson et al. *(201)*[a]	1989	*Sporothrix cyanescens*	4	—	—	Dust created during renovations
Nye et al. *(202)*[a]	1990	*M. chelonae*	4	—	—	Terminal rinse with contaminated tap water
CDC *(203)*[a]	1991	*M. chelonae*	14	—	—	Automated washer/disinfector; 10 min disinfection, terminal tap water rinse
Fitch et al. *(204)*	1991	*M. chelonae*	21	0	0	Multiple: terminal tap water rinse, automated washer/disinfector
Nicolle et al. *(205)*	1992	*Blastomyces dermatitidis*	2	—	—	Failure to properly clean scope (microorganism rendered nonviable)
Gubler et al. *(206)*[a]	1992	*M. chelonae, M. gordonae*	12	—	—	Water tank of automated washer/disinfector
Fraser et al. *(207)*[a]	1992	*M. chelonae*	14	—	—	Automated cleaner/disinfector
Whitlock et al. *(208)*[a]	1992	*Rhodotorula rubra*	11	—	—	Suction valve and rubber biopsy valve
Maloney et al. *(209)*[a]	1994	*M. abscessus*	15	—	—	Automated washer/disinfector
Bennett et al. *(210)*[a]	1994	*M. xenophi*	13	—	—	Terminal tap water rinse; contaminated hot water tank
Kolmos et al. *(211)*[a]	1994	*P. aeruginosa*	8	—	—	Suction channels (not cleaned prior to disinfection)
Wang et al. *(212)*[a]	1995	*M. chelonae*	18	—	—	Suction channels
Hagan et al. *(213)*[a]	1995	*R. rubra*	11	—	—	Suction channels
Cox et al. *(214)*[a]	1997	*M. chelonae*	34	—	—	Lidocaine sprayers used on multiple patients
Blanc et al. *(215)*[a]	1997	*P. aeruginosa*	35	—	—	Automated washer/disinfector
Agerton et al. *(216)*[a]	1997	*M. tuberculosis (MDR)*	4	2 (disease 1)	—	Improper disinfection, bronchoscopes not fully immersed in disinfectant
Michele et al. *(217)*	1997	*M. tuberculosis*	1	1	—	Improper disinfection; failure to use enzymatic cleaner, sterilize biopsy forceps, and completely immerse bronchoscope

(*Continued*)

TABLE 66-3

Pseudoepidemics and Infections Transmitted by Flexible Bronchoscopes (*Continued*)

Reference	*Publication Year*	*Microorganism*	*Isolates*	*Infections*	*Deaths*	*Source of Contamination*
Mitchell et al. *(218)*[a]	1997	*Legionella pneumophilia*	3	—	—	Use of contaminated rinse, failure of 70% ethanol flush
Wallace *(219)*[a]	1998	*M.abscessus*	12	—	—	Automated endoscope reprocessor and manual disinfection
Wallace *(219)*[a]	1998	*M.abscessus*	30	—	—	Automated endoscope reprocessor
Wallace *(219)*[a]	1998	*M. fortuitum*	4	—	—	Automated endoscope reprocessor
CDC *(220)*	1999	*M. tuberculosis*	4	0	—	Automated endoscope reprocessor
CDC *(220)*[a]	1999	*M. avium-intracelluare*	7	—	—	Automated endoscope reprocessor: use of channel adapters provided by bronchoscope manufacturer instead of connector kit provided by automated endoscope reprocessor manufacturer
Strelczyk *(221)*[a]	1999	Acid-fast bacilli	10	—	—	Automated endoscope reprocessor: inadequate channel connectors provided by bronchoscope manufacturer
Schelenz *(222)*	2000	*Pseudomonas aeruginosa*	—	—	—	Automated endoscope reprocessor
Gillespie *(223)*[a]	2000	*Mycobacterium chelonae*	2	—	—	Automated endoscope reprocessor
Wilson *(224)*[a]	2000	*Aureobasidium species*	10	—	—	Reuse of single-use stopcocks
Larson *(225)*[a]	2001	*M. tuberculosis*	2	—	0	Automated endoscope reprocessor and improper cleaning
Kressel *(226)*[a]	2001	*M. chelonae, methylo-bacterium, mesophilicum*	20	—	0	Automated endoscope reprocessor
Kramer *(227)*[a]	2001	*P. aeruginosa*	2	—	0	Automated endoscope reprocessor: contaminated disinfectant due to inadequate concentration
Sorin *(228)*	2001	*P. aeruginosa*	18	3	1	Automated endoscope reprocessor: inappropriate channel connectors
Ramsey *(229)*	2002	*M. tuberculosis*	9	3	0	Defective bronchoscope
Srinivasan *(230)*	2003	*P. aeruginosa*	—	—	—	Defective bronchoscope: loosened biopsy port
Kirschke *(231)*	2003	*P. aeruginosa*	17	1	—	Defective bronchoscope: loosened biopsy port
Rossetti *(232)*[a]	2002	*M. gordonae*	16	0	—	Automated endoscope reprocessor
Singh *(233)*[a]	2003	*Trichoporum mucoides*	6	0	0	Defective bronchoscope
Silva *(234)*[a]	2003	*P. aeruginosa, S. marcescens*	41	0	0	Inproper rinsing
Corne et al. *(235)*	2005	*P. aeruginosa*	16	4	0	Damaged internal channel caused by defective biopsy forceps
Bou et al. *(236)*	2006	*P. aeruginosa*	10	10	—	Failure to properly clean and disinfect bronchoscopes
Ahn et al.[a]*(237)*	2007	*S. maltophilia*	7	0	0	Failure to properly clean and disinfect bronchoscopes
Shimono et al. *(238)*	2008	*P. aeruginosa*	7	7	—	Automated endoscope reprocessor was defective
Chroneou et al.[a] *(239)*	2008	*M. chelonae*	9	0	0	Automated endoscope reprocessor
DiazGranados et al. *(240)*	2009	*P. aeruginosa*	12	2	0	Damaged bronchoscope
Schuetz et al.[a]*(241)*	2009	*L. pneumophilia*	13	0	0	Immersion of uncapped saline filled syringes in contaminated ice

[a]Pseudoepidemic.

(Adapted in part from Weber, DJ, Rutala, WA. Lessons from outbreaks associated with bronchoscopy. *Infect Control Hosp Epidemiol* 2001;22:403–408.)

to humidify wall oxygen may also support the growth of *P. aeruginosa (259)* and have been linked to respiratory infections with this pathogen *(260,261)*.

Inhaled Medication

Direct instillation of aerosolized contaminated medications is a well-established, although unusual, cause of lower respiratory tract infection *(77)*. Both colonization and pneumonia caused by *Klebsiella pneumoniae* resulted from the use of a contaminated stock bottle containing a bronchodilator *(262)*. Use of contaminated inhaled budesonide with sulbutamol led to seven cases of *B. cepacia* bacteremia in a pediatric intensive care unit (ICU) *(77)*.Contamination of saline vials used in respiratory care equipment has led to multiple outbreaks *(81,263–265)*. Use of contaminated multidose saline vials for IPPB treatments was reported to lead to both pneumonia and sepsis with *S. marcescens (81)*. Intrinsic contamination of single-dose vials of tracheal irrigant solution has led to multiple outbreaks of pulmonary colonization with *Ralstonia pickettii (263,265,266)*. Following one of these outbreaks, experiments revealed that *R. pickettii* is capable of proliferating in 0.9% sodium chloride solution and that *R. pickettii* is not fully retained by a 0.2-μm cartridge filter *(267)*. Manipulation of disposable saline squeeze vials for use during suctioning frequently leads to contamination of the vial contents with coagulase-negative staphylococci, *Staphylococcus aureus,* streptococci, and enterococci *(268)*. In several cases, the contaminating pathogen was isolated from the nurse's hands, suggesting that contamination occurred during opening of the vial. Despite its frequency, whether such contamination leads to lower respiratory tract infection has not been evaluated. Of note, symptoms resembling neonatal sepsis have resulted from inadvertent administration of inhaled epinephrine *(269)*.

In 2000, the FDA released a regulatory rule regarding the sterility requirements for production of aqueous-based drug products to be distributed and used for oral inhalation *(270)*.

Aspiration of Contaminated Medications

An outbreak of neonatal listeriosis was traced to bathing of infants with mineral oil from a multidose container that was contaminated by *Listeria monocytogenes (271)*. Aspiration of the contaminated oil presumably led to clinical infection and sepsis. Aspiration of commercial charcoal has reportedly led to colonization and, possibly, infection with *Aspergillus niger, Paecilomyces variotti,* and *Penicillium* species *(272)*. The authors noted that commercial charcoal is not a sterile preparation, and its use may lead to colonization in immunocompromised patients.

Ingestion of Contaminated Foods or Medications

Ingestion of contaminated ice led to the development of HAP due to *Legionella pneumophila* in a long-term ventilated patient *(273)*. Ice machines may serve as the reservoir for healthcare-associated pathogens, and appropriate management, including periodic cleaning, is indicated *(241,273—277)*.

The addition of food dye contaminated with *P. aeruginosa* to nasogastric tube feedings to monitor for possible aspiration led to a cluster of infections in ventilated patients *(278)*. The outbreak was terminated by replacing the multidose bottles with single-use vials.

An investigation of nursing home outbreaks of respiratory infection caused by *Legionella sainthelensi* identified history of a stroke and eating pureed food as risk factors for infection *(279)*. The association of these variables with swallowing disorders suggests that aspiration of contaminated potable water was the cause of *Legionella* infection.

Contaminated mouthwash led to a large pseudo-outbreak of *B. cepacia* from respiratory tract specimens of intubated patients at two hospitals *(280–282)*. Swabbing with the mouthwash was used for routine oral care for all case patients. *B. cepacia* was grown from unopened bottles of the mouthwash, and the pseudo-outbreak ended after use of the mouthwash was discontinued.

Hospital Personnel with Dermatitis

Healthcare-associated infections have occasionally been linked to colonized or infected respiratory therapists. An epidemic of healthcare-associated respiratory tract infections due to *A. calcoaceticus* was linked to a respiratory therapist with chronic dermatitis who had persistent hand colonization and who contaminated sterile respiratory care equipment *(283)*. Healthcare-associated hepatitis B was reported to have been acquired from a therapist with exudative dermatitis during placement of intra-arterial catheters *(284)*. Careful hand hygiene (water and a disinfectant or waterless alcohol-based product) and the use of sterile gloves should minimize transmission of infection during invasive procedures *(285)*. Healthcare workers with weeping or exudative dermatitis should refrain from direct patient care or handling of patient care equipment until the dermatitis has resolved (see also Chapter 93).

Suctioning Apparatus

The collection of body fluids using suction is accomplished by portable pumps or wall vacuum lines. Suction is most commonly used to clear the upper respiratory tract (pharynx and trachea) of secretions in sedated or intubated patients. Suction collection units can lead to healthcare-associated infections either by producing aerosols containing potential bacterial pathogens or by serving as an environmental reservoir *(286)*. Transmission to patients can occur through contamination of the hands of healthcare personnel during manipulation of the suction unit or through retrograde spread to the patient undergoing suction.

The use of older or improperly designed suction units has resulted in aerosolization of potential microbial pathogens, most commonly aerobic gram-negative bacilli or *S. aureus (287–289)*. Contaminated suction units that generate aerosols have led to outbreaks caused by *Klebsiella aerogenes (290)*, *P. aeruginosa (291)*, and *Salmonella montevideo (292)*. Contaminated suction units, along with other environmental reservoirs, have been linked to neonatal infections caused by *P. mirabilis (293)* and *P. aeruginosa (291,294,295)*, and to adult infections caused by *K. aerogenes (290)* and *P. aeruginosa (296–298)*.

Prevention of healthcare-associated infections caused by spread of the contaminated secretions contained in suction units requires use of units designed to prevent aerosolization of body fluids or overflow, disinfection between

patient uses, disposal of fluids in a non–patient-care area, and hand washing after handling (29,68).

Tracheal suctioning has occasionally led directly to healthcare-associated infections. Withdrawal of the suction catheter across the patient's face has reportedly led to serious healthcare-associated eye infections, most frequently due to *P. aeruginosa (299)*. Van Dyke and Spector *(300)* reported transmission of herpes simplex virus type I from a physician with herpes labialis to an infant during suctioning for meconium aspiration *(300)*. Standard guidelines should be used by hospital personnel performing tracheal suctioning to minimize the risk of healthcare-associated infection (Table 66-2).

Several studies have compared "open" and "closed" methods for suctioning patients *(168–170)*. Some did not detect a difference in the incidence of HAP. "Closed" suctioning was associated with fewer arrhythmias and less desaturation in one study *(169)* but with an increased rate of colonization in a second study *(168)*. However, in a different study, open suctioning was associated with a 3.5-fold increase in VAP *(170)*. The current data do not favor either mode of suctioning as superior in regard to prevention of pneumonia, though some experts state clearly that a "closed" method is superior in terms of VAP prevention *(100)*.

Several studies have compared the incidence of pneumonia in patients when endotracheal tubes that allowed continuous aspiration of subglottic secretions versus standard endotracheal tubes were used *(154,301–303)*. The vast majority of studies demonstrated that the use of continuous aspiration of subglottic secretions reduced the rate of pneumonia (RRs, 0.22–0.61), but not all studies had reached statistical significance *(154,303)*. Continuous aspiration of subglottic secretions appears to be an effective method to prevent VAP, and it is currently incorporated into multiple VAP prevention guidelines (5,*100*,151).

Suction regulator devices are used to intermittently drain gastric secretions in ventilated patients. In a recent study, it was demonstrated that these devices can become colonized rapidly (median duration of 1 hour) by pathogens such as *P. aeruginosa* and *S. aureus*, and that both sides of the canister, that is, patient side and wall side, can rapidly become colonized *(304)*. In a simulated model, bacteria were able to move throughout the tubing systems, and were isolated in both the apparatus connected to the unit wall and the experimental "mock" stomach *(304)*.

SUMMARY

Respiratory tract infections and infections associated with respiratory devices are well-established complications of modern medicine. Numerous devices have been associated with both endemic infection and outbreaks in ICU settings. In the past decade, multiple guidelines from leading medical societies have been published. The guidelines have helped to incorporate the most updated scientific knowledge and technology into process "bundles" to facilitate efforts by clinicians and administrators to prevent respiratory tract infections. Evidence-based processes have been incorporated into the clinical setting as well into the process of high-level disinfection and sterilization of respiratory equipment. Adherence to basic clinical concepts, such as rigorous adherence to hand hygiene and infection control practices and guidelines, and minimizing the duration of mechanical ventilation are instrumental in minimizing the infectious risks associated with respiratory therapy.

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CHAPTER 67

Healthcare-Associated Infections Following Transfusion of Blood and Blood Products

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The transfusion of blood and blood products exposes recipient patients to both noninfectious and infectious adverse events (1). Approximately 15 million units of blood are collected and processed into 29 million products annually, with an average of 2.7 units administered per recipient (2). In a recent review of noninfectious early and late adverse events after transfusion, mortality rate estimates are one per million to 8 million transfused components, much lower than prior estimates (0.0001–0.00001%; 3). Infections account for 8% to 17% of these deaths. The remainder of deaths are related to early or late, frequently immunologic, reactions, or to errors of processing or administration. The nonfatal adverse effects range from minor inconveniences to life-threatening emergencies; they may occur immediately during or within hours of the transfusion (early events) or may be delayed for weeks, months, or years (late events). The physician should always consider the risk of such ill occurrences in the decision to transfuse. The public desires absolute safety in a product regardless of cost *(4,5)*; accordingly, there has been a marked increase of safety of transfused blood in the United States over the last 20 years (6,*7–12*). This chapter reviews the potential infections transmitted by blood and blood products (Table 67-1) and their prevention.

NONINFECTIOUS COMPLICATIONS

Noninfectious complications of blood transfusion have emerged as the most common cause of fatal transfusion reactions and have become the focus of hemovigilance by the National Healthcare Safety Network (NHSN; *13*). The noninfectious complications of blood transfusion include acute transfusion reactions (within 24 hours) and delayed reactions (>24 hours after transfusion; 1,3,*13*). *Acute reactions* include acute hemolytic reactions, which may be immunologically or nonimmunologically mediated and account for the majority of deaths, and nonhemolytic reactions, which are usually febrile or allergic in nature and account for 19% to 25% of deaths resulting from transfusion (1,*13*). Other nonhemolytic reactions include volume overload, transfusion-related acute lung injury (TRALI), sepsis from bacterial contamination (*vide infra*), air embolus, hypertension associated with coadministration of an angiotensin-converting enzyme inhibitor, hypocalcemia, and hypothermia (1,3,*13*). Delayed reactions include hemolysis due to anamnestic antibody responses, alloimmunization to red blood cell (RBC) or human leukocyte (HLA) antigens, posttransfusion purpura, hemosiderosis, graft-versus-host disease (GVHD) in severely immunosuppressed hosts, and processing errors (1,3,*13*). Some of these noninfectious complications are obviated by routine measures. Most are not life threatening and can be medically managed when they occur. Macroaggregate leukocyte filters during transfusion may reduce some of these reactions *(9,14)*. Leukocyte reduction (LR) before storage with third-generation filters is very important for reducing transfusion reactions associated with the presence of cytokines generated by leukocytes in the plasma phase of stored donor units *(15,15a,16)*. Since implementation in Canada and European countries, LR has resulted in decreased transfusion-associated mortality, fever, transfusion-related immunomodulation (TRIM), and decreases in the incidence of TRALI and its associated mortality *(17–21)*. LR in the United States has resulted in similar benefits (3,*13*). Prestorage LR was advocated by the American Red Cross (ARC) in the summer of 1995 and by the summer of 2000, 95% of ARC donor centers had implemented this policy. In 2010, over 95% of ARC centers continue to use prestorage LR; many but not all non-ARC donation centers in the United States are doing likewise (personal communication, ARC).

INFECTIOUS COMPLICATIONS

It was not until the early 20th century that transfusion was made feasible for nonterminally ill patients. The new methods included anticoagulation techniques, classification of blood type isoagglutinins *(22)*, and storage of donor blood. Previously, only direct donor-to-recipient transfusions were reluctantly and rarely performed because of the high frequency of often severe complications *(23)*. With the advent of this technology, the infectious complications of blood transfusion became recognized. By World War I, potential donors with malaria, syphilis, and fever were excluded *(24)*. The increased number of transfusions during World War II led to the recognition of posttransfusion hepatitis (PTH) *(25)*. However, even before this description, the American Red Cross Donor Service had deferred all potential blood donors with a history of jaundice within 6 months *(26)*.

TABLE 67-1

Infectious Complications of Transfusion of Blood or Blood Products

I. Transfusion-related immunosuppression with secondary infection
  a. Postsurgical patients
  b. Patients with burns affecting more than 10% of body surface area
II. Infections potentially transmitted by transfusion:
  a. Hepatitis
    1. HAV, HEV
    2. HBV
    3. HCV
    4. HDV
    5. HGV (GBV-C)
    6. CMV
    7. EBV, HHV-8
  b. Other viral infections
    1. HIV-1 and HIV-2
    2. HTLV-I and HTLV-II
    3. Other non-A, non-B, non-C agent(s) (TT virus, SEN virus)
    4. West Nile virus, Colorado tick fever virus
    5. Erythrovirus B-19
    6. Vaccinia virus
    7. Yellow fever virus, dengue virus, chikungunya virus
    8. Xenotrophic murine leukemia virus–related virus (XMRV)
  c. Prion disease
  d. Protozoal diseases
    1. Malaria
    2. Babesiosis
    3. Trypanosomiasis
    4. Toxoplasmosis
    5. Leishmaniasis
  e. Spirochetal infections
    1. Syphilis
    2. Lyme disease
    3. Relapsing fever
  f. Bacterial infections
    1. Brucellosis
    2. Salmonellosis
    3. Yersinosis
    4. Gram-positive or gram-negative contaminants
  g. Parasitic infestations (loiasis, other filaria)
  h. Rickettsioses

CMV, cytomegalovirus; EBV, Epstein-Barr virus; GBV-A, B, GB viruses A and B, respectively; HAV, HBV, HCV, HDV, HEV, HGV, hepatitis A, B, C, D, E, G viruses, respectively; HIV-1, HIV-2, human immunodeficiency virus types 1 and 2, respectively; HTLV-I, HTLV-II, human T-cell leukemia virus types I and II, respectively.

The organized collection of blood and blood products for civilian use began in 1947. Hepatitis B virus (HBV) was defined serologically by 1972; its partial control has led to our understanding of other causes of PTH, including hepatitis C virus (HCV), hepatitis delta virus (HDV), hepatitis G virus (HGV), other non-A, non-B, non-C hepatitis viral agents, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and, rarely, hepatitis A virus (HAV) and hepatitis E virus (HEV) *(8,10,27–33)*. The epidemic of human immunodeficiency virus type 1 (HIV-1) infections led to its recognition in the early 1980s as transmissible by blood and blood products *(34)*. Other infectious agents transmitted by blood and blood products include protozoa, filaria, spirochetes, other viruses, and bacteria (1,*8–10,27–31*).

The remainder of this section reviews each of these pathogens and the prevention of their transmission by blood transfusion after a brief discussion of the recently recognized phenomenon that blood transfusion may cause immunosuppression and thereby predispose the recipient to infections. Table 67-2 summarizes the most recent donor selection criteria of the American Association of Blood Banks (AABB) for the protection of recipients of donor blood (35).

Infections after Noncontaminated Blood Transfusion

Several authors have reviewed the observations that blood transfusions may result in suppression of the recipient's immune defenses (TRIM), leading to secondary infections *(36–39)*, in addition to an association of transfusion with recurrence of malignancy and increased (renal) allograft survival *(14,38,40–42)*. Using multivariable analysis, Tartter *(43)* and others *(44–47)* have presented data associating blood transfusion with infection after various types of surgery. Subsequently, reports have made similar associations after surgery for trauma *(48–53)*, Crohn's disease *(54)*, gastrointestinal bleeding *(55)*, open fractures of an extremity *(56)*, and coronary artery bypass surgery *(57,58)*, and with healthcare-associated infections in critical care patients *(59,60)*. Recent studies have shown that RBC transfusions have also been associated with infections, in addition to pulmonary dysfunction, TRALI, and enhanced mortality in critical care *(61)*. Increased rates of infection after noncontaminated blood transfusion have also been documented in humans with burns affecting more than 10% of their bodies *(62)*; initial studies in an animal burn model indicated similar findings *(63,64)*. However, reports after elective surgery have failed to document such an association *(65,66)*, and others have questioned the relationship of transfusion to TRIM and infection in critically ill patients *(67)*.

The proposed mechanism accounting for these observations is immunosuppression induced by the transfusion; Waymack and Alexander *(68)* noted a higher incidence of tumor recurrence and reduced survival among oncologic surgery patients who received perioperative blood transfusions. Waymack et al. *(69,70)* suggested that the mechanism of this immunosuppression may be alteration of macrophage arachidonic acid metabolism, given elevations of prostaglandin E and a decrease of interleukin-2 (IL-2) production documented in animal models after allogeneic transfusion *(69–71)*. Lenhard et al. *(72)* reported decreased lymphocyte antigen responsiveness in transfused patients with chronic renal failure before renal transplantation; Lenhard et al. *(73)* also documented increased circulating blood monocytes with augmented prostaglandin E production in transfused patients with chronic renal failure. An analogy with the immunosuppression of pregnancy resulting from a blunted IL-2 response and upregulation of interleukin-4

(IL-4) and interleukin-10 (IL-10) has been summarized *(40)*. These altered cytokine kinetics may lead to enhanced Th2 and depressed Th1 responses. Other authors have suggested optional mechanisms, including antigen-induced anergy and immune tolerance, and the effects of transfused cytokines *(38,40–42,74,75)*. These reported immunologic abnormalities in transfusion recipients have not been linked with potentially transfused agents (e.g., CMV). Given that the transfusion of RBC units after 14 days' storage is more often associated with pneumonia in trauma patients

TABLE 67-2

American Association of Blood Banks Criteria for Protection of Recipients of Donor Blood (2009)

1. Appearance of good health in donor, including lack of major organ disease, malignancy or bleeding tendency.
   a. Oral temperature of donor ≤37.5°C (99.5°F); age 16 y or older, hemoglobin/hematocrit ≥12.5 gm/dL/>38%
   b. Permanent exclusion for stigmata of injectable drug use or for use of a needle, even once, for nonprescription drug administration
   c. Deferral for active alcoholism
   d. Medication deferral: finasteride, isotretinoin (1 mo), dutasteride (6 mo), acitretin (3 y), etretinate (permanent), aspirin, piroxicam (48 h), clopidogrel, ticlopidine (14 d), and warfarin (1 wk).
   e. Deferral if pregnant within last 6 wk.
2. Deferral of donor for 2 wk after live attenuated bacterial or viral vaccine receipt (measles, mumps, oral polio, oral typhoid, yellow fever), except for 4 wk after rubella or varicella zoster vaccine and for 1 y after rabies vaccine given for a rabies prone animal bite.
3. Donor deferral for 12 mo after HBIG
4. Donor deferral if during the previous 12 mo the donor was given blood or potentially infected blood products (components, human tissue or plasma-derived clotting factor concentrates).
5. Permanent donor deferral:
   a. If history of hepatitis after age 11 y,
   b. If HBsAg (confirmed) or anti-HBc positive (positive at two different donations),
   c. If anti-HCV, HTLV-I/II, or HIV-1/2 seropositive,
   d. If in a high-risk group for HIV-1/2 infection, including having sex with a person from Africa,
   e. If prior donation led to hepatitis, HTLV-I/II, or HIV-1/2 infection in recipient
   f. A history of babesiosis or Chagas' disease,
   g. Donors with a family history of Creutzfeldt-Jakob disease, donor after receipt of human pituitary growth hormone or dura-mater grafts, and donor at risk for variant Creutzfeldt-Jakob disease (e.g., receipt of bovine insulin made in United Kingdom, having spent more than 3 mo in United Kingdom between 1980 and 1996, having lived in Europe for ≥5 y, or having received blood transfusion in the United Kingdom. or France between 1980 and the present),
   h. Having made payment for sex or having received any payment for sex, or, if the blood donor is a male, having ever had sex with another male.
6. Donor deferral for 12 mo after:
   a. Unsterile body piercing or application of a tattoo or permanent make-up unless performed aseptically in state-regulated facility,
   b. Mucous membrane exposure to blood or skin penetration by an instrument contaminated with blood or a body fluid,
   c. Sexual exposure to a person with symptomatic viral hepatitis or confirmed positive test for HBsAg or HVC antibody,
   d. Sexual contact with a person infected with or at high risk for HIV-1 infection,
   e. Incarceration for >72 h in a correctional institution,
   f. History of syphilis or gonorrhea, reactive screening test or confirmatory test for syphilis, or completion of therapy for syphilis or gonorrhea,
   g. After return from an area endemic for leishmaniasis.
7. Donor deferral due to malaria (plasma donations excepted):
   a. 3-y deferral for those after recovery from malaria or for persons who lived in a malaria endemic area for ≥5 y,
   b. 12-mo deferral for travelers after return from a malaria endemic area if free of symptoms suggestive of malaria,
   c. 3-y deferral for immigrants after departure from malaria endemic areas if asymptomatic,
   d. 12-mo deferral of residents from countries that are malaria free but who have traveled to an area where malaria is endemic (acceptance as donor if symptom free).
8. Donor deferral until 14 d after recovery from suspected or documented West Nile virus (WNV) infection, or until 28 d from onset of illness (suspect or known to be WNV)
9. Donor deferral after smallpox vaccination without complications for 21 d or until scab has fallen off, whichever is longer; donor deferral after smallpox vaccination with complication until 14 d after resolution of complication
10. Donor is provided opportunity in confidence to declare collected blood unsuitable for transfusion by call-back system.

Anti-HBc, antibody to hepatitis B core antigen; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV-1/2, human immunodeficiency virus types I and II, HTLV-I/II, human T-cell leukemia virus types I and II.
(From Price TH, ed. *Standards for blood banks and transfusion services*, 26th ed. Bethesda, MD: American Association of Blood Banks, 2009.)

(76,77), the transfusion of cytokines leading to TRIM is even more plausible because cytokine levels increase with duration of storage without LR *(75)*.

Current data clearly suggest that transfusion is a modulator of the immune system, although an independent role for transfusion as an immune suppressant is not yet definitive *(37,40–42)*. However, in one prospective randomized trial of postoperative infection *(74)*, as well as other reports *(39,59,60)*, a dose-dependent relationship of transfusion to infection risk and immune suppression has been supported.

Several methods are available for avoiding the potential immunosuppressive effects of transfusion associated with surgery and trauma. Improved surgical techniques with attention to hemostasis may avoid much of the need for transfusion. Furthermore, there is minimal scientific justification for the current hemoglobin level (10 g/dL) at which transfusion is advocated *(78,79)*. The decreased blood viscosity associated with reduced hemoglobin concentrations of anemia may increase cardiac output and partially compensate for decreased oxygen delivery to tissues *(79,80)*. Acceptance of reduced indications for transfusion according to hemoglobin concentration and the use of autologous blood for transfusion (self-donated preoperatively or intraoperatively recovered blood) will also reduce the immunosuppressive effects of transfusion *(79)*. Furthermore, restrictive transfusion strategies in critical care and patients with acute coronary syndromes have reduced TRALI and mortality *(81–84)*. Hebert et al. have reported noteworthy benefits from a restrictive transfusion strategy (hemoglobin was maintained from 7–9 g/dL) in critical care patients at 25 Canadian hospitals; observed reductions were seen in ICU and hospital mortality, organ dysfunction, and length of ICU and hospital stay *(85)*. Restrictive transfusion criteria are now being advocated for various types of surgery, after trauma, and in critical care and are advocated by the Society of Critical Care Medicine in its latest guidelines (*82*,*86*,*87*,*88*,*89*,*90*,91). In the past, prior to near-universal prestorage LR, other preventive techniques have included the use of leukocyte-reduced blood products, such as frozen deglycerolized RBCs or RBCs after treatment with second-generation micropore or third-generation absorption blood filters, and the use of blood alternatives (e.g., hemoglobin solutions depleted of erythrocyte stroma, chemically modified hemoglobin solutions, and artificial RBCs or neohemocytes) *(14,92–97)*. These leukocyte-reduction techniques also prevent many febrile transfusion reactions *(97)*. The stimulation of the patient's bone marrow with erythropoietin to produce RBCs is another method to avoid transfusion and has been effective in dialysis patients, despite side effects *(98)*.

The concepts of immunomodulation and increased infection risk after allogeneic blood transfusion have been unified mechanistically through the appreciation of cytokine release by leukocytes during blood storage *(16,41,42,44,75)*. A number of studies have demonstrated that leukocyte-depletion of transfused RBCs may have favorable effects on infection rates, morbidity, and/or mortality *(75,99–102)*. These studies further support the role of cytokines, in a variety of clinical settings, derived from leukocytes as a cause of described ill effects of transfusion. Additionally, while LR of RBCs is not universally accepted *(103,104)*, LR programs have reduced infection risks post operationally and after trauma *(75,105–109)*. Much of the confusion about the benefit of LR of all donor units stemmed from the lack of understanding of the need for prestorage LR to avoid cytokine accumulation during storage (110). The ARC has implemented LR prestorage for all donor units since 2000.

Infections after Transfusions Contaminated with Pathogens

Febrile reactions, defined as a temperature rise of 1°C (2°F) or more, may be associated with 1% to 2% of all RBC transfusions (3,*13*,*97*). In addition to an infective cause, either ongoing in the recipient or rarely resulting from bacterial contamination of the transfused blood product (see later discussion), fever may also follow a hemolytic transfusion reaction or may be associated with cytokines or antibodies in the transfused blood products, or antibodies in the recipient against leukocyte or platelet antigens *(16,97)*. Such febrile, nonhemolytic transfusion reactions may present as acute noncardiogenic pulmonary edema resulting from either reactive lipid products or antileukocyte antibodies or in association with the platelet refractory state (failure of the platelet count to rise after transfusion because of rapid antibody-mediated clearance). These febrile reactions are most commonly seen in multiply transfused, alloimmunized recipients, in multiparous female recipients of transfused blood or blood products, or after transfusion of blood or blood products from multiparous female donors. These reactions can be avoided by using leukocyte-reduced blood products (3,*9*,*16*,*21*,*42*,*97*). Febrile antiplatelet reactions may resolve with LR, but the platelet refractory state is seldom benefited.

Another febrile reaction related to transfusion of immunoincompetent and, rarely, normal hosts is a delayed reaction occurring 1 to 2 weeks after transfusion with the presentation of fever and erythroderma *(111,112)*. This often fatal transfusion-associated GVHD is not infectious, is usually not confused with a febrile transfusion reaction, and is obviated by irradiation of cellular blood products for at-risk patients (3) and by universal LR *(21)*.

The most frequent serious transfusion complication is the transmission of infection, of which hepatitis and, more recently, HIV-1 are the most important. Parenteral transmission of hepatitis was not recognized until 1883 when an outbreak occurred among recipients of a smallpox vaccine of human origin *(113)*. In 1938 and again in 1942, a yellow fever (YF) vaccine stabilized with human serum was reported to have caused jaundice among recipients *(114,115)*; a virus was presumed to have contaminated the human serum. Subsequently, epidemiologic studies and human volunteer experiments defined two forms of viral hepatitis: hepatitis A or infectious hepatitis, believed to be transmitted only orally (short incubation period of 15–50 days), and hepatitis B or serum hepatitis, associated with parenteral exposure (long incubation period of 50–180 days; *116*). Although it was known that both forms of hepatitis could be transmitted parenterally by blood and that hepatitis A could be acquired orally from various body fluids, physicians identified the form of hepatitis by exposure history until 1965 when Blumberg et al. *(117,118)* serendipitously associated Australia antigen with the surface

TABLE 67-3

Established Posttransfusion Hepatitis Viruses

Virus	*Virus Synonym*	*Family*	*Nucleic Acid*	*Incubation Period (d)*	*Chronicity*
HAV	Infectious hepatitis	Picorna	RNA	15–50	None
HBV	Serum hepatitis	Hepadna	DNA	50–180	Yes
HCV	Classic NANB hepatitis	Flavi	RNA	28–60	Yes
HDV	Delta agent	Deltavirus[a]	RNA	21–50	Yes
HEV	Epidemic NANB hepatitis	Hepeviridae	RNA	28–40	None
HGV	NANBNC hepatitis	Flavi	RNA	ND	Yes
CMV		Herpes	DNA	ND	No[b]
EBV	Herpes		DNA	ND	No[b]

[a] The genus of HDV.
[b] Establishes latent infection in leukocytes.
CMV, cytomegalovirus; EBV, Epstein-Barr virus, HAV, HBV, HCV, HDV, HEV, HGV, hepatitis A, B, C, D, E, G viruses, respectively; ND, not defined; NANB, non-A non-B; NANBNC, non-A non-B non-C.

antigen of hepatitis B. The development of serologic assays for hepatitis B and subsequently for hepatitis A opened the door to our evolving understanding of the other agents of PTH (*119–121*; Table 67-3).

Hepatitis A Much of the epidemiologic information contrasting hepatitis A and hepatitis B resulted from human volunteer studies performed in the 1940s *(116)* and at the Willowbrook State School in New York between 1956 and the late 1960s *(122,123)*. These and other studies defined the differences of incubation periods and antigenicity, the presence of HAV in feces, and the lack of chronic carriage of HAV *(116,122–124)*. HAV was first visualized in stool using immune electron microscopy in 1973 *(125)*; this finding ultimately led to methods for detection of serum antibody to HAV. The periods of viremia, clinical illness, and aspartate aminotransferase elevation have been related (Fig. 67-1); the transience of the immunoglobulin M (IgM) antibody response, followed by a persisting immunoglobulin G (IgG) response, has also been defined by both radioimmunoassays (RIAs) and enzyme immunoassays (EIAs) *(126–129)*. Although IgM antibody usually disappears within 3 to 6 months after infection, it may persist for more than 300 days in 10% to 15% of patients *(130)*.

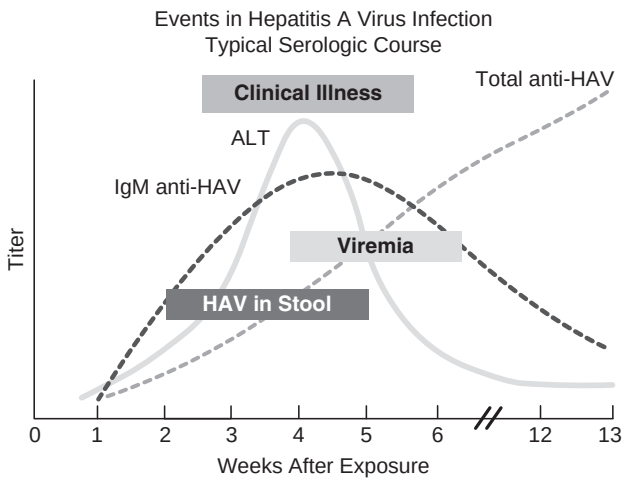

FIGURE 67-1 The clinical, virologic, and serologic course of acute hepatitis A virus infection. (Redrawn from *http://www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/gr_hav.htm*)

Because of the lack of an HAV carrier state and the brevity of HAV viremia (usually 2 weeks or less, with onset of viremia 7–10 days before onset of clinical symptoms, Fig. 69-1), frequent episodes of PTH A are unlikely *(9,26,120,121,131,132)*. With few exceptions, this has been the case *(133–141)*. Usually, PTH A occurs as a sporadic case report after blood donation during the incubation period of the illness *(139–141)*. Unfortunately, several outbreaks have been due to single contaminated units of blood being transfused to multiple infants, resulting in nursery outbreaks with secondary and tertiary cases *(134,136,137,139)*. One outbreak occurred among cancer patients treated with IL-2 and lymphokine-activated killer lymphocytes apparently resulting from contaminated serum in the lymphocyte culture medium *(138)*; another outbreak has occurred among patients with hemophilia given clotting factor concentrates inadequately treated to inactivate HAV *(142)*. These few reported outbreaks might have been prevented by serologic testing for antibody against HAV; however, the 50% seroprevalence rate for HAV IgG antibody among Americans by age 50, the possible persistence of IgM antibodies for 3 to 6 months after infection despite lack of infectivity, the frequency of symptoms during the viremic phase of the illness *(123)*, and the rarity of fatal illness resulting from HAV are strong arguments against the economic or the medical merit of routine testing of donor blood for HAV antibody *(9,27,132,143)*. The estimated current residual risk of acquiring HAV from a unit of transfused blood is estimated at 0.0001% (*9*,144). The prompt administration of immune serum globulin (ISG) prophylaxis would be appropriate for a recipient of blood found after transfusion to contain HAV *(27)*. The elimination of febrile symptomatic patients as blood donors generally prevents HAV transmission. Frequent recipients of clotting factor concentrates are candidates for receipt of HAV vaccine *(30,142)*.

Hepatitis B Blumberg et al.'s classic seroepidemiologic studies of diverse populations led to the discovery of a

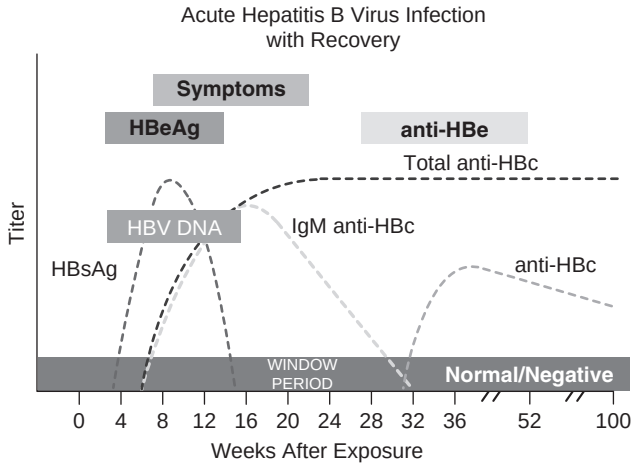

FIGURE 67-2 The clinical and serologic course of hepatitis B infection. (Redrawn from *http://www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/gr_hbv_acute.htm*)

unique antigen in Australian aborigines and recipients of multiple transfusions, which was called "Australia antigen" *(117,118,145,146)*. The terminology subsequently evolved from hepatitis-associated antigen to hepatitis B antigen and finally to hepatitis B surface antigen (HBsAg) when it was associated with the surface lipoprotein of HBV *(147,148)*. HBsAg can be found in serum of patients developing acute hepatitis B for 30 to 60 days before illness and may persist for variable periods after clinical recovery (Fig. 67-2). Persistence for longer than 6 months is defined as the chronic carrier state. Antibody against HBsAg (anti-HBs) develops as HBsAg disappears and accounts for long-term immunity *(149)*.

Hepatitis B core antigen, reflecting active viral replication, transiently appears in the blood during acute infection, only to be replaced by its antibody (anti-HBc) *(150)*. Anti-HBc appears during acute infection as an IgM antibody and is replaced in up to 80% of patients by a persistent IgG antibody during convalescence *(151)* (Fig. 67-2).

Hepatitis B e antigen (HBeAg) is a soluble product of HBV infection found transiently in serum during acute hepatitis B and in the serum of patients with chronic hepatitis *(152–154)* (Fig. 67-2). The presence of HBeAg correlates with the presence of HBV virions in serum. Antibody to HBeAg is more commonly found in chronic asymptomatic carriers of HBsAg *(153,154)*. The presence of HBeAg is associated with increased risk of maternal-fetal HBV transmission and transmission via accidental needle stick *(155–157)*.

Transmission of HBV occurs through percutaneous or transmucosal inoculation of HBV in blood or infectious body fluids (primarily semen and breast milk). Inoculation may occur by contaminated needles, during sexual contact, at birth, or during transfusion. Continuous household or institutional contact with an infected person may presumably transmit infection via unapparent exposures.

Acute hepatitis B causes a chronic viral carrier state in 6% to 10% of infected adults and 90% of infected newborns with or without chronic hepatitis (25% of carriers). The most serious sequelae in chronic carriers of HBsAg are cirrhosis and hepatocellular carcinoma. It is estimated that approximately 800,000 to 1.4 million chronic HBsAg carriers live in the United States as of 2007 *(158)*. These individuals serve as a potential reservoir within the pool of blood donors. High-risk groups for chronic carriage of HBV are shown in Table 67-4.

TABLE 67-4

High-Risk Groups for Acquiring Hepatitis B Infection

Group	*Seroprevalence[a] (%)*
Parenteral drug users	60–80
Heterosexual men and women and homosexual men with multiple partners	20–80
Household contacts and sexual partners of chronic HBV carriers	30–60
Infants born to HBV-infected women	40–95
Patients and staff in institutions for the developmentally disabled	35–40
Hemodialysis patients	20–80
Healthcare and public safety workers with frequent exposure to blood	≤10[b]
Persons born in areas endemic for HBV	70–85
Alaskan natives	40–70
Prison inmates	10–80

[a]Any serologic assay positive.
[b]Prior to immunization of these groups.
HBV, hepatitis B virus.

Before the development of assays for HBsAg, it was believed that HBV accounted for most cases of PTH. When use of the first-generation immunodiffusion assays for HBsAg was initiated voluntarily on donor blood in 1969 and became mandatory in 1972 (Table 67-5), it was anticipated that PTH would be virtually eliminated. Although there were marked reductions in the frequency of PTH (30–55%) and mortality related to transfusion, the problem persisted. Hepatitis B may still account for up to 10% of cases of PTH *(9,159,160)*. Recently published risk estimates for PTH resulting from HBV are 1 infected unit per 220,000 donor units (0.00045%; 144,161); among first-time blood donations, 19.14 units are positive for HBsAg per million units donated *(162)*.

The transmission of HBV via transfusion has been reduced to present levels because of the screening of all blood donors for HBsAg with more sensitive assays. Counterimmunoelectrophoresis was introduced in 1972 to 1973, and sensitivity for HBsAg detection was further increased by currently available RIAs, reversed passive hemagglutination, chemiluminescence immunoassays, and EIAs *(159,160,163–166)*. With the successive introduction of second-generation counterimmunoelectrophoresis and current third-generation tests for HBsAg (Table 67-5), Alter et al. *(167–169)* documented the parallel reduction of PTH resulting from HBV. This reduction was likely augmented because of current ARC donor selection and deferral procedures and the elimination of paid donors in favor of all-volunteer donors *(9,10,159,160,167–170)*. HBeAg has been found more frequently in paid blood donors (15%) compared with volunteer donors (5%; *171*). Further

TABLE 67-5

Serologic Tests for Infectious Agents Performed on Blood and Blood Products before Transfusion

Assay	*Target Disease*	*Date Initiated*
Nontreponemal test[a]	Syphilis	1939–1941
HBsAg (immunodiffusion)	Hepatitis B	July 1972[b]
HBsAg (CIE)	Hepatitis B	1972–1973[b]
HBsAg (RIA, EIA or ChLIA)	Hepatitis B	Sept 1975[b]
HIV-1 antibody (EIA)	HIV-1 infection	March 1985[b]
HTLV-I antibody (EIA)[c]	HTLV-I infection	Dec 1988[b]
ALT	Hepatitis B, C, and non-A, non-B, non-C	Summer 1986[b,d]
Anti-HBc (EIA or ChLIA)	Hepatitis B, C, and non-A, non-B, non-C	Fall 1987[b]
Anti-HCV 1.0 (EIA)	Hepatitis C	May 2, 1990[b]
Anti-HCV 2.0 (EIA)	Hepatitis C	March, 1992[b]
HIV-1/2 antibody (EIA)	HIV-1, HIV-2 infection	June 1, 1992[b]
HIV-1 p24 antigen	HIV-1 infection	Mar 14, 1996[b,e]
Anti-HCV 3.0 (EIA, ChLIA)	Hepatitis C	May 1996[f]
HTLV-I/II (EIA or ChLIA)	HTLV-I and HTLV-II	Feb 15, 1998[b]
NAT for HIV-1, HCV[g]	HIV-1, HCV	April, 1999
NAT for WNV	West Nile Virus	July 14, 2003
Bacterial detection[h]	Bacterial contamination	March 1, 2004
Anti–*T. cruzi* EIA	*T. cruzi*	January 29, 2007
NAT for HBV[g]	Hepatitis B	2006–2010

[a]Most large centers are now using a nonreponemal EIA or a treponemal test, (automated MHA-TP, FTA-Abs, TPI, or TPHA).
[b]Required by Food and Drug Administration (FDA).
[c]With significant HTLV-II cross-reactivity.
[d]Requirement deleted June 20, 1995.
[e]Requirement now deleted.
[f]FDA approved.
[g]NAT, nucleic acid testing (polymerase chain reaction—PCR, or transcription-mediated amplification—TMA); 6–16 minipool or single donor testing currently utilized.
[h]Bacterial detection—culture or alternative detection method (CO_2 production, O_2 consumption, fluorescent labeling, pH > 6.4).
ALT, alanine amino transferase; anti-HBc, antibody to hepatitis B core antigen; anti-HCV, antibody to hepatitis C virus; ChLIA, chemiluminescence immunoassay; CIE, counter immunoelectrophoresis; EIA, enzyme immunoassay; HBsAg, hepatitis B surface antigen; HIV-1/2, human immunodeficiency virus types 1 and 2; HTLV-I/II, human T-cell leukemia virus types I and II; RIA, radioimmunoassay.

reduction of PTH due to HBV may also result from the fact that asymptomatic HBsAg carriers continue to be removed from the donor pool through repeat donor testing *(27,172)*. Figure 67-3 presents the current algorithm for screening donor blood for HBV.

The residual frequency of PTH resulting from HBV is apparently due to the fact that HBsAg is circulating at undetectable levels for current screening assays; some of these donor units can be eliminated by screening for anti-HBc *(173–178)*. Such donor unit screening was initiated in 1986 (Table 67-5) as a surrogate test for non-A, non-B PTH but is believed to have contributed further to the reduction of HBV-related PTH. It is estimated that because of the institution of surrogate screens for non-A, non-B PTH (anti-HBc and alanine aminotransferase [ALT], the latter no longer performed), the incidence of HBV-associated PTH has further decreased by up to 84% to current levels (144,*179*). However, this reduction may also have been affected somewhat at that time (and currently; 35) by more stringent donor population screening to prevent transfusion-related HIV-1 transmission *(159)*, because the incidence of PTH was already further dropping before the initiation of anti-HBc screening *(180)*. Regardless, the risk of HBV-related PTH has currently dropped at least to 0.00045% per transfusion recipient *(8,146,159)*. However, further reduction may require more sensitive assays, because 4% to 12% of HBV-DNA carriers are identified by nucleic acid testing (NAT) and are seronegative for HBsAg, HBcAb, and other HBV serologic markers *(30,181)*. Such NAT positive but HBV serologically negative donor units may not transmit HBV infection *(181)*. HBV mutations or genotypes may contribute to falsely negative HBsAg serologic tests *(8,30,182)*.

In addition to the marked reduction of PTH caused by HBV resulting from HBsAg and anti-HBc testing of each donor unit of blood, the development of the NAT for whole blood (to assay for HBV DNA in plasma of donors without HBsAg) has the potential to decrease the already low rate of PTH resulting from HBV *(183,184)*. It is projected that an additional 81 HBV infected units of blood would be detected annually among the 12 million screened units *(8)*, thereby potentially reducing the risk of HBV transmission due to transfusion by 42% to 0.00045% per unit (*8*,*9*,144,*172*). NAT screening for HBV was introduced for all US blood donor

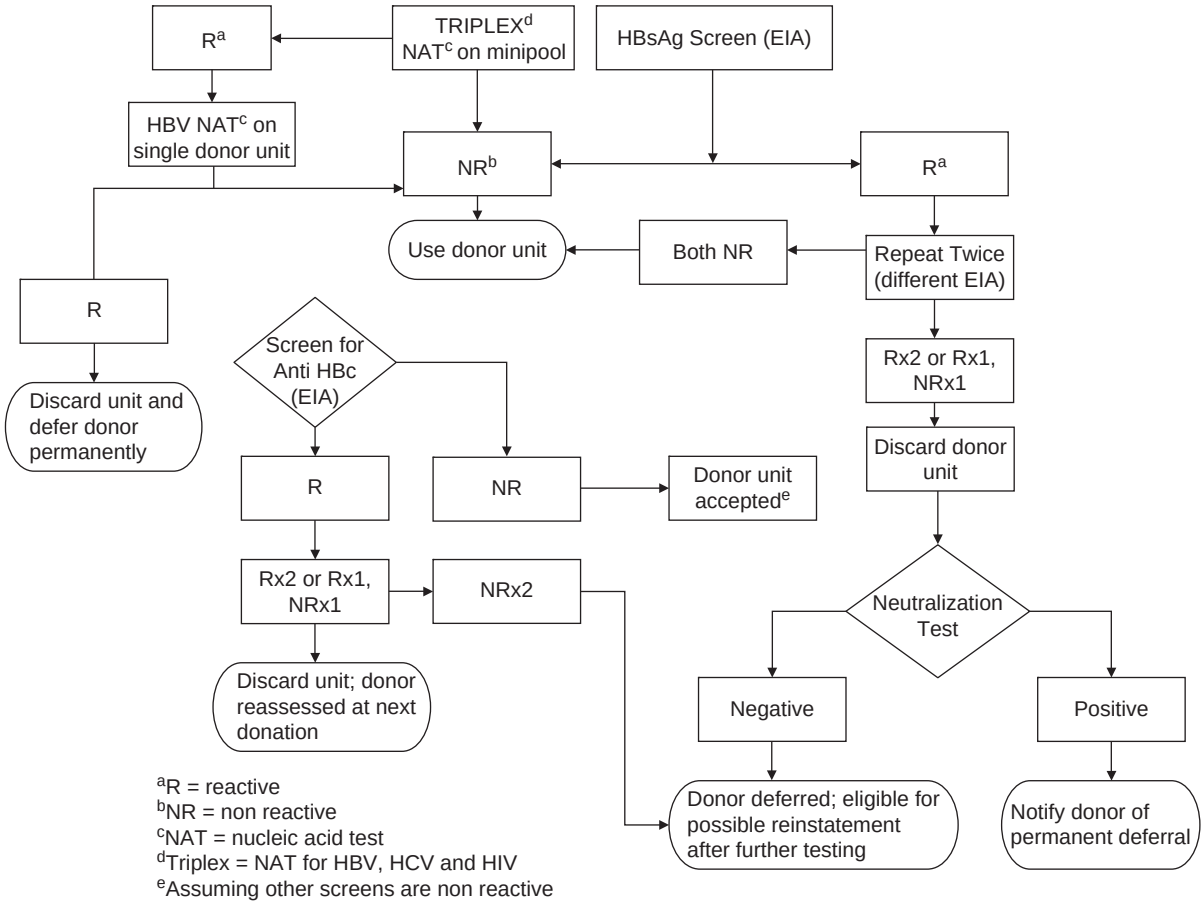

FIGURE 67-3 Algorithm for screening of donor blood for hepatitis B.

units between 2006 and 2010 as a triplex screen with HCV and HIV-1 (Table 67-5). The clinical benefit of NAT for HBV remains controversial (185). The addition of NAT for HBV, while expected to avoid 9 to 37 HBV transfusion–transmitted infections annually, adds an additional $39 to $130 million dollars per year to donor unit screening costs *(186)*.

If it were established within 1 to 2 weeks of receipt that a patient had been administered a unit of HBV-contaminated blood, there are no data that the use of HBV vaccine or hepatitis B immune globulin would be of value. In this unusual situation, one could argue for the use of both preparations, as after accidental parenteral exposure, in an attempt to modify the anticipated illness. When it can be anticipated that a person is going to receive multiple future transfusions (e.g., a hemophiliac), HBV vaccine should be administered as early in life as possible. However, the mainstays of prevention of PTH B for most patients are deferral of high-risk donors and serologic testing and NAT of donor units. Given the recommendations of the Immunization Practices Advisory Committee for universal childhood HBV vaccination, the risk of PTH resulting from HBV should become even smaller *(187)*. Before NAT for HBV, the risk of transmission of HBV via transfusion had remained stable in the United States *(9,10,172)*. This stability and the lack of an increasing relative risk of HBV transmission probably reflect an effect of universal childhood immunization, in addition to continued refinement of donor deferral criteria and use of antigen and antibody testing and possibly NAT.

Delta Hepatitis Delta agent hepatitis was initially described in 1977 by Rizzetto et al. *(188)* in Turin, Italy, and was reviewed by Hoofnagle in 1989 *(189)*. Although endemic to southern Italy, this virus has a worldwide but geographically variable distribution, including the Middle East and parts of Africa and South America. In nonendemic areas, such as the United States and Western Europe, the delta virus is found primarily in injectable drug users and multiply transfused patients, including hemophiliacs *(190)*. HDV is a defective RNA virus that replicates only in the presence of HBV with circulating HBsAg *(189)*. It is composed of an inner low-molecular-weight RNA genome associated with the internal delta antigen protein and coated with HBsAg as the surface protein *(191)*.

HDV infection occurs in only two settings: as a simultaneous coinfection with acute HBsAg-positive hepatitis B or as a superinfection superimposed on the chronic HBsAg carrier state *(189–191)*. During coinfection, although the ensuing hepatitis may be severe, biphasic, and protracted with a 2% to 20% mortality rate, most patients recover as hepatitis B resolves and fewer than 5% of patients develop chronic hepatitis *(190,192)*. The mortality rate resulting from coinfection of HDV with HBV contrasts with the <1% mortality rate associated with hepatitis B alone *(189)*. Illness associated with HDV is defined by a resurgence of the ALT serum levels after an initial decline, concomitant with the appearance of a transient anti-HDV–IgM response and followed by the development of low titer anti-HDV–IgG *(189,192)*. These

antibody responses may be detected by commercially available RIAs and EIAs *(193,194)*.

In contrast to acute coinfection, when HDV infection is superimposed on the chronic HBsAg carrier state, most patients (70%) develop chronic hepatitis with continued presence of HBsAg and HDV in the serum *(192)*. Sixty percent to seventy percent of patients with chronic delta hepatitis develop cirrhosis, and most of these die from liver disease *(195)*. Chronic HDV infection is documented by the persistence of anti-HDV–IgM in high titer *(192)*. HDV antigen may also be detected in the liver.

Because HDV is usually parenterally spread, its frequency in PTH associated with HBV (HBsAg positive) has been evaluated; 3.5% of 262 patients with PTH resulting from HBV were positive for anti-HDV *(196)*. Of these patients, 2.5% of those with self-limited disease were anti-HDV positive, whereas 14.5% of those with fatal hepatitis were infected with HDV. These data raise serious concerns for transfusion recipients; however, screening for HBsAg and NAT in each donor unit provides a high degree of protection for HBsAg-negative blood donor recipients *(196)*. HDV antibody screening is not needed. However, the HBsAg-positive prospective transfusion recipient is at some risk, especially if multiply transfused. In addition to the usual HBsAg screen of donor blood, blood-derivative recipients who are HBsAg carriers should be given products from single or minipool plasma sources *(196)*. Furthermore, all donors whose ALT is known to be elevated should be eliminated as blood sources for HBsAg-positive recipients.

Hepatitis C and Non-A, Non-B Hepatitis After the introduction of testing of all donor blood for HBsAg, it quickly became apparent that not all PTH was due to HBV *(27,120,121)*. Hepatitis A was also quickly excluded as a potential cause of the residual PTH *(120,131)*, as were CMV and EBV *(120,197,198)*. It was concluded that another virus (or viruses) accounted for most of PTH cases in the United States, initially designated "non-A, non-B or type C PTH" *(199,200)*. Much of the epidemiologic description of non-A, non-B hepatitis is now applicable to HCV, which caused most cases of non-A, non-B PTH *(201–204)*.

HCV is believed to be the most common cause of nonalcoholic liver disease in the United States. The prevalence of HCV in the US population is approximately 1.8%; 73% of patients with chronic infection have genotype 1, with the remaining predominately genotypes 2 and 3 *(205)*. The risk factors for infection somewhat parallel those of HBV. Among well-defined factors, transfusion (5–10%) and injectable drug use (60%) have accounted for most infections; transfusion is a virtually eliminated risk today (1,*8–12*,*172*,*202*,*205–207*). The risk of transfusion-related HCV infection declined between 1981 and 1988 from 17% to 6% before antibody screening *(208)*. Antibody to HCV is found in up to 85% of injectable drug users *(209,210)*. Other high-risk groups include prisoners, patients with transfusion-dependent bleeding disorders, and hemodialysis patients *(207,209–212)*. Sexual, household, and perinatal transmission and receipt of intravenous immune globulin are less important risks for HCV *(207,209,213–215)*; sporadic cases without defined exposure have declined (from 40% to 50%) to 5% of new cases *(207,208,216)*. In the contemporary era of home intravenous infusion therapy,

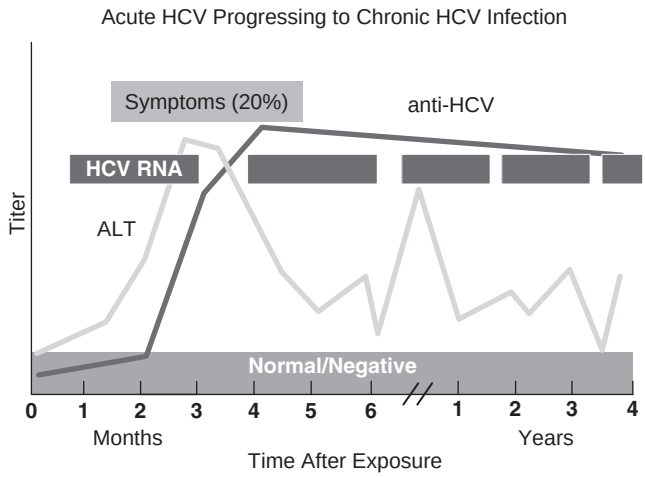

FIGURE 67-4 The clinical, biochemical, and serologic course of hepatitis C infection. (Redrawn from *http://www.cdc.gov/hepatitis/Resources/Professionals/Training/Serology/gr_hcv.htm*)

risks for HCV infection previously recognized in other sites have emerged in the household setting; a recent report suggests that transmission of HCV from an HCV-infected mother to her hemophiliac child may occur via accidental percutaneous (ungloved) needle stick during venipuncture for clotting factor infusion *(217)*. A family history of liver disease and prior history of blood transfusion, tattooing, sexual promiscuity, injectable drug use, intranasal cocaine use, and male ear piercing have been associated with anti-HCV positivity among blood donors *(218,219)*.

Approximately 75% of cases of HCV are subclinical, but, when symptomatic, hepatitis C is clinically and biochemically identical to other forms of hepatitis *(201,207)*. Figure 67-4 depicts the clinical, serologic, and biochemical course of HCV infection. Up to 85% of patients with hepatitis C develop chronic hepatitis *(31,201,220,221)*. Despite resolution of hepatitis after HCV infection, HCV RNA can often be detected by PCR, indicating HCV persistence in asymptomatic, biochemically normal patients (about 30% of chronic carriers; *207,220*). Symptoms or serum ALT level do not correlate with disease severity *(220,222)*. Most patients develop chronic active hepatitis with or without cirrhosis *(220–224)*. Cirrhosis may variably appear in 20% to 50% or more of patients *(201,207,224)*. Chronic hepatitis C has also been linked with hepatocellular carcinoma *(207,225–227)*. Patients seropositive for HCV antibody but with normal ALT values, no HCV RNA in serum, and normal hepatic histology, although uncommon, (up to 15% of those infected) probably have recovered from HCV infection *(221)*.

There are several studies assessing the outcome of PTH resulting from HCV. Seeff et al. *(228)* reported a study of long-term mortality after non-A, non-B PTH in 568 patients matched with two control groups, both of which comprised patients who had been transfused but had normal ALT values after transfusion. After an average of 18 years of follow-up, there was a small statistically significant increase in deaths resulting from liver disease in the patients with PTH (3.3% vs. 2.0% and 1.1% in the control groups). In a retrospective study, Tong et al. *(229)* defined that PTH resulting from HCV evolves into a progressive disease; chronic active hepatitis (23%), cirrhosis (51%), and hepatocellular

carcinoma (5.3%) are noteworthy sequelae. Goedert et al. *(230)* recently reported 137 hemophiliac patients with end-stage renal disease (ESRD) and HCV infection; ESRD was significantly associated with HIV-1, older age, HBV coinfection, and a low CD4 cell count. Another study has suggested a more benign outcome (45% viral clearance by PCR) in children infected via transfusion *(231)*.

Before the development of the current serologic tests to detect HCV, surrogate markers for non-A, non-B hepatitis were used as screening methods for donor blood. Initially, *ALT assays* were proposed to help reduce non-A, non-B PTH *(232–234)*. Up to 45% of donor units implicated in transmission of PTH have ALT elevations >60 IU/L *(179)*. Discarding units of blood positive for *anti-HBc* was subsequently shown to reduce posttransfusion non-A, non-B hepatitis (*177,178*; Fig. 67-5). Approximately 53% of blood donors implicated in PTH and positive for anti-HCV have anti-HBc *(179)*. The use of these assays instituted in 1986 and 1987, respectively, led to an approximately 30% to 40% reduction of PTH *(179)*. After 1985, blood transfusion as a source for acquiring HCV decreased to only 4% of new cases *(220)*.

Contemporary molecular biologic techniques led to the discovery of HCV. Nucleic acid extraction of infectious chimpanzee plasma led to the isolation of viral RNA, its transcription to DNA, and expression after insertion into a phage. Screening of several million DNA sequences for production of proteins that reacted with antibody in the serum of patients with non-A, non-B PTH led to the discovery of a polypeptide (C100-3) that was developed as an antibody-capture RIA for HCV *(204)*. This assay was quickly shown to detect 65% of donor blood capable of transmitting chronic PTH and 17% of acute PTH *(235)*. This commercially available antibody capture RIA was adapted also to an EIA, which has been shown to detect HCV as a cause of PTH *(236–238)*. Initial enthusiasm for this assay dampened because of the delayed seroconversion and, therefore, potential seronegativity of blood donors infected with HCV (despite the greater sensitivity of first-generation EIAs compared with RIA; *210*, *239–242*). The sensitivity of the EIA and RIA for preventing non-A, non-B PTH resulting from HCV was variably estimated at 60% to 85% *(206,239,243)*. First-generation assays for anti-HCV became positive up to a year after acute hepatitis C, and up to 20% of patients remained seronegative by these assays due to the insensitivity of the first-generation screening assays *(210,237,244)*. Regardless, contrasting the period when only surrogate tests for non-A, non-B PTH were used to the period after 1990 when the first-generation assays were implemented, Donahue et al. *(245)* demonstrated an 84% reduction of the risk of PTH resulting from HCV among transfused cardiac surgery patients (Table 67-6).

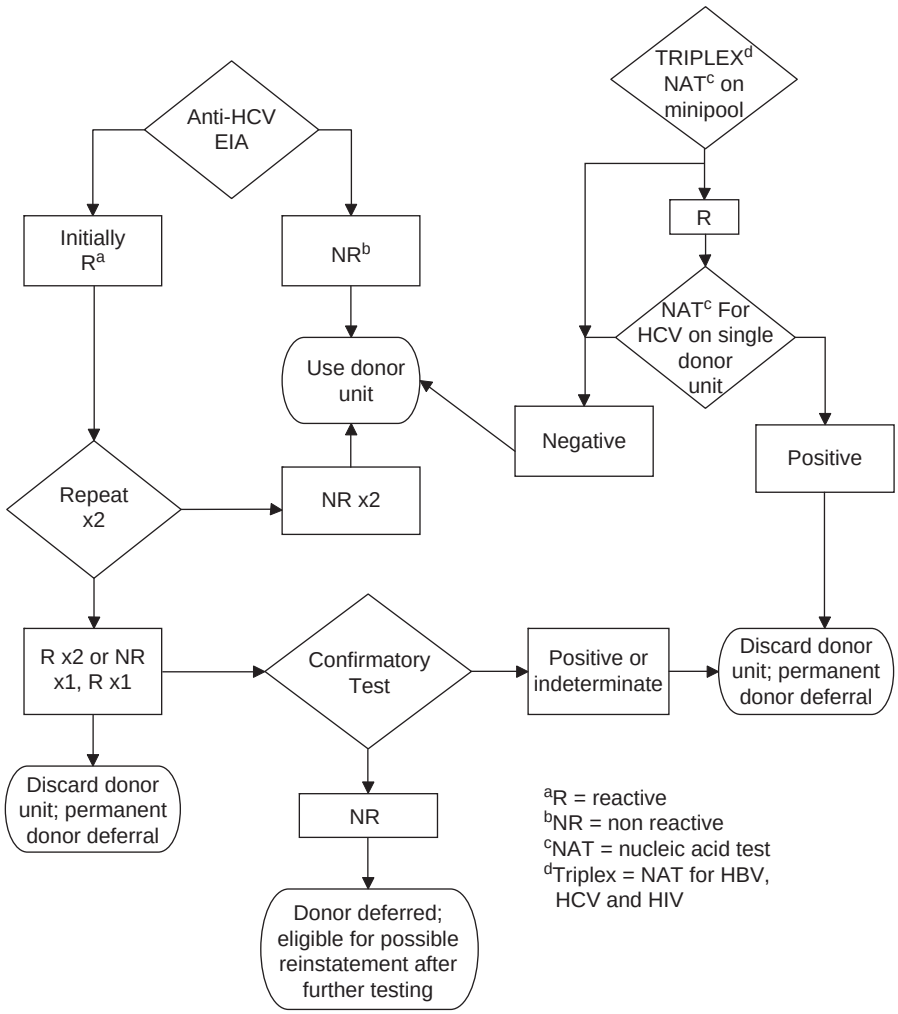

FIGURE 67-5 Algorithm for screening of donor blood for hepatitis C and hepatitis non-A, non-B, and non-C.

TABLE 67-6

Estimated Transmission Risk of Various Potentially Transfusion-Transmitted Infections, USA (Based on 2008 Data)

Agent	*Percentage of Risk*	*Risk Per Unit of Blood/ Blood Product Transfused*
Hepatitis B	0.04545	1:220,000
Hepatitis C	0.000056	1:1,800,000
HIV-1, HIV-2	0.000044	1:2,300,000
HTLV-I, II	0.000033	1:2,993,000
Cytomegalovirus(HHV-5)	—	Unknown, probably rare[a]
Epstein-Barr Virus (HHV-4)	—	Unknown, probably rare[a]
Human Herpes Virus 8(HHV-8)	—	Unknown, probably rare[a]
Hepatitis A	<0.0001	Unknown, probably <1:1,000,000
Hepatitis E	—	Rare case reports outside United States
GB viruses	—	Well documented–no disease risk
Parvovirus B-19	0.005–0.002	1:20,000–1:50,000 usually asym
Sen virus, Torgue Teno Virus	—	Well documented, no disease risk
West Nile Virus	Variable[b]	Rare (1:10,000–1:1,000 prior to NAT)
Bacteria[a]	0.0013	Platelets—1:75,000
0.0002	RBC—1:500,000	
Babesia sp.	≤0.0556	Unknown, up to 1:1,800 in endemic areas
Ehrlichia chaffeensis	Rare	
Anaplasma phagocytophilia	Rare	
Leishmania sp.	Unknown, described in endemic areas[a]	
Plasmodia sp.	0.000025	1:3 million to 4 million
Trypanasoma cruzi	0.01–0.004	1:5,400 to 1:25,000[d]

[a]Risk reduced by universal leukocyte-reduction of cellular blood products.
[b]Seasonally and geographically variable.
[c]Coagulase-negative Staphylococci, *Staphylococcus aureus*, *Streptococcus* sp., *Serratia liquefaciens*, *Yersinia enterocolitica*, *Acinetobacter* sp., *Enterobacter* sp., *E. coli*, *Pseudomonas* sp., *Providencia rettgeri*.[d]Geographically variable.
(From Feibig EW, Busch MP. Infectious disease screening. In: Roback JD, Coombs MR, Grossman BJ, et al., eds. *AABB technical manual*, 16th ed. Bethesda, MD: AABB, 2008:241–282.)

The ability to prevent PTH resulting from HCV was further improved by second-generation EIAs, which incorporated detection of antibodies to the core antigen (C22-3 protein) and the C200 antigen, which combines the epitopes included in the c33c and C100-3 proteins (coded by the NS-3 and the NS-4 regions of the RNA genome) *(30,206)*. Wang et al. *(246)* demonstrated 100% sensitivity of a second-generation EIA incorporating these three antigens, compared with 83% sensitivity of the first-generation assay; the newer assay also detected anti-HCV 6 weeks earlier than the single-antigen EIA. Using dot-blot assays, several groups demonstrated that antibodies to the c33c or core proteins (C22) consistently appeared before those to C100-3, from 4 to 13 weeks after transfusion *(247,248)*.

In addition to their sensitivity, another concern with the first-generation anti-HCV EIAs and RIAs was their positive predictive value. A positive EIA or RIA was confirmed by the more specific recombinant immunoblot assay (RIBA) in only 19% to 60% of cases *(243,249–252)*, with only one study showing 100% correlation of the screening EIA with RIBA *(239)*. Newer RIBA and matrix (a semiautomated immunoblot) assays each contain four recombinant antigens *(253)*. In keeping with Bayes' theorem, in high-risk populations, 70% to 100% of sera repeatedly reactive by second-generation EIAs were determined to be true positives by the RIBA or matrix assays, whereas fewer than 50% of repeatedly reactive second-generation EIAs are true positive in low-risk populations *(220,253)*.

Despite the limitations of first-generation EIAs, on May 2, 1990, an anti-HCV first-generation screening assay became mandatory on all donor blood (Table 67-5). Blood banks began using the second-generation EIA to screen for HCV antibody on April 6, 1992. Because of the previously discussed suboptimal sensitivity of these assays for HCV infection in a donor unit, the screening of donor blood for ALT level and anti-HBc was considered as important and was retained as required assays until June 20, 1995, when the requirement for ALT assays was rescinded (Table 67-5 and Fig. 67-5) (*29*,35,*206*,*243*,*249*,*250*,*254*).

Third-generation EIAs were initially tested in Europe and then approved by the FDA in May 1996 for use by blood donation centers. Similar to the second-generation assays, these third-generation assays incorporate recombinant antigens and include those described previously for the second-generation products, in addition to the protein product of the NS-5 region of the genome (RNA polymerase) *(30,255,256)*. These assays detect all genotypes and offer marginal improvement in reducing the seroconversion window (by 12 days) and the potential infectivity of a donor unit (15% reduction of an already low rate) *(30,255,256)*.

All HCV-antibody positive specimens by EIA are confirmed as positive by RIBA; a second-generation RIBA now incorporates the same recombinant antigens as the newer EIAs.

The risk of PTH was estimated to be <0.5% per patient transfused with the use of the third-generation EIA *(30,220,253)*. In addition to screening for HBsAg and antibody to HIV-1 and the adoption of a totally volunteer blood donor system with donor screening for HIV-1 infection risks, screening for ALT, anti-HBc, and especially anti-HCV had a major impact on the reduction of PTH. Donor questionnaire screening and donor unit serologic screening produced an overall low prevalence of anti-HCV positivity among volunteer blood donors (<0.5%) *(210,239,240,243,249,253)*. The frequency of anti-HCV positivity has been found to be higher among paid blood donors (10%; *257*), compared with volunteer groups (0.36%); anti-HCV positivity has been estimated to be 53.6 donor units positive for each million units collected *(162)*. Despite this low prevalence in volunteer donors, anti-HCV screening has demonstrated an impact (Table 67-6) because of the frequency of PTH (58–95%) after transfusion of anti-HCV reactive donor units and because of the ability of second- and third-generation EIAs for anti-HCV to detect 90% or more of donor units that transmit HCV *(206,210,237,239,241,243,253)*. The residual risk with the third-generation EIA was related to the possible 12- to 14-week window period after infection with HCV before the appearance of antibody *(258)*.

With these added screening tools, but before NAT, the risk of PTH had declined to <0.5% of transfused patients, a risk comparable with or less than the risk of hepatitis in nontransfused hospitalized patients *(202,206,253)*. Furthermore, 58% to 80% of the patients developing PTH in the past have developed persistent ALT elevations and 26% to 85% have chronic hepatitis; 90% of these patients are anti-HCV reactive *(179,188,198,215,219,231)*. Therefore, with current blood donor unit serologic screening, there is the potential not only to reduce PTH resulting from HCV by 90% or more but also to reduce chronic hepatitis resulting from HCV after transfusion by 80% to 90% *(235,253)*. On June 20, 1995, the prior requirement for ALT assays on all donor units was made optional because of rejection of many acceptable donors, especially males, because ALT assays are subject to interlaboratory variation and because the risk of PTH in groups receiving blood screened with or without ALT testing was equivalent *(254)*.

The use of NAT has further enhanced the ability to decrease the already low frequency of PTH resulting from defined HCV infection in donor blood *(207,259–262)*. PCR can detect HCV RNA within 59 days of infection *(8)*. With resolution of PTH resulting from HCV, HCV RNA detected by PCR has been shown to clear from blood as antibody levels decrease *(248)*. Before NAT for HCV, the risk of PTH resulting from HCV had been reduced to approximately 0.001% per unit of blood *(8,9)*. The addition of NAT in 1999 (initially as a duplex screen with HIV-1, and now a triplex screen also with HBV) has further reduced this risk to 0.00005%, an estimated 72% further risk reduction (*8*,*9*,144,*172*,*263*). Despite NAT, HCV can still be transmitted by anti-HCV- and NAT-negative blood products *(264)*. However, Dodd et al. *(172)* have documented the very low risk of HCV hepatitis after transfusion; they reported only 74 units of blood from more than 19 million drawn between March 1999 and February 2002 that were HCV antibody negative but HCV-RNA positive, for a rate of one positive unit per 267,700 units. This low rate has been confirmed by two more recent studies, one of which assessed 66 million donor units between 1999 and 2008 (185,265). In addition, the Centers for Disease Control and Prevention (CDC) has reported no transfusion-related HCV seroconversions among 11,171 hemophiliac patients between May 1998 and June 2002 and no transfusion-related cases during 2007 *(132,266)*. These improved safety data reflect an estimated decrement of the window period of infectivity of donor blood for HCV from 82 days with current antibody tests alone to 23 to 36 days by also incorporating NAT (8,267). NAT has been estimated to avert 56 to 59 HCV infections annually at a cost of several hundred million dollars annually *(186)*. PTH has become an uncommon event, reflecting the current safety of the blood supply.

Additional potential methods to prevent PTH resulting from HCV await development of a vaccine. Studies evaluating pretransfusion or post-transfusion administration of ISG have demonstrated conflicting results *(268–270)*. The variable efficacy probably reflects inconsistent anti-HCV content of preparations. ISG is not given in this setting *(207)*.

Other unsolved issues regarding non-A, non-B PTH remain. Only 91% of non-A, non-B PTH is associated with anti-HCV reactivity *(206,209,237)*. Although the incubation periods for anti-HCV–positive and anti-HCV–negative PTH are the same (6–12 weeks) *(244)*, anti-HCV–positive patients are more seriously ill and have twice the incidence of chronic hepatitis *(206,244)*. Other agents remain yet to be defined to account for the 9% of cases of PTH that are not due to HAV, HBV, or HCV *(8–10,172,244,271,272)*.

Hepatitis E Hepatitis E virus (HEV) is a single-stranded RNA virus in the Hepeviridae family. The epidemiology of HEV is similar to HAV in terms of fecal-oral transmission; HEV is more common in developing countries in tropical areas (144). The seroprevalence is <2% in the United States. Pigs, chickens, and other animals may be infected with HEV and serve as a source of human infection *(273)*. Illness is more severe than HAV infection, with 2% fatality (higher in pregnancy; 144). There are rare reports of transfusion-related infection, both in developing and developed countries *(33,274,275)*. Although HEV is a recently recognized pathogen, with our understanding of HEV yet evolving, as with HAV, there is not a need at this time to consider screening for HEV given its lack of chronic infection and likelihood of donor self-deferral during acute illness.

Hepatitis G Similar to the original work with HCV, in 1996 Linnen et al. *(276)* reported the cloning of HGV from the plasma of two patients, one with non-A, non-B hepatitis and the other asymptomatic with intermittent enzyme elevations. This group reported that HGV was genomically similar to another human virus isolate from a surgeon ill with hepatitis in the 1960s, termed "GB virus C." HGV is a member of the Flavivirus family, along with HCV and GB virus C. Using reverse transcriptase PCR technology, 2 of 12 patients with PTH were found positive for HGV RNA by Linnen et al. *(276)*, as were 5 of 38 patients with non-A to non-E community-acquired hepatitis. Four of the latter five patients remained HGV-RNA positive for 2 to 9 years

without evidence of chronic hepatitis. In addition, Linnen et al. reported 13 of 779 (1.7%) of volunteer blood donors with normal ALT values positive for HGV RNA, as were 11 of 709 donors (1.5%) with ALT elevations. These authors reported HGV to be globally distributed. More recent screening studies have confirmed these findings *(277)*.

Subsequent studies have confirmed this work and have found HGV in hemodialysis and postoperative patients, presumably transfusion associated *(278–280)*. Several authors have reported on the clinical disease associated with HGV, whether alone or in association with HCV; HGV is at worst a cause of mild acute hepatitis *(280,281)*, but frequently infection with HGV is asymptomatic without evidence of hepatitis *(280–282)*. HGV does not augment disease when accompanying HCV *(280–284)*. HGV was not associated with chronic hepatitis *(279,280,282)*. HGV is persistent in HIV-1 infected men and had variable effects on short- and long-term survival *(285)*. HGV is also prevalent in injectable drug users and hemophiliacs; HGV can be passed vertically mother to child and after heterosexual or homosexual contact with HGV-positive partners *(280)*. Its modes of transmission parallel HCV generally. Tanaka et al. *(283)* reported HGV responsiveness to interferon-α, but most patients relapsed.

Despite the prevalence of HGV in the volunteer blood donor population (1–4%), its role in PTH remains to be determined, because 75% of patients with transfusion-acquired HGV lack biochemical evidence of hepatitis *(280,281)*. Those with hepatitis have only mild elevations asynchronous with their HGV-RNA levels *(281)*. The relevance of HGV (and GB virus C) to PTH remains to be defined with broader seroepidemiologic, biochemical, and clinical studies. Currently, there appears to be no reason to test blood donors for HGV *(286,287)*.

Cytomegalovirus CMV is a member of the herpes virus family of DNA viruses (human herpes virus 5, HHV-5). Like other members of this group of viruses, latency is the rule after recovery from acute infection. Acquired CMV infection rarely presents as hepatitis, but may do so in adult patients *(288)*. Epidemiologically, CMV is acquired by human-to-human contact, congenitally or perinatally from mother to child by contact with cervical secretions, postnatally by an infant via breast milk, and in settings for the care of multiple children (e.g., in neonatal nurseries, in day care centers, and in the family setting) *(289)*. CMV is also transmitted by heterosexual or homosexual contact, by transfusion of donor blood, and by transplantation of donor organs *(289)*.

CMV infections are classified as primary (with seroconversion from negativity to positivity), reactivation of an endogenous infection, or reinfection with a new exogenous strain of CMV (in a seropositive host) *(288,289)*. The latter two forms of infection can be distinguished by using restriction enzyme DNA analysis, but this is not routinely practical *(290)*. Because there are no accurate data on the proportion of reactivation and reinfection for CMV post-transfusion infections, these two forms of infection are called "recurrent infections" *(288,289)*.

Depending on socioeconomic stratum and age, the seroprevalence of CMV ranges from 25% to 88% (144, *287–294*). In studies of CMV infection after transfusion in normal hosts before 1972, the incidence varied from 16% to 67% *(288)*. Most of these infections were asymptomatic. Risk factors for transmission included increasing number of units of blood transfused, use of fresh blood, and use of seropositive blood *(288)*. After 1972, transfusions became less common and involved little or no fresh whole blood, especially in cardiac surgery. Concomitant CMV post-transfusion infections have decreased to 1.2% to 17% *(288)*. In contrast to fresh whole blood, leukocytes containing CMV (monocytes and polymorphonuclear leukocytes) survive storage poorly at 2°C to 6°C *(288)*. This observation correlates with the observed reduction of CMV post-transfusion infection rates; studies have shown that 86% of patients infected with CMV after transfusion had received fresh whole blood, compared with 11% of uninfected patients *(295,296)*. Dworkin et al. *(297)* demonstrated a greater likelihood of isolation of CMV from donor blood during the first 5 days after collection, with infrequent isolation thereafter. In addition to fresh whole blood, granulocyte transfusions have been associated with an especially high risk of CMV infection in compromised hosts *(298–300)*. The difficulty with isolating CMV from donor leukocytes may be a reflection of the small number of leukocytes infected or the need for a posttransfusion host-versus-graft reaction to reactivate the virus *(288)*.

The reduction in overall CMV-related transfusion infections since 1972 also suggests that only a subset of CMV-infected donors (most of whom are seropositive) can transmit infection via donated blood *(288,301)*. This observation is paralleled by the infrequency with which CMV can be isolated from donor blood *(288)*. The receipt of blood from a CMV-seropositive donor significantly correlates with the infrequent residual post-transfusion CMV infections observed since 1972 *(302)*; this has been very well defined in transfused neonates *(303)*. An increased frequency of transmission also correlates with receipt of blood from a donor positive for CMV-IgM antibody *(302,304)*. The pathogenesis and presentation of CMV infection after transfusion involves several factors: the volume of blood transfused, activation of leukocytes harboring CMV, and survival of donor cells in the recipient to allow CMV replication *(304)*.

CMV infection can be diagnosed by direct examination of tissues or exfoliated cells for intranuclear inclusions; however, this lacks sensitivity for active infection *(305,306)*. Isolation of CMV in cell culture from blood (leukocytes) is more sensitive and specific for active infection but labor intensive (1–4 weeks for positivity). The development of fluorescein-labeled monoclonal antibodies for "immediate-early" and "early" antigen detection permits the diagnosis of CMV infection in cell culture within 24 to 48 hours *(307–310)*. Such antibodies can also be used directly to stain biopsied tissue *(307,311,312)*. CMV DNA probes with hybridization and electron microscopy of tissues and leukocytes are limited to research applications generally and have been reported to have lower sensitivity *(288,294)*. "Nested" quantitative PCR has been applied to various body fluids, including cerebrospinal fluid and blood, for the diagnosis of active CMV infection in HIV-1 infected patients *(289)*. This has not been applied to the blood donor setting.

CMV-specific antibodies can be detected by a variety of techniques (complement fixation, indirect hemagglutination,

indirect immunofluorescence, anticomplement immunofluorescence, latex agglutination, RIA, and EIA) *(288,289)*. Several of these can be applied to the detection of CMV-IgM antibody, including RIA and EIA *(313)*.

CMV disease most frequently occurs in a seronegative individual after primary infection and usually manifests as mononucleosis; however, post-transfusion CMV infection is usually asymptomatic. Therefore, there is no need to provide CMV-seronegative blood or blood products to immunocompetent recipients *(288,304)*.

The groups at risk for serious post-transfusion CMV infection are seronegative pregnant women, seronegative premature infants, seronegative organ transplant recipients who received an organ from a seronegative donor, seronegative oncology patients receiving chemotherapy, and seronegative patients with HIV-1 infection *(289,314,315)*. Seronegative premature neonates (<1,200 g) receiving CMV-seropositive blood are at greater risk for pneumonia, hepatitis, hemolytic anemia, and thrombocytopenia *(304,316)*. Mortality may reach 40%. This subgroup warrants routine receipt of CMV-seronegative blood.

Transplant patients developing primary infection (via a transplanted organ or transfusion) develop more serious disease *(289,315)*. In renal transplantation, the seropositive kidney donor is the major source of CMV *(317,318)*; seronegative transplant recipients receiving kidneys from seronegative donors rarely become infected and have better graft survival than those receiving kidneys from seropositive donors *(319–321)*. It is prudent to provide seronegative recipients of seronegative renal transplants with CMV-seronegative blood *(288,289,304)*. The same comments apply to heart transplantation *(304,322)*. Better-controlled studies in solid-organ transplant patients are needed, however *(304)*. The data are less clear and less well defined for donor blood in the bone marrow transplantation setting; however, prophylactic granulocyte transfusions, if given during bone marrow transplantation, should be from CMV-seronegative donors if the recipient is seronegative because of the high frequency of symptomatic and fatal infections *(298–300,304,323)*. The use of CMV-seronegative or leukocyte-reduced cellular blood products is warranted in seronegative recipients of bone marrow transplants from CMV-seronegative donors *(14,304,314,315,323,324)*. Such practices have reduced the risk of transfusion-associated CMV infection in this setting (23–37%) to 1% to 4%.

Preiksaitis et al. *(325)* documented the low risk of transfusion-related CMV disease in CMV-seronegative children with malignancy because of their low frequency of exposure via transfusion and because of LR of transfused units. In oncology patients, currently available data do not support screening donor blood for CMV *(288)*. Leukocyte-reduced cellular blood products are indicated in patients with hematologic malignancies who are CMV-seronegative to prevent CMV-associated morbidity *(14,315,326)*. A similar argument can be made for the exceptional HIV-1–infected patient who is seronegative for CMV *(304,314,315)*. However, LR lowers but does not absolutely prevent CMV infection from donor blood; seronegative blood components are more efficacious (*327*,328,*329*).

When indicated and necessary, the screening of donor blood for CMV antibodies is problematic because of the high frequency of seropositivity in the population *(294,330)*. At least in the neonatal setting, screening only for evidence of acute or reactivated CMV infection (i.e., CMV IgM) in donor blood will increase the size of the donor pool while reducing post-transfusion disease *(288,331)*. It has been demonstrated that the risk of transmitting CMV is diminished by using leukocyte-reduced blood, either as frozen deglycerolized RBCs or leukocyte-filtered RBCs (*14*,*304*,*326*,*327*,328,*329*,*332–336*). Differential centrifugation of platelet units may also enhance their safety *(304)*. The use of CMV immune globulin may have some role for preventing CMV-related complications in premature neonates born to CMV-seropositive mothers and in bone marrow transplant recipients, but ganciclovir appears to be more effective in the latter setting and in patients with HIV-1 infection *(288,289,337–339)*. The effect of the attenuated CMV vaccine in preventing CMV complications of transfusion has been disappointing *(289)*.

Epstein-Barr Virus and Human Herpes Viruses 6 and 8 EBV (human herpes virus 4; HHV-4) is another member of the herpes virus family of DNA viruses that is prone to latency in B lymphocytes and pharyngeal epithelial cells. Transfusion-related EBV infection is rare, with only a few recognized cases in the literature despite a 90% seroprevalence among blood donors *(315,340–344)*. Seroconversion after transfusion is usually associated with mild or inapparent clinical illness *(341,344)*. However, Alfieri et al. *(345)* documented the development of B-cell lymphoproliferative disease in a liver transplant patient after transfusion of EBV-positive donor blood. Because of the seroprevalence of prior infection in the population, screening donor blood is not indicated. Leukocyte-reduced RBCs may prevent transmission from a seropositive donor even during acute infection; LR is prudent in compromised hosts, especially in the transplant setting *(315,344–346)*.

Although no precautions are yet indicated for human herpesvirus-6 (HHV-6) uninfected potential transfusion recipients (60–100% of adults are infected), further experience is needed before use of seronegative donor blood can be recommended for seronegative compromised hosts *(315,344)*. HHV-6 has limited recognized pathogenic potential in immunocompromised adults *(315)*.

Human herpes virus 8 (HHV-8) has been associated with Kaposi's sarcoma, primary-effusion lymphomas, and multicentric Castleman's disease *(347)*. HHV-8 remains latent in peripheral blood mononuclear cells *(348)*. Its seroprevalence is 0% to 3.5% of volunteer blood donors, but from 12% to 36% in homosexual males and injection drug users and >40% in African countries *(347,349,350)*. In a study of women who had a history of injection drug use or high-risk sexual behavior, HHV-8 seropositivity was associated with black race, Hispanics, lower level of education, and infection with syphilis, HBV, HCV, and HIV-1 *(350)*. Although there is the potential for transmission by transfusion, the low seroprevalence of HHV-8 in US volunteer blood donors makes transmission unlikely. However, HHV-8 seroprevalence in transfusion recipients is 21% higher than the donor population *(351)*; in a study of seroconverting transfusion recipients, risk was greater with PRBC stored ≤4 days *(352)*. There are no recognized consequences of transfusion-mediated infection at this time *(315,347)*. A recent editorial concluded that testing for

HHV-8 in volunteer donor units is not an option and that LR is likely to reduce risk of transmission; therefore, no action was deemed needed at present regarding HHV-8 *(353–355)*.

Human Immunodeficiency Virus Type 1 Within several years after the epidemic of the acquired immunodeficiency syndrome (AIDS) was recognized, its epidemiology was recognized to include transmission by sexual contact and by sharing blood-contaminated needles *(356–358)*. Avoiding sexual contact and needle sharing with homosexual males, individuals with multiple sexual partners, and individuals using injectable drugs became confirmed methods for avoiding infection with HIV-1, the cause of AIDS. Initially, the only mechanism for reducing what appeared to be transmission by transfusion was voluntary self-deferral of donors in high-risk groups, including sexual partners of members of the high-risk groups mentioned previously *(359)*. The directive to blood banks for voluntary blood donor deferral was issued on March 4, 1983 *(358)*. The first cases of transfusion-associated AIDS were reported in patients with hemophilia A *(360)*. Subsequent reports included infants and other adults without risk for AIDS other than transfusion *(359)*. The risk of transfusion was subsequently stressed to potential recipients by the recommendation for signed informed consent for nonemergent transfusions, issued on May 8, 1986.

Whole blood, blood cellular components, plasma, and clotting factors were implicated in transmission of HIV-1, but not immune globulin preparations and plasma-derived hepatitis B vaccine *(34,361)*. Ninety percent to hundred percent of patients transfused with blood contaminated with HIV-1 became infected *(8,362,363)*. Because blood donors with HIV-1 infection are usually asymptomatic, self-deferral by those in high-risk groups was important, in addition to assaying for antibody. The risk of HIV-1 infection was great for hemophiliacs before 1985; coupled with donor deferral and HIV-1 antibody testing, moist heat or solvent detergent treatment of clotting factors reduced this risk to a very low level for pooled plasma products *(364–368)*.

After the isolation of HIV-1 in 1983 to 1984 *(369–372)*, serologic tests for detection of antibodies to HIV-1 in patients with AIDS were described *(373–375)*. The assay techniques for these antibodies were quickly developed by private industry as an EIA, and blood centers within the United States initiated donor screening in March 1985 *(376)*. The blood supply was thereby rendered safer *(377)*. Despite the lack of specificity of an initially positive EIA, this screening EIA soon was also used as a diagnostic test, coupled with a confirmatory Western blot (WB).

Because of this evolving diagnostic function of the EIA, the CDC and the ARC established alternate test sites in April 1985 for anonymous testing to prevent high-risk individuals from using blood donor sites for diagnostic purposes *(378)*. Individuals recommended for testing gradually evolved to include, in addition to the high-risk groups mentioned previously, pregnant women at high risk for HIV-1 infection, attendees of sexually transmissible diseases clinics and drug abuse clinics, and recipients of transfusions between 1978 and 1985. During this time, the definition of high-risk behavior warranting HIV-1 antibody testing and deferral from donating blood was expanded to include a single homosexual encounter since 1977, sexual contact with a prostitute, and residence in sub-Saharan Africa (because of HIV-2 risk). These attempts at high-risk donor self-deferral were effective, except among injectable drug users *(379,380)*. This broadened definition of high-risk individuals was promulgated because of the window period after infection before antibody to HIV-1 was detected (see later discussion).

In June 1986, notification was mandated for recipients of units of blood or blood products transfused before March 1985 that were subsequently determined to be seropositive for HIV-1. This "lookback program" allowed earlier medical evaluation, management, and observation of the natural history of HIV-1 infection in patients with well-defined dates of exposure.

With the use of the EIA, WB, and an antigen-capture EIA *(375,381,382)*, the serology of HIV-1 infection was defined (Fig. 67-6). HIV-1 is composed of several structural (glyco) proteins that elicit antibodies *(375)*. The core protein of 24,000 molecular weight (p24) correlates with active viral replication, appears early after infection, and coincides generally with plasma HIV-1 RNA levels (Fig. 67-6); its disappearance correlates with development of anti-p24. The envelope glycoprotein of 160,000 molecular weight (gp 160) is composed of a transmembrane subunit

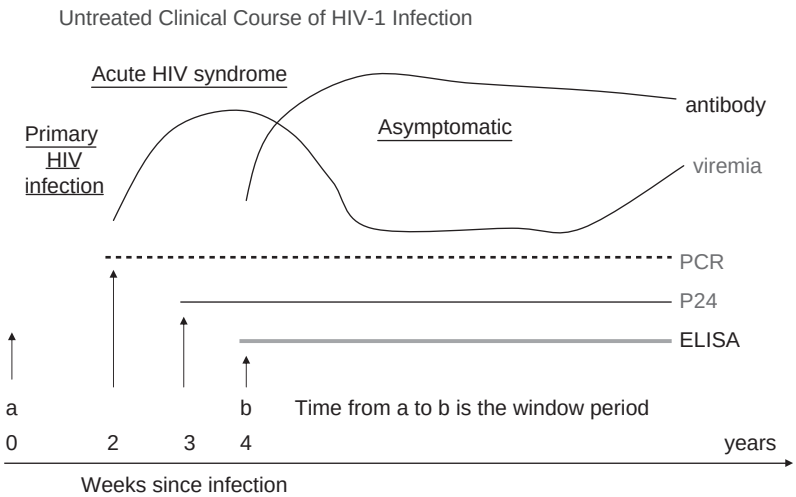

FIGURE 67-6 Chronology of human immunodeficiency virus type 1 infection defined by presence of core (p24) antigen, viral RNA by PCR and antibodies by ELISA. (*Source*: S Conway and John G. Bartlett, 2003; Courtesy of John G. Bartlett, Johns Hopkins University).

(gp 41) and an attachment subunit (gp 120); the host makes an antibody to each of these components. Internal polymerase gene products include the reverse transcriptase protein (p66, p51) and an endonuclease (p31); antibodies are made against each of these gene products. The first-generation EIA detected antibody to any of these proteins, because an impure virus lysate was used; however, the WB (and a radioimmunoprecipitation assay) allow differentiation of antibodies to each antigen *(375)*. Other confirmatory antibody assays used to demonstrate infection with HIV-1 are available, but further testing of blood beyond antibody assays necessitates tests for HIV-1 detection (p24 antigen capture EIA, viral culture, or NAT [proviral DNA or viral RNA]) *(375)*.

Because a lysate of human cells infected with HIV-1 was used as the antigen source for the first-generation EIA, antibodies to human cell antigens (and not viral antigens) in human serum caused false positivity of the EIA and resulted in its lack of specificity despite sensitivity; although the WB assay for antibodies used the same lysate, the viral (glyco) proteins were separated from each other and from contaminating human cell antigens electrophoretically, thereby allowing differentiation of antibodies and greater specificity *(378)*.

The sequence currently utilized for testing for HIV-1 in donor units is depicted in Figure 67-7. The criteria for a positive WB have been defined by the CDC as the presence of antibody to p24 and antibody to either gp 41 or gp 120/160 *(383)*. Using this sequence of testing (Fig. 67-7), estimates of the frequency of transfusion of donor blood infected with HIV-1 ranged from 3 to 26 per 1 million transfusions with early EIAs *(384–388)*. The most recent estimate using contemporary antibody assays approximates the lower frequency of 1 in 493,000 donor units (0.0002%) or less *(8)*. The entire antibody testing sequence, even with first-generation EIA and WB, had a positive predictive value of 81% to 100% with a 99% to 100% specificity *(389)*. Follow-up evaluations of blood donors with indeterminate WB patterns (Fig. 67-7)—the presence of one or more antibodies but not enough to meet the definition of positive—have shown that these donors or recipients of their blood never develop serologic evidence of infection *(390–394)*.

Because of the window period with EIAs for HIV-1 antibody (between infection of a patient and seroconversion), rare transmission of HIV-1 could occur by transfusion *(8,395,396)*. The window period was estimated at 42 to 45 days with the HIV-1 viral lysate EIAs and at 22 to 25 days with the contemporary HIV-1 recombinant protein supplemented EIAs (second- and third-generation EIAs) *(8,30,397,398)*. This window period may be further reduced to 6 to 16 days by assaying for p24 antigen or HIV-1 DNA in

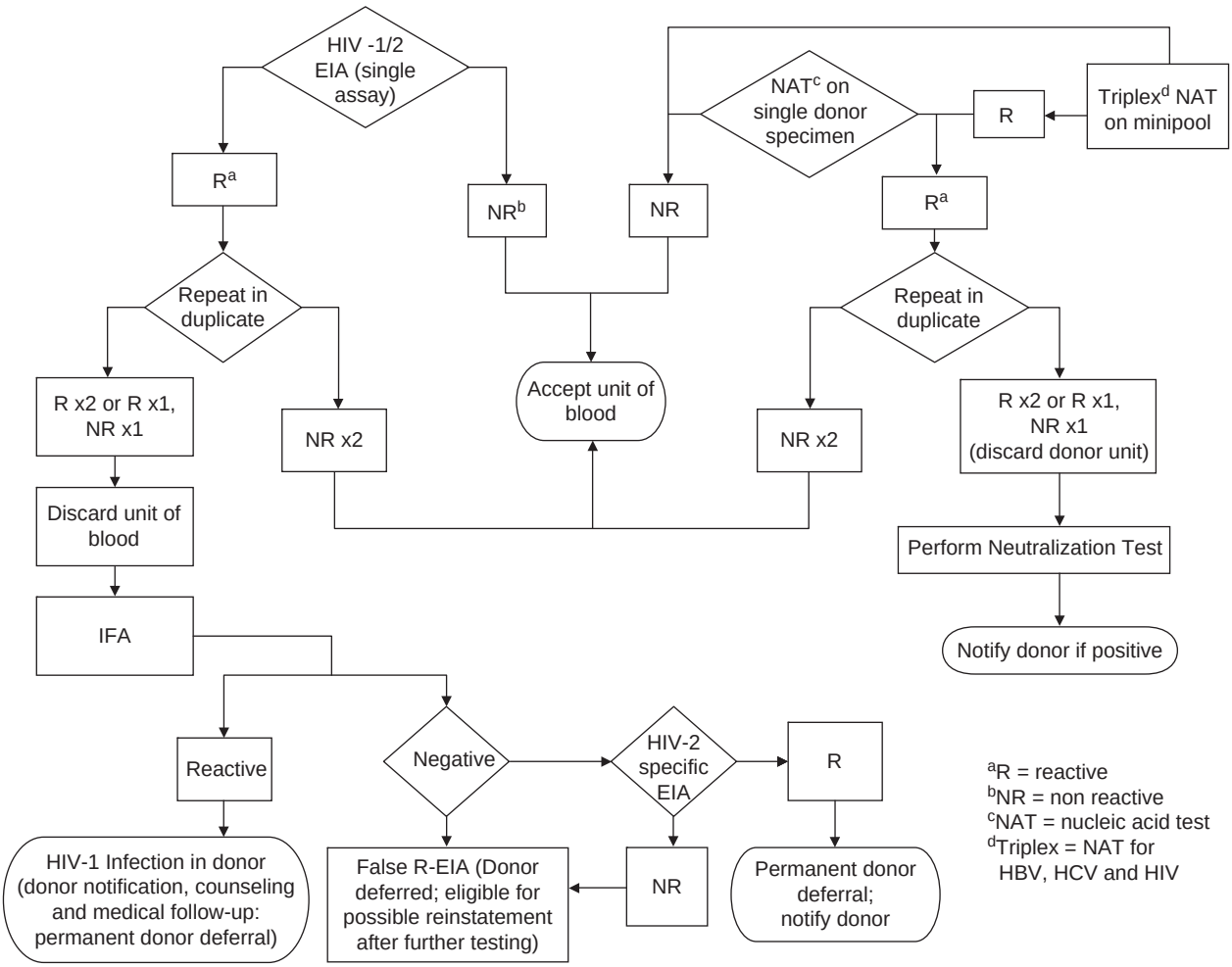

FIGURE 67-7 Algorithm for screening donor blood for human immunodeficiency virus type 1 and type 2 infections.

leukocytes by PCR *(8,30,398,399)*. Detection of HIV-1 RNA by PCR may reduce the window period after infection to 11 to 13 days *(8,30,398)*. Proposals to initiate p24 antigen testing on all blood and plasma donor units were not supported in the scientific community because of minimal estimated benefit (5–10 infected donor units detected per year in the United States) *(30,398–401)*. Despite this, in August 1995, the FDA recommended p24 antigen detection assays on all donor units *(402)*. The first p24 test was licensed in March 1996, at which time antigen screening of donor blood ensued *(30)* (Table 67-5). This assay is no longer used due to application of NAT.

In an attempt to make the blood supply additionally safe, in April 1999 NAT for HIV-1 was initiated on all donor blood in the United States *(403)*. PCR for both HIV-1 and HCV was initially combined and this duplex assay was applied to minipools of plasma from 16 donated units of blood for cost efficiency *(404–406)*; when positive by the combined assay, individual units that were part of the plasma minipool then undergo NAT for HIV-1 and HCV. It is estimated that the window period (preseroconversion) was shortened by PCR for HIV-1 by 14 to 15 days (the window for HCV is also shortened by 26 days) *(267)*. Dodd et al. *(172)* reported that from March 1999 through February 2002 more than 19 million units of blood were tested by NAT; five of these units were seronegative for HIV-1 but positive for HIV-1 RNA, for a rate of 1 per 3,962,000 units. These safety data reflect an estimated decrement of the window period of infectivity of donor blood for HIV-1 from 22 days with current antibody tests alone to 8 to 11 days by also incorporating NAT *(9,267)*. This rate is very close to that projected by Schreiber et al. *(8)* and in keeping with the fact that the risk of receiving an HIV-1 infected unit of blood today is so low that it is more easily estimated than measured *(8,172)*.

The prevalence of HIV-1 infection in donor units with antibody screening alone was very low (7.7–13 per 100,000 units; *407–409*). With antibody screening plus NAT, the current prevalence of HIV-1 infection in a volunteer donor unit is estimated to be 1.8 to 2.2 positive units per million donors (*162*,185). As a result of the current blood donor unit testing algorithm, including the third-generation EIA and PCR for RNA (the NAT for HIV-1 is now combined with HCV and HBV into a triplex NAT), the risk of receiving a unit of blood transmitting HIV-1 is estimated to be 0.00004% to 0.00005% (or 1 per 2,300,000 units transfused; *9,132*,144,*172*). Despite such sensitivity of this testing algorithm and very low risk, transmission of HIV-1 from an infected unit to two recipients has been reported in Singapore using identical screening assays *(410)*. The cost of NAT testing for HIV-1 is several hundred million dollars annually to avert 4 to 7 HIV-1 positive units being transfused *(186)*. Other transfusion risks now deserve more attention for their potential clinical benefit than further efforts at risk reduction for HIV-1.

The rarity of HIV-1 infection in seronegative blood donors has been confirmed by the use of HIV-1 culture, in addition to PCR, to detect HIV-1 infection in donor blood (*9,132*,144,*411*). In addition to all blood donors being screened for HIV-1 infection, all organ, tissue, and semen donors undergo self-deferral for high risk and are screened for antibody to HIV-1 *(367)*; transmission has occurred in this setting *(412)*. Because 40% of HIV-1–seropositive individuals also have anti-HBc, screening for this surrogate marker of HCV and for prior HBV infection has also contributed somewhat to the risk reduction for HIV-1 transmission when antibody tests alone were used as screening *(179)*. However, the continued value of the anti-HBc assay in this regard has been questioned *(413)*. Screening donated blood for syphilis also possibly contributed to further risk reduction for HIV-1.

In addition to self-deferral for those in high-risk groups and antibody screening, other attempts have been made to enhance the safety of blood for HIV-1 infection. EIAs and to some extent PCR tests for HIV-1 infection have been modified to include non-B subtypes (M subtype and group O) to broaden the scope and sensitivity of the assays *(414)*. LR may reduce but not eliminate the infectivity of donor blood *(415)*. Experimental studies of photoinactivation of HIV-1 in whole blood have been reported *(368,416)*. Immune globulin preparations are already safe because of Cohn fractionation, and clotting factor and plasma products have been made safe by the application of heat treatment with steam vapor and solvent–detergent treatment *(361,363,368)*. Additional chemical treatments of clotting factors have been suggested, in addition to the possible future use of monoclonal antibodies to inactivate HIV-1 *(363)*. Synthetic production of clotting factors by genetic engineering and the use of artificial blood may also become available (see later discussion).

Human Immunodeficiency Virus Type 2 HIV-2 is a retrovirus currently endemic in West Africa. Producing a similar illness, it has been reported in immigrants to the United States *(417–419)*. Despite the low prevalence of HIV-2 infection in the United States, screening of donor blood for antibodies to HIV-2 began in June 1992 using a combined HIV-1 and HIV-2 recombinant viral protein antigen preparation in an EIA *(420)*. The testing algorithm for HIV-2, if the combined HIV-1 and HIV-2 EIA is positive but assays for HIV-1 are negative, follows that outlined in Figure 67-7. If the serum specimen is repeatedly reactive by the combined HIV-1 and HIV-2 EIA, a WB for HIV-1 is performed; if this is negative or indeterminate, an HIV-2–specific EIA is performed, followed by an HIV-2–specific WB *(420)*. The first two cases of HIV-2 infection among blood donors have been reported *(421)*, but this is a rare event.

Human T-Cell Leukemia Virus Types I and II Human T-cell leukemia virus type I (HTLV-I) is a chronic latent retrovirus infection epidemiologically linked to the islands of southwestern Japan and the Caribbean, where 20% of adults and 2% to 5% of blacks are seropositive *(418,419)*. This virus is also endemic in the southeastern United States. HTLV-I infection is rare overall in the United States population, occurring in 9 to 80 of 100,000 blood donors *(407,417,422–424)*. In Italy, this infection has been found serologically in 290 of every 100,000 donors; this higher rate of infection is believed to reflect frequent infection among persons using injectable drugs in Italy *(425)*. Transmission occurs from mother to child primarily through breastfeeding; transmission also occurs by sexual contact, by contaminated needles, and by transfusion of whole blood, packed cells, and platelets (144,*418,419*). Although not totally safe, blood derivatives such as coagulation

factors seem to be free of transmission risk because of the intraleukocytic location of the virus *(418,419)*. From 30% to 63% of recipients of cellular blood products, 40% of platelet recipients, and 28% of recipients of RBC units from infected donors become infected; cell-free products may pose no risk *(423,426–428)*. Storage of units of RBCs for more than 14 days may eliminate the risk of transmission of HTLV-I and HTLV-II from an infected donor *(427)*. Antibodies have become detectable by 3 to 6 weeks after transfusion with units seropositive for anti-HTLV-I; IgM antibodies, detected early, became undetectable within a few months. Although the risk of transmission of HTLV-I infection by transfusion had been estimated at 0.024% per unit before HTLV-I EIA screening *(388,428)*, estimates of this risk after introduction of the EIA suggest a rate as low as 0.00015% to 0.002% before LR *(8,429)*. The combined HTLV-I and HTLV-II viral lysate and recombinant antigen EIAs have resulted in this lowered risk. Since implementation of LR, it is believed that the risk of receipt of an infected donor unit is now 1 per 2,993,000 units (Table 67-6) (0.00003%; 144).

Infection with HTLV-I has been linked with the development of human T-cell leukemia, which may be either a smoldering or a fulminant leukemia, associated with hypercalcemia, hepatosplenomegaly, lymphadenopathy, and skin lesions *(418)*. Circulating lymphocytes with indented nuclei are suggestive of the disease. After a latency of up to 20 years, the risk of developing this leukemia after HTLV-I infection is estimated at 1 in 80 *(418)*. HTLV-I infection has also been linked with tropical spastic paraparesis *(430)*.

HTLV-II is not linked definitively with any particular disease process but has been associated with atypical hairy cell leukemia and a chronic neurodegenerative disease *(418,419,428,431,432)*. Transmission of HTLV-II is epidemiologically linked with transfusion but primarily with injectable drug use in the United States *(407,433–435)*. Murphy et al. *(424)* have associated HTLV-II transmission, focused on the West Coast, with injectable drug use and secondary sexual transmission; seroprevalence among blood donors from 1991 to 1995 was 0.0223%.

Because of the 84% homology of the p24 core antigens of HTLV-I and HTLV-II, the EIA for HTLV-I may detect infection with HTLV-II *(429,434)*. Although the incidence of HTLV-II infection in the United States is low, in some areas HTLV-II is at least as common as HTLV-I *(424,427)*. A specific HTLV-II screening test for donor blood is currently not performed; a combined recombinant antigen HTLV-I and HTLV-II EIA serves this function *(428,434)*.

Serologic methods used to document HTLV-I and HTLV-II infection include EIA, immunofluorescence, WB, and radioimmunoprecipitation assay *(418,428,434)*. The EIA and the WB are similar to those performed for HIV-1, with similar gene products. The first-generation EIAs used HTLV-I viral lysates or recombinant gene products as antigens for antibody detection *(428)*; these assays had a high degree of crossreactivity for HTLV-II but failed to detect 9% to 45% of HTLV-II–positive blood specimens *(422,428,434)*. They were also prone to some false positivity for HTLV-I; however, surveys suggest a specificity of 98% and sensitivity of 96% to 99% for HTLV-I–infected donor units *(434)*. There was no crossreactivity of HTLV-I–positive specimens in the HIV-1 EIA *(418)*; however, 70% to 78% of HIV-1 EIA positive, WB indeterminate specimens reacted in the HTLV-I EIA *(418)*. On November 29, 1988, the FDA issued the initial directive for anti-HTLV-I testing of all blood donated for cellular products (but not for plasma). The algorithm for testing follows that for HIV-1 (Fig. 67-7).

Second-generation EIAs for HTLV-I and HTLV-II have combined the viral lysate or recombinant gene antigens with a recombinant transmembrane envelope antigen (rgp21e) that crossreacts between HTLV-I and HTLV-II *(428,436)*. Although this assay remains incompletely sensitive for HTLV-II, its specificity and sensitivity for HTLV-I antibodies was further improved *(428)*. Newer third-generation EIAs for HTLV-I and HTLV-II were introduced, combining both HTLV-I and HTLV-II recombinant antigens or viral lysates; these assays are variably more sensitive than second-generation assays *(428)*. In 1998, the combined third-generation HTLV-I and HTLV-II viral lysate or recombinant antigen EIA was implemented by blood centers (Table 67-5).

For repeatedly reactive anti-HTLV-I and HTLV-II EIA donor units, specimens are initially tested with a WB that can differentiate infection with HTLV-I or HTLV-II *(428)*. However, the WB is indeterminate in 38% to 75% of anti-HTLV-I and anti-HTLV-II reactive donor units *(428)*. Most of these indeterminate specimens are PCR negative, implying a high WB false positivity resulting from indeterminate reactions. A recently developed RIBA is more specific, resolving 66% of WB indeterminate reactions *(428)*. Therefore, the RIBA may be a more sensitive and specific confirmatory assay for HTLV-I and HTLV-II than WB, because it can detect antibodies to the viral envelope glycoprotein; WB is more sensitive for antibodies to core proteins, which are the frequent cause of false positivity *(425)*. However, other surveys report improved HTLV-I and HTLV-II WB specificity (>97%), but there are also continued problems with its sensitivity (<65%) *(434)*.

DNA PCR has been used to confirm HTLV-I and HTLV-II infection in lymphocytes of seropositive donors. Of patients with a positive HTLV-I and HTLV-II EIA, DNA PCR confirms infection with HTLV-II in 42% to 52% *(422)*. By DNA PCR, up to 15% of persons with a positive EIA may be uninfected with either virus *(422)*.

HTLV-I or HTLV-II infection has been found in 0.014% to 0.021% of all blood donors in the United States *(422)*. After institution of donor questionnaire screening and testing of all donor blood by the HTLV-I EIA, this rate dropped for HTLV-I and HTLV-II to about 0.0014% *(422,429)*. The risk of HTLV-II is about three times higher in first-time blood donors compared with HTLV-I *(10)*. There is considerable geographic variation in seroprevalence. Generally, higher seropositivity rates for blood donors for HTLV-II are seen on the West Coast and in women *(162,422,424)*. Rates are highest among African Americans, Hispanics, and Asians; among injectable drug users or their sexual contacts; among persons born in the Caribbean or Japan; and among persons with a history of blood transfusion. In addition to serologic screening, self-deferral of these high-risk groups (as for HIV-1) is an important adjunct. The risk of transmitting HTLV-I or HTLV-II is now estimated at 1 in 2,993,000 transfused units (0.0003%; 144). In addition, the overall risk for HTLV-II infection in blood donors has declined due to LR (144,*172*).

TT Virus and Sen Virus Torgue Teno virus (TTV) is named for the initials of the patient in whom it was initially

defined in 1997; this patient had hepatitis, thereby linking TTV possibly to non-A, non-B, non-C, non-D, non-E hepatitis *(437,438)*. TTV is a circular, single-stranded DNA virus with up to 16 genotypes, which was initially thought to be another agent of PTH *(437)*. TTV is present in 5% to 50% of volunteer blood donors in the United States but has a much greater seroprevalence in less well-developed areas of the globe, varying from 14% to 86% of populations (144,*437*). TTV is epidemiologically linked to multiply transfused patients and injectable drug users but probably also has a fecal–oral route of spread *(437)*. Although TTV is transmitted by transfusion and found in higher titer in liver than in serum, it is not associated with hepatitis or other liver disease, despite its apparent replication there *(437,439–442)*. Given these data, there is no reason to assess prospective donor units for the presence of TTV at this time.

SEN virus (SENV) was isolated from an injectable drug user and reported in 2000 *(443)*. SENV is a circular, single-stranded DNA virus with eight strains (A through H) and is related to TTV with a seroprevalence in blood donors of 1.8% to 13%; up to 70% of multiply transfused patients are seropositive *(443–445)*. SENV DNA becomes undetectable in serum within 6 months in 55% of patients after transfusion acquisition *(445)*. SENV-H is most common in the United States; 7% to 76% of patients with HCV and 20% to 60% of HBV infected patients are SENV seropositive *(444,445)*. However, the presence of SENV does not affect the severity of HCV or HBV infection, or the response to therapy for HCV, despite long-term persistence of SENV *(445)*. Other studies continue to find no etiological role of SENV in chronic hepatitis *(445a)*. Without a relationship to hepatitis or other disease, there is no reason to test donor units for SENV presently.

West Nile Virus Considerable discussion has developed in the last 5 to 10 years about emerging pathogens, especially as they relate to the safety of the blood supply (*354*,*355*,446,447). Included among these potential threats to the safety of transfused donor units are West Nile virus (WNV), parvovirus B-19, prion disease, malaria, Babesiosis, Tryponasomiasis, leishmoniasis, Dengue, and Chikungunya viruses, among other less likely transmissible agents (*354*,*355*,446,447). Much of such discussions center around the political (and unreasonable) demand for a "zero-risk" product, an unachievable goal *(354)*. Within this chapter a number of these realistically potential emerging pathogens will be covered.

WNV is an Old World Flavivirus, previously endemic in Africa, Asia, the Middle East, and southern Europe *(448)*. Since its initial recognition in 1937 in an ill woman in the West Nile region of Uganda, there were infrequent human outbreaks; notable exceptions have been an Israeli nursing home outbreak in 1957 and outbreaks in Romania (1996), Russia (1999), and Israel (1999, 2000) *(448,449)*. In late summer 1999, eight patients with encephalitis were initially recognized as a WNV outbreak in New York City; this led to the recognition of 59 patients hospitalized for WNV infection *(450)*. In subsequent years, WNV spread via its mosquito vector and/or its migratory bird definitive hosts (crows, ravens, blue jays) to at least 44 of 48 continental United States *(451)*. Humans and horses are dead-end hosts after the bite of an infected mosquito *(448)*. In the United States, there were 3,389 human cases during 2002 with 201 deaths. Four of every five patients are asymptomatic, and only 1 in 10 infected patients seek medical attention *(448)*. One in one hundred and fifty infected patients develops meningoencephalitis or a poliolike syndrome *(448,452)*.

Because of the presence of mild illness after infection, especially in young adults (the likely blood donor population), and because of an incubation period of 3 to 14 days *(448,449)*, the potential for transfusion transmission associated with viremia was evident. Viremia rarely lasts more than 2 weeks (at high levels) without antibody, though may persist for 2 months occasionally; viremia averages 6 days' duration *(354,453)*. During the WNV epidemic of 2002, at least six patients developed confirmed WNV infection via transfusions, with an additional 27 suspected occurrences *(454)*. During the epidemic in New York City in 1999, the risk that a blood donor would have WNV in the blood was estimated at 2 per 10,000 donors *(455)*. Because of these risks, the FDA initially released its guidance for assessing donor suitability and blood product safety regarding possible WNV infection in the donor on October 25, 2002 *(456)*. Self-reported symptoms were and continue to be of little value in predicting WNV infection in the donor *(457,458)*. Transfusion and donor-organ related transmission of WNV continued to occur *(459,460)*.

For these reasons, NAT for WNV RNA was initiated in all donor centers by July 14, 2003 (Table 67-5) *(453)*. Minipools of 6 or 16 specimens (MP-NAT) were assayed. If the MP-NAT were positive, specimens from individual donor units (ID-NAT) are tested. However, despite MP-NAT of donor units, transfusion-related WNV infections did occur, probably related to donor units with low-level viremia *(461–464)*. It had previously been noted that some donor units were only positive for WNV-RNA testing by ID-NAT and not by MP-NAT *(465)*. Due to this issue of false-negative MP-NAT for WNV, selected ID-NAT was implemented at many centers in 2004 and 2005 *(466)*. In 2008, the FDA issued guidance for each blood donation center to develop criteria for switching from MP-NAT to ID-NAT for WNV during periods of high WNV activity *(467,468)*. Some centers make such a switch when two MP-NAT are confirmed positive from donors living in the same postal zip code within a 7-day period, while others make this switch if only one MP-NAT is positive for WNV within their collection area *(468)*. With the sensitivity and positive predictive value of ID-NAT for WNV estimated at 92% to 99%, respectively, and with the current adjustments to screening techniques depending on WNV activity, the blood supply is quite safe from risk of WNV transmission by donor units (Table 67-6) *(468,469)*.

COLORADO TICK FEVER VIRUS, ERYTHROVIRUS B-19

Other potential viral causes of post-transfusion infection include Colorado tick fever virus (CTFV) and parvovirus, now Erythrovirus B19. The rarity of reports of transmission by transfusion and the usual association of illness in the potential blood donor with CTFV infection argue for no additional donor precautions at this time despite the development of a PCR assay for CTFV RNA in human serum *(344,470–472)*.

Erythrovirus B-19 is now divided into genotypes 1 to 3 *(473)*. After respiratory acquisition of infection, the immunocompetent patient (usually a child) develops viremia with or without symptoms 1 week after infection; by 3 weeks specific IgG immunoglobulin develops and viremia clears, usually by 6 months after infection *(473)*. However, persistence of viremia for 6 months or longer can be seen in normal hosts, usually without symptoms *(474,475)*.

Questions continue to be raised about the need for studies to define the risk of B19 transfusion-related infection, studies to improve detection techniques, and studies to refine inactivation techniques *(473,474,476)*. These concerns are raised because of continued but infrequently recognized episodes of transfusion-related infection *(477–480)* and one reported episode of B19 transmission by intravenous immune globulin *(481)*. B-19 DNA positivity rates are 37% to 67% for untreated plasma pools, 25% for albumin, 100% for factor VIII, and 20% for IV-Ig *(473)*. Ten percent of clotting factor concentrates are contaminated because of incomplete inactivation by dry heat, wet heat, or solvent/detergent treatments and may transmit infection *(476,482–486)*. Plasma pools usually have detectable B19 DNA after treatment *(473,487)*. The frequency of B19 DNA among blood donors is stated to be 1 in 20,000 to 50,000 donor units but may be higher (144,*354*,*473*,*487–489*). The frequency among Pittsburgh blood donors was reported to be 0.1% during June and July, the peak of the B19 season *(490)*; 2 of 11 recipients of B19 DNA positive blood developed clinically apparent infection. However, clinically consequential B19 posttransfusion infection is uncommon *(474,486,487,491)*. Given the problems with persistence of B-19 viremia, though often at lower levels with the presence of IgG, currently only plasma pools are tested for B-19 DNA *(474,487)*. If the pool has $<10^6$ IU/mL of B-19 DNA by NAT or $<10^4$ genome equivalents/mL, it is accepted; this technique has made plasma pools more safe with low or undetectable levels of B19 DNA *(492)*.

There is a report of adding high-titered IgG to plasma pools to neutralize residual B-19 *(493)*. Additional efforts to reduce or eliminate B-19 infectivity of blood donor units or plasma derivatives are focused on use of amotosalen or riboflavin treatment, followed by ultraviolet (UV) light exposure *(473,494)*; riboflavin treatment with UV light would be applicable to platelets, RBCs and plasma, while amotosalen has been applied to platelets.

Regarding the risk of RBC donor units at present for transmitting B-19, no adverse clinical outcomes have been demonstrated *(473,474,484,487,491)*. These observations are probably the result of the high frequency of B-19 IgG in the recipient population and likely low levels of B-19 DNA in donor units when present *(473,474)*. Use of NAT screens for DNA on donor blood does not seem warranted *(474)*.

VACCINIA VIRUS

Vaccinia virus is a double-stranded DNA virus, related to cowpox virus, which has been used to immunize humans against smallpox (caused by variola virus). Use of this vaccine on a routine basis had ceased in 1971 to 1972, and in 1977 the last case of smallpox was documented in Somalia *(495)*. Because of the terrorist threat to use biologic weapons, on December 13, 2002, a presidential decision was made to initiate a smallpox vaccination campaign for individuals likely to encounter the first patients after a bioterrorist exposure. During a secondary phase additional healthcare workers, emergency personnel, policemen, and firemen on a voluntary basis were to receive the vaccine.

After percutaneous inoculation, vaccinia virus multiplies locally causing in succession a papule, vesicle, and pustule, which ruptures, crusts, and heals with scab formation. Investigations using the New York City Board of Health strain of vaccinia had previously documented viremia during disseminated vaccinia infection *(496,497)*; there are reports from 1930 and 1953 of isolation of vaccinia virus from blood 3 to 10 days after immunization *(498)*. Accordingly, because of the potential for vaccinia viremia in a recent recipient of smallpox vaccine, the FDA issued a "Final Guidance" in December 2002 recommending blood donor deferral for 21 days after vaccine receipt or until the scab has separated if there are no complications to vaccination; this and deferral if complications develop are summarized in Table 67-2 *(498)*. However, recent observations have failed to detect viremia in the plasma or blood of vaccinees by cell culture *(499)*.

OTHER ARTHROPOD-BORNE VIRUSES WITH A TRANSFUSION RISK

YF virus is endemic in Central and South American and in sub-Saharan African countries. A live attenuated virus vaccine is available; the Red Cross asks recipients to defer donation of blood for 2 weeks after vaccine receipt (35). The report of collection of donor blood from US active duty military trainees 4 days after YF vaccine receipt resulted in an investigation *(500)*; six units of blood products were transfused into five recipients. While one of the recipients died of an unrelated cause, the four remaining recipients had serologic evidence of response to YF vaccine virus. This report verified the relevance of deferral of recent recipients of live virus vaccines.

Perhaps more relevant are reports of two other arthropod-borne viruses and their threat to transfusion medicine. Dengue hemorrhagic fever was recently transmitted from an asymptomatic blood donor to the donor unit recipient in Singapore *(501)*; given the continuous threat of importation of Dengue virus (DV) from the Caribbean into the United States and the presence of its vectors, such a threat to the US blood supply is very real but yet not a reality (*354*,*355*,446,*502*). Using transcription-mediated amplification, DV has been detected in blood donor units in Honduras, Brazil, Australia, and Puerto Rico *(502)* and has been recognized as a considerable risk in Singapore *(503)*.

Chikungunya virus (CHIKV) has recently caused outbreaks originating in Kenya with spread to islands in the Indian Ocean, parts of India, Southeast Asia, and Europe (Northeast Italy; *504*). This epidemic has been fostered by a single amino acid substitution due to a base mutation, leading to enhanced transmissibility by its previously secondary mosquito vector, *Aedes albopictus*, while retaining *Aedes aegypti* as a vector. Given the high levels of viremia associated with CHIKV, the propensity of *A. albopictus* for

twice daily feeding and given our "Global Village" due to the ease of world travel, spread of CHIKV seems inevitable (as evidenced by WNV; *355*,446,*504*,*505*). The transfusion transmission risks of CHIKV have already been realized in epidemic areas; during the CHIKV epidemic on Reunion Island in the Indian Ocean, the risk of transfusion transmission of CHIKV peaked at 1,500 units per 100,000 donor units *(506)*. A crisis was averted by interrupting blood donations on the island. On Reunion Island, photochemical inactivation of CHIKV was effective for platelets as a pathogen inactivation technique *(507)*. A similar risk of blood donor unit transmission was averted in Northeast Italy after CHIKV was introduced by a traveler, with 217 secondary cases due to spread by mosquitoes; donor collections were reduced to avoid contamination of the blood supply *(508)*. The presence of both *A. aegypti* and *A. albopictus* in the United States, especially in the Southeastern states, makes the United States especially susceptible to the introduction of CHIKV and its threat to transfusion medicine.

RECENTLY RECOGNIZED POSSIBLE VIRAL THREATS TO THE BLOOD SUPPLY

Xenotrophic murine leukemia virus–related virus (XMRV) is a gammaretrovirus initially recognized in the prostatic cancer tissue of men undergoing radical prostatectomy *(509)*; subsequent assessments of similar tissue specimens have failed to confirm this association *(510)*. In 2009, a report noted the presence of XMRV proviral DNA in mononuclear blood cells of 67% of patients with chronic fatigue syndrome (CFS), compared to 3.7% of controls *(511)*. Reports from the UK and the Netherlands have failed to confirm this association *(512–514)*. The seroprevalence of XMRV in US blood donors may be 0.1%, but little else is known at present about the transfusion and health risk of XMRV. However, the Canadian Blood Donor Services has already opted to exclude CFS patients from blood donation.

PRION DISEASE

Sporadic Creutzfeldt-Jakob disease (sCJD) is transmitted by a proteinaceous infectious particle (prion). After a 4- to 25-year latency, sCJD has been recognized as acquired by corneal and dura mater transplants from infected donors, through use of human pituitary-derived growth hormone, and through reuse of electroencephalographic electrodes. A group in the United Kingdom has reported the transmission of bovine spongiform encephalopathy (BSE) to sheep via transfusion of whole blood from a sheep with incubating BSE *(515,516)*. There are no data in humans to support transfusion of blood or blood products as a mechanism for transmission of sCJD (*354*,446,*517*). More than 100 recipients of blood from patients who later developed CJD are being followed, some for more than 27 years; none has developed sCJD during follow-up *(518)*.

There is a greater concern for transmission of variant CJD (vCJD) by blood products (*354*,446,*518*); it is postulated that variant vCJD protein might be transmitted more efficiently with a shorter incubation period. Surveillance and lookback studies have defined at least 184 patients with vCJD acquired through transfusion worldwide *(518–521)*. Uncertainty surrounds the means to assure that plasma products are rendered safe *(522,523)*. Attempts using LR only partially reduced infectivity for cellular products (42–72% reduction; *524,525*). Prion reduction filters, if the infectious unit is not red cell bound and in lower titer, have had limited success *(526–530)*. Substantial removal of vCJD protein has been achieved with washed RBCs *(531)*.

In 1987, the FDA required permanent deferral of potential blood donors treated with human pituitary-derived growth hormone; on August 8, 1995, permanent donor deferral was also required for recipients of dura mater grafts and for donors with a family history of CJD *(30)*. The twenty-sixth edition of the AABB guidelines also apply permanent deferral status to anyone at risk for vCJD (35) (Table 67-2). Donor deferral remains the backbone of prevention, with prudent utilization of blood and blood products *(527)*. There has been minimal loss of potential donors using these deferral criteria *(532)*.

MALARIA

Transfusion-related malaria is the most common transfusion-induced parasitic infection worldwide, especially in the tropics, but it is rare in the United States (*354*,*355*,446,*533*,*534*). The average annual rate has remained 0.25 cases per million units of blood collected through 1987 or about three cases per year *(354,533,534)*. Mungai et al. *(535)* reported 93 cases of transfusion-transmitted malaria between 1963 and 1999 in the United States; 35% were due to *Plasmodium falciparum* and 27% each were due to *Plasmodium vivax* and *Plasmodium malariae*. Due to delay in diagnosis, 10 of these 93 patients died (11%) and approximately 62% of these cases could have been prevented by appropriate application of donor guidelines. Since its eradication from the United States in the 1940s, *P. malariae* had been the most common form of malaria associated with transfusion in nonendemic areas because of its persistence; however, *P. falciparum* and *P. vivax* are now becoming more important because of immigration and air travel associated with tourism *(534,535)*. This is also the experience in Canada *(536)*. In the last decade, most infected donors were immigrants *(535)*. Recently, *P. knowlesi*, previously restricted to monkeys, has infected humans (446); whether or not this evolution will affect the epidemiology of malaria is unclear.

Malaria has been transmitted by transfusion of whole blood, fresh plasma, and platelets *(533,534)*. The incubation period after transfusion is from 1 to 4 weeks. Diagnosis in the transfused patient often is delayed because of lack of a history of travel to an endemic area. Increased morbidity and occasional mortality result. Malaria has also been transmitted by renal transplantation *(534)*. Healthcare-associated transmission by needle stick and a multidose vial have been described *(534)*. The current guidelines recommended by the AABB (Table 67-2) should enhance prevention of this transfusion-related illness but do not obviate risk in all circumstances *(537,538)*. The current risk of transfusion of a unit of blood in the United States from a donor with malaria is estimated at one for every 3 to 4 million units (Table 67-6) *(354,368)*. Some European

Countries and Australia perform an antibody test on deferred potential donors (EIA); if negative, the donor is reinstated (*355*,446,*539*).

Previous options to donor deferral (which is deemed wasteful of potential donors in current format) include microscopic exam of blood smear, EIA for IgG in nonendemic countries, and providing antimalarials to transfusion recipients in endemic areas (540). Direct smear of donated blood for parasites is insensitive for detection *(535)*. Serologic screening with indirect fluorescent antibody, indirect hemagglutination or EIA is one of the most sensitive methods available for diagnosing plasmodial infection, but its disadvantages as a screening test include cost, seronegativity during early parasitemia, and exclusion of immune donors after adequate treatment (*534*,540,*541*,*542*,*543*). Detection of circulating antigens and nucleic acids (e.g., by PCR) is a very sensitive technique that may become useful (540,*544*,*545*). A combination of antigen and antibody detection can enhance sensitivity for plasmodial infection to 88% *(542,546)*. Due to the effects of donor deferral upon donor unit supply and the need to recapture such deferrees *(547,548)*, a number of suggested changes to the current reliance on donor deferral in the United States have been recently suggested, including decreasing the deferral duration to 3 months for travel to Mexico, universal use of LR filters (to which *P. faciparum* RBC adhere), and use of pathogen inactivation for RBC units *(549–552)*. No doubt there will be modifications forthcoming to current malaria prevention guidelines.

BABESIOSIS

Babesia microti is a zoonotic protozoal parasite of RBCs first reported in 1966 and transmitted to humans by tick bite and occasionally by transfusion (*354*,*553*,*554*,*555*,556). Babesiosis is second only to malaria as a reported transfusion-transmitted protozoal infection *(554)*. Most infections in endemic areas (primarily the Northeast, California, northern Midwest, and Northwest) are asymptomatic or subclinical, unless in a splenectomized host, when infection may be fatal *(553)*. Seroprevalence ranges from 0.3% in Connecticut residents to 9.5% of patients with confirmed Lyme disease (556). Serosurveys of blood donors in the Northeast have shown seropositivity rates of 0.9% to 4.3% without a clinical history consistent with infection, and parasitemia occurs in 50% or more of seropositive patients (*368*,556,*557*,*558*). Because of the subclinical nature of acute infection, with parasitemia, the possibility of transfusion-related illness is expected, especially during May through September, when the primary vector, the nymphal tick, feeds. The estimated annual incidence of transfusion-associated babesiosis is one to two cases per million units transfused *(554)*, but this estimate is likely low due to underreporting (556); many such cases may be unrecognized. In Connecticut, the risk from one unit of PRBC may be as high as 0.17% (144,556). There is a 1.1% seroprevalence among blood donors in Connecticut *(557)*.

Transmission by packed RBCs, frozen-thawed blood, and platelets (because of free parasites in plasma) from asymptomatic donors has been well documented *(534,555, 559–563)*. The parasite may survive for up to 35 days at 4°C liquid storage *(563)*. The incubation period in posttransfusion babesiosis is 6 to 9 weeks, which is somewhat longer than for tick-borne disease (1–3 weeks; 556). The longer incubation period after transfusion is surprising, because up to 30% of RBCs may be parasitized in the infected normal host *(564)*. Clinical disease in transfusion recipients is unusual, however *(554)*. Interestingly, recent reports reflect either better reporting due to hemovigilance or increasing mortality over the last decade (nine deaths between 2005 and 2007; *565,566*).

Prevention of transfusion-related babesiosis relies on recognizing acute illness in a potential blood donor, deferring individuals from highly endemic areas from donating blood during May through September, avoiding donors with fever within the 2 months before donation, and eliminating potential donors with a history of tick bite *(553,554)*. A history of babesiosis is cause for permanent donor deferral (35) (Table 67-2). Serologic screens using indirect fluorescent antibody are not practical and are insensitive early in disease *(553,554)*. PCR is not yet available. Inactivation techniques applied to donor blood with promising results have included gamma irradiation, combined psoralens with UV light, and photosensitization with pheophorbide *(417)*. Pathogen reduction techniques have been advocated in endemic areas *(567)*. As deer herds increase in endemic areas, transmission by tick bite will increase, thereby enhancing the likelihood of an infected blood donor. Physicians must remain aware of babesiosis as a potential transfusion-related illness in an endemic area.

TRYPANOSOMIASIS

African trypanosomiasis (or sleeping sickness) is rarely transmitted by transfusion, because infected patients are usually symptomatic when parasitemic and thereby unsuitable blood donors; unusual asymptomatic parasitemic patients have accounted for rare transfusion-related disease *(534,563)*.

In contrast, blood transfusion is the second most common means for transmission of American trypanosomiasis, or Chagas' disease, in the endemic countries of Central or South America *(568,569)*. This was first recognized in 1952 *(534,563). Trypanosoma cruzi,* the etiologic agent, is naturally transmitted by various species of hematophagous triatomine insects (or reduviid bugs). Both mammals and humans are infected. The signs and symptoms of acute infection are so mild that they are unnoticed by the host or at least not attributed to *T. cruzi*. Untreated, such hosts remain infected for life, and parasitemia may be detected years after infection in up to 50% of patients *(368,534,563,569)*. Up to 20% to 40% of infected patients may develop cardiac or gastrointestinal symptoms after years or decades.

In Central and South America, 18 to 20 million people may have been infected in the past, but this number has fallen to 7.6 million by 2006 due to eradication efforts in Latin America *(569)*. However, Chagas' disease remains the most common transfusion-transmitted infection in endemic

areas *(368,568–570)*. Because of recent immigration to the United States from these areas, especially from Mexico, it is estimated that 100,000 persons in the United States are infected with *T. cruzi (569,571)*. The seroprevalence of *T. cruzi* antibodies in the US blood donor population ranges from 0.004% to 0.01% (1 in 25,000 to 1 in 5,400 donor units; *569,572*). The potential for infection of the US blood supply has been recognized, but concerns have been heightened by several reports of acute symptomatic infection in immunocompromised hosts *(534,573–575)*. Whole blood, packed RBCs, and platelets have a higher risk of infection than plasma; the parasite can survive storage at 4°C for 18 to 21 days and can survive freezing *(563)*. There have been seven reported episodes of transfusion acquired tryponasomiasis in the United States *(569)*. Transmission by renal transplantation has also been documented *(534,563)*. Although the likelihood of transmission by blood from an infected donor may range from 13% to 49%, most post transfusion infections are asymptomatic in immunocompetent hosts *(568,576)*. Those reports of more serious illness typical for compromised hosts raise concern about more widespread transfusion-related infection. Seropositivity rates in Los Angeles County have been reported to be 2.4% to 4% *(577,578)*. A report of questionnaire results of blood donors in 18 California donor centers identified risk factors for Chagas' disease in 1 of every 340 donors (living in endemic area for more than 1 year, living in dwellings with mud walls or thatched roofs, transfusion in endemic area, or history of Chagas' disease; *578*). With an up to 4% serologic positivity rate in a similar population, an infection rate of 1 in 8,500 donors can be estimated in this donor population *(578)*. Other serosurveys demonstrated infection in populations in Texas and New Mexico *(578)*. A Southwest Region American Red Cross serosurvey demonstrated 3 reactive units among 100,089 tested *(572)*.

Prevention in the United States is problematic. LR is not effective *(579)*. Detection of parasitemia is unlikely during chronic infection. Serologic testing with complement fixation, indirect hemagglutination, EIA, and the direct agglutination or recombinant immunoassays are used in areas of high endemicity; a lysate-based EIA for *T. cruzi* has been found to have 97.7% to 100% sensitivity and 99.9% to 100% specificity in the United States *(580–582)*. Despite low infection rates of blood donors in the United States, an EIA for *T. cruzi* was licensed on December 13, 2006, and universal blood donor screening was begun on January 29, 2007 (Table 67-5) *(582)*. As suggested by the AABB, deferral of donors with a history of Chagas' disease continues (Table 67-5) (35,*568*). A transfusion history in an area endemic for Chagas' disease should also be included as a deferral criterion *(578)*. Heightened awareness by health professionals about the potential transmission of *T. cruzi* by blood transfusion is also warranted, especially where Latin American immigrants have concentrated, such as Los Angeles, Chicago, New York City, Washington, DC, Miami, and possibly Texas and New Mexico *(541,563,568,572,578)*. If begun for other diseases (e.g., Babesiosis), efforts at pathogen inactivation with riboflavin, amotosalen, or thiopyrylium followed by UV light have been successful against *T. cruzi (583–585)*. Treatment of donor blood with gentian violet or crystal violet has also been described and used with good results *(568)*.

TOXOPLASMOSIS

Toxoplasmosis is a common infection of mammals and humans, usually acquired orally or congenitally and possibly by aerosol. The etiologic microorganism *Toxoplasma gondii* may survive at 4°C for up to 50 days *(563)*. Transmission by a transplanted organ (heart, kidney, bone marrow) has been documented *(534,541,563)*. Because asymptomatic prolonged parasitemia is uncommon, transmission by transfused blood is possible but has been documented only rarely *(586,587)*. Recent reports from Turkey, India, and Mexico have documented a 2.3% to 3.6% prevalence of IgM by EIA in blood donors from each country *(588–590)*; in Mexico, 78% of donors positive for IgM by EIA were positive for toxoplasma DNA by PCR *(588)*. Though declining from 1999 to 2004, the seroprevalence of toxoplasma IgG antibody by EIA in the United States is 10.8% among 6- to 49-year-old persons *(591)*. Given the infrequency of transfusion transmission and declining seroprevalence in the United States, routine screening of blood donors seems unwarranted *(368)*. Prevention of transmission by donor serologic screening or by use of prophylactic pyrimethamine in the transplant recipient in selected settings has been described *(534,541)*.

LEISHMANIASIS

Leishmania species have worldwide distribution in humans and mammals; the microorganism is transmitted by sandflies (or by *Phlebotomus* species in India). *Leishmania* microorganisms parasitize leukocytes and the organs containing tissue monocytes/macrophages; when found in blood, the microorganism is within leukocytes. Asymptomatic parasitemia is common with visceral leishmaniasis and such patients could be candidate blood donors. Transfusion transmitted infection is rare, with only a few reported cases, most recently in endemic areas of Greece and India *(534,563,592–594)*. None has occurred in the United States *(541,563)*. Among 21 EIA-positive asymptomatic volunteer blood donors in Rio de Janeiro, 5 were positive by NAT for DNA of *Leishmania donovani (595)*. PCR is actually more sensitive than antibody assays for diagnosis *(596)*.

In the United States, the immigrant or the traveler with infection would possibly be deferred because of signs of acute or chronic infection. No preventive measures are usually warranted except those for donor deferrals outlined in Table 67-2 *(368)*. However, military operations in the Middle East during 1991 resulted in a few cases of viscerotropic *Leishmania tropica* infection among returning military personnel. For this reason, the AABB, with the military, recommended deferral of military and civilian blood donors until January 1, 1993, if they had recently been in this area. Similar deferrals apply to those returning from subsequent conflicts in endemic areas (35). However, donors of plasma for further processing were not and need not be deferred. However, LR prestorage as practiced by American Red Cross Centers and many other blood collection agencies in the best recourse to prevent transfusion-transmitted leishmoniasis *(597,598)*. If implemented in the future, photochemical inactivation (with amotosalen, riboflavin, or thiopyrylium) also is effective on promastigotes in various preparations *(599–601)*.

SYPHILIS

Treponema pallidum is usually transmitted sexually or congenitally; less commonly, infection occurs by kissing, direct inoculation or, in the remote past, by transfusion *(602,603)*. Infection with *T. pallidum* induces a disseminated vasculitis with spirochetemia and secondary cutaneous, cardiovascular, neurologic, and other organ system effects. Transmission via transfused blood was recognized as early as 1915 *(602,603)*. Most infectious donors were in the primary or secondary stages of disease. However, many transfusion-related cases were probably unrecognized. Transfusion-related syphilis has not been recognized since 1966 *(604)*. The reasons for the lack of transfusion-transmitted syphilis include (i) serologic screening of all donor blood, (ii) the low incidence of syphilis in blood donors, (iii) an all volunteer blood donor pool, (iv) deferral of high-risk individuals, (v) the impact of refrigeration on spirochete survival, and (vi) the frequent administration of antibiotics to transfusion recipients *(605)*.

Although *T. pallidum* can survive in stored blood at 4°C for up to 4 days, its survival at clinically relevant concentrations may be only 2 days. During storage of blood at 4°C that was highly contaminated experimentally with *T. pallidum,* blood remained infectious for up to 5 days *(606)*. Platelets, which are stored at 22°C, may also transmit syphilis *(606)*.

Today, donated blood is routinely screened for syphilis in the United States, with a nontreponemal EIA or, most recently, an automated microhemagglutination-*T. pallidum*; the nontreponemal tests generally have lower sensitivity and specificity than treponemal tests *(602,605)*. It is argued that donor blood should continue to be screened for syphilis for multiple reasons: (i) the incidence of syphilis is increasing; (ii) there is an increasing demand for fresh blood components, obviating the inactivation of *T. pallidum* with storage for 72 hours at 4°C; (iii) screening identifies donors at high risk for other sexually transmissible diseases (e.g., HIV-1 infection; *606a*); (iv) the cost of screening is low; (v) screening remains legally required by the FDA, despite a decision by the AABB in 1985 to drop its requirement for syphilis screening; and (vi) screening identifies patients in need of therapy *(602,605,607)*. Other preventive measures for deferring donors who might be infected with *T. pallidum* are defined in Table 67-2.

Despite these arguments for continued screening, a strong case has been defined by Schmidt *(603)* to discontinue such screenings. Several recent publications add support to this opinion; Orton et al. *(608)* reported that between 1998 and 1999, among 169 sera that were FTA-ABS positive, none was positive for *T. pallidum* DNA and/or RNA. Therefore, even among units of blood screened as seropositive for *T. pallidum,* none is likely to be infectious. A recent publication also documented the lack of surrogate value of syphilis screening for other transfusion-transmissible infections *(609)*. An accompanying editorial comments that most positive screening tests for syphilis are biological false positives; those true positives are in donors with remote, treated infection *(610)*. Policy evolution in this regard awaits further study, given the desire for a zero-risk blood supply (446,*605*,*610*).

LYME DISEASE

Lyme disease is a tick-borne borreliosis caused by *Borrelia burgdorferi*. Like syphilis, Lyme disease results from vasculitis with associated spirochetemia. Its serologic diagnosis has become more reliable but remains somewhat cumbersome to differentiate active versus treated disease *(611)*. Although knowledge of the pathogenesis of Lyme disease supports the potential of transmission by transfusion, no case has yet been reported *(551,612)*. The microorganism has been shown to survive in stored blood experimentally for up to 60 days at 4°C, in fresh frozen plasma at <18°C for 45 days, and in platelet concentrates for 6 days at 20°C to 24°C *(612–614)*. At this time, serologic screening of donor blood is not needed nor are additional historical questions for the donor *(368)*. Noteworthy is a report documenting the lack of seroconversion among nine recipients of antibody-positive donor blood *(615)*. In addition, Perdrizet et al. *(561)* have reported a renal transplant patient who acquired babesiosis from a unit of blood donated by a patient who also developed Lyme disease 2 days after blood donation; the transfusion recipient remained free of Lyme disease *(561)*.

RELAPSING FEVER

Relapsing fever is another form of borreliosis transmitted by a louse or a tick; the former serves as a vector from human to human, whereas the latter serves as a vector from the mammalian reservoir to humans. *Borrelia recurrentis* and the *Borrelia* species of the tick-borne form of the disease can apparently survive in citrated blood, because there are rare case reports of infection by transfusion *(616,617)*. These are unusual events, and no donor-related preventive screening is appropriate.

BACTERIAL INFECTIONS

Transfusion reactions resulting from bacterial contamination of RBC units are usually due to one of two sources: contamination during collection and processing or a bacteremia undetected in the donor at the time of collection *(9,368,618–625)*. It is difficult to distinguish these two potential mechanisms in a given circumstance. The risk of such an event after RBC transfusion is estimated to be one per 5 million donor units *(626)*. Most contaminants of units of RBCs have been gram-negative microorganisms with low pathogenicity, including *Serratia*, *Pseudomonas* species, and *Klebsiella* sp., suggesting processing contamination *(627)*. The relatively few gram-positive isolates are most likely skin flora that contaminated the blood at the time of collection. One recent epidemic of *Serratia marcescens* bacteremia was traced to contamination of blood collection bags during manufacture *(628)*. A recommendation was made for production of blood packs with sterile exterior surfaces.

One report documented that during transfusion of contaminated RBC units, adverse reactions developed in 38 of 76 patients, including fever (80%), chills (53%), hypotension

(37%), and nausea with vomiting (26%) *(618)*. There was a 35% mortality rate overall. In the remainder of the patients, reactions developed from 15 minutes to 17 days after the transfusion *(618,619)*.

A subset of the gram-negative rods contaminating transfused RBCs or blood products in reviews *(618–623)* and other reports *(629–637)* most likely reflected disease in the donor. The report of two thalassemic patients with transfusion-acquired brucellosis and a later report reflect the potential for chronic asymptomatic *Brucella* species bacteremia with acquisition by transfusion *(629,637)*.

Most striking, however, are reports of *Yersinia enterocolitica* acquired via transfused RBCs *(619,621,622,631–636,638). Yersinia* species account for up to 80% of episodes of sepsis syndromes secondary to transfusions with RBCs from a donor infected with a bacterium *(621)*. Up to 60% of donor recipients may die with this syndrome *(621,622)*. This scenario reflects the recognized potential for this microorganism to persist in the intestinal mucosa and lymphoid tissue after acute illness resolves, followed by occult bacteremia *(639)*. Furthermore, storage conditions for RBCs are almost ideal for supporting growth *(621)*. This microorganism can grow at 4°C in blood and survives intracellularly in leukocytes; in addition, during storage, some hemolysis occurs, releasing hemoglobulin and iron; the latter is a growth factor for the microorganism. After an initial drop in bacterial counts following blood collection (obviating sensitivity of culture at the time of collection), bacterial counts surge within leukocytes during storage *(635)*. This has prompted recommendations for decreased storage times from 42 to 25 days, among others *(622,635)*. This microorganism also becomes resistant to complement-mediated lysis at temperatures below 20°C, especially when plasma has been removed *(640)*. Prestorage LR of RBC units after initial storage at 20°C for 3 to 8 hours does reduce but not totally eliminate the risk of transfusion of *Yersinia* (and coagulase-negative staphylococci) contaminated units of blood *(622,641,642)*.

Bartonella bacilliformis, a gram-negative bacillus, is an intraerythrocytic parasite endemic to the highlands of the western Andes in Peru, Ecuador, and Colombia, where it is transmitted by sandflies. Bacteremia is detected in 5% of apparently healthy persons in these areas. Transfusion-related infection might occur if a carrier immigrated to the United States *(563)*.

There are approximately 9 million platelet unit concentrates administered each year *(643)*. Platelet units, especially random donor pools compared with single-donor apheresis products, have emerged as the major problem with regard to bacterial contamination, because they are stored at room temperature for up to 5 days before use *(30,620,623–626,643–645,*646*,647)*. The incidence of a serious transfusion-associated sepsis episode is 1 in 15,000 to 1 in 100,000 for platelets, 10-fold higher than for RBCs *(623,625,626,643)*. Among transfusion-related fatalities reported to the FDA between 1986 and 1991, platelet transfusions accounted for 21 of 29 bacterially mediated deaths *(30,648)*. The eight remaining deaths were due to transfused RBC units. Today, platelets account for up to 77% of transfusion-related deaths *(643)*. It has been estimated that up to 10% of platelet pools used for transfusion are contaminated with bacteria *(649)*, but the risk of bacterial contamination of platelet pools is currently estimated at 1:1,000 to 1:3,000 units *(625)*. Bacterial contamination has been documented by culture in 0.06% to 0.28% of pooled platelet concentrate transfusions and in 0.005% to 0.03% of single-donor apheresis platelet transfusions *(30,648)*. Mechanisms of contamination are similar to those for RBC (*vide supra*). Most contaminants are skin flora such as *Bacillus* species and coagulase-negative staphylococci, but gram-negative microorganisms may also play a role *(619,620,648,650)*. The use of pH and glucose measurements on stored platelet concentrates to detect bacterial contamination immediately before transfusion has been variably successful *(651,652)*. Automated microbiologic culturing of platelet concentrates is established as a technique for reduction of the risk with random donor pools *(653,654)*.

Given the potential problem of bacterial contamination of platelet concentrates and to a lesser extent single donor apheresis platelet units, as well as blood and blood products with associated morbidity and mortality, suggested revisions for handling of donor blood were promulgated. Platelet storage time is limited to 5 days. Efforts for the prevention of contamination during collection and processing were re-emphasized *(618–620,623,*646*,647)*. On March 1, 2004, the AABB announced a new standard requiring platelet units to be tested within 24 hours of collection for bacterial contamination (Table 67-5) *(643)*; optional detection methods included glucose or PH (>6.4) monitoring and culture (three systems approved; *643*). Each is susceptible to false-negative results *(643)*. Enhanced physician awareness of the potential for bacterial contamination of transfused products is needed; should a reaction with or without fever occur, the platelet concentrate being transfused and the recipient's blood should be cultured *(618–620,643)*. Staining the residual material in the bag might give a more immediate answer as to the cause. The CDC has suggested testing RBCs stored for 25 days or more for bacteria before administration *(633)*. This can be accomplished with microscopy using various stains, with culture, with nucleic acid hybridization or PCR, and with a detection of endotoxin *(620–623)*. However, reactions to bacterial contaminants in transfused products are probably more common than reporting would reflect *(618,623)*.

The residual risk of sepsis after implementation of testing for bacterial contamination following platelet transfusions is now estimated to be one in 74,804, and the residual risk of fatality is estimated at 1 in 498,711 (Table 67-6) *(*646*)*. Regarding the use of platelet transfusions in thrombocytopenic patients, recent data suggest that the reduced platelet threshold before transfusion should be lowered to 10,000/mm^3 *(655–658)*. A reduction of the number of platelet-related episodes of sepsis and mortality may thereby be further achieved.

PARASITIC INFESTATIONS

Several tissue nematodes pose a remote potential transfusion hazard because of chronic asymptomatic microfilaremia; these include the microfilariae *Brugia malayi, Loa loa, Wuchereria bancrofti, Mansonella ozzardi,* and

Mansonella perstans (534,541,563). Transfused microfilaria are unable to complete their life cycle after intravenous inoculation; they are cleared rapidly in the recipient or may persist in the circulation for up to 2 years, usually without associated symptoms or only a mild febrile reaction *(541)*. The unlikelihood of such contamination of donor blood in the United States and the good outcome argue against a need to screen donors or donated blood *(541)*. However, in our "global village," the concern about filariasis after transfusion continues to be raised *(659)*.

RICKETTSIOSES

The rickettsia produce illness after insect vector inoculation (except for *Coxiella burnetii*) by producing a vasculitis. With microorganism replication in endothelial cells and the organs with tissue monocyte/macrophages, rickettsemia occurs during the incubation period and during acute illness. There are two remote reports of rickettsioses being transmitted by blood taken from donors during the incubation period of their illness; one was associated with Q fever in the recipient *(660)* and the other was associated with Rocky Mountain spotted fever *(661)*. *Ehrlichia chaffeensis* has survived experimental inoculation into refrigerated, stored RBCs for 11 days *(553)*. *Ehrlichia phagocytophilia* has been transmitted by blood transfusion in sheep and isolated from refrigerated stored blood from naturally infected patients for up to 2 weeks *(553)*. Eastlund et al. *(662)* reported a case of human granulocytic ehrlichiosis in a 75-year-old man after RBC transfusion. None of these rare occurrences with rickettsia or *Ehrlichia* sp. warrants donor screening other than that outlined in Table 67-2 *(553)*.

OTHER MECHANISMS FOR REDUCING TRANSFUSION RISKS

Additional attempts to reduce the risk of infection after transfusion have proceeded along several avenues other than serologic screening; these include physical or chemical treatment of blood or blood products for sterilization, the use of directed and autologous (instead of allogeneic) blood transfusion, intraoperative blood salvage and reinfusion, and the development of blood substitutes.

Factor VIII and IX concentrates are produced as lyophilized products after Cohn ethanol fractionation of plasma pools. These products unfortunately contained infectious hepatitis viruses and HIV-1 before 1984 when dry heat treatment of the lyophilized powder at 60°C for 24 hours was begun. However, although HIV-1 was inactivated, HBV and HCV remained viable. Subsequently adopted procedures, such as pressurized steam treatment of wetted lyophilized concentrates, pasteurization (liquid factor VIII and IX are heated at 60°C for 10 hours), and purification of these factors with monoclonal antibody affinity columns, have succeeded in rendering these products safe (1,*663,664*). The shortcoming of these procedures is reduction of factor yield.

The balance between pathogen reduction and retention of blood derivative activity is a difficult to achieve goal. Therefore, more promising methods using virucidal solvents or detergents are now used; also, further purified factor concentrates (by anionic exchange chromatography) to reduce alloantigen contaminants that might stimulate the immune system in an HIV-1–infected patient (thereby augmenting viral replication) are used *(368,665)*. Virus inactivation in fresh-frozen plasma has been accomplished by treatment with methylene blue, solvents and detergents, radiation, and heating *(664,666,667)*. Inactivation of pathogenic viruses has also been reported with amotosalen and UV light, as well as riboflavin followed by UV light (the latter can be applied to cellular products in addition to plasma and platelet units; *668,669*). Dilutional neutralization with antibody has also been reported *(669)*. While already implemented in Europe, published commentaries after US conferences have recommended adoption of the above two photoinactivation techniques for platelets and plasma, and riboflavin plus UV light for RBCs *(670–672)*.

Plasma protein fractions and albumin are also products of Cohn ethanol fractionation of plasma pools. After separation from plasma, they are subjected to pasteurization at 60°C for 10 hours; all infectious viral particles are inactivated, along with clotting factors (1).

In addition to photoinactivation of malaria parasites and other protozoa in blood, including leishmania and trypanosomes, as a physicochemical means of rendering blood noninfectious (see previous discussion), several authors have reported chemical inactivation of HIV-1 and other viruses in whole blood and plasma with aluminum phthalocyanine derivatives that left erythrocytes intact *(416,673,674)*. Such chemical sterilization of blood may offer hope for an even safer blood supply in the future. Photochemical inactivation procedures for virus and bacterial pathogens, including riboflavin, have been recently assessed for cellular blood products *(368,668–672, 675–677)*. Riboflavin is the only photoinactivator currently described, which is applicable to cellular products.

During the last decade, there has been a decline in the collection of allogeneic volunteer donor blood *(9,678)*. Fortunately, this has not compromised the national blood supply, because it was initially offset by autologous donations to some extent and a decline in the use of transfused blood and blood products *(9)*. After the definition of HIV-1 epidemiology, there was initial interest in the use of directed donations by friends, family, or another selected person for an individual recipient *(679)*. The disadvantages of such a policy were emphasized by many advisory bodies. These problems included the following: (i) a valid medical history is more uncertain when obtained from a solicited donor known to the recipient than from a volunteer donor; (ii) the anonymity of the donor is not preserved, leading to potential legal liability; (iii) such nonvoluntary donors have a higher risk of transmitting PTH *(679,680)*; (iv) such directed donors create an apparent double standard of transfusion medicine that may be, ironically, less safe; and (v) there are logistic problems with such a program *(679)*. Autologous donations are very limited today *(681,682)*; such donations were associated with a 12-fold increased risk of an adverse event and were not cost effective *(682)*.

Autologous blood donation (ABD) is immunologically perhaps the safest form of transfusion therapy, because it avoids isoimmunization and eliminates the risk of transmission of infectious agents except for contaminating bacteria *(683–685)*. Autologous transfusion can be one of

four types: (i) remote preoperative storage; (ii) immediate preoperative phlebotomy with acute normovolemic hemodilution; (iii) intraoperative recovery; and (iv) postoperative recovery (from drainage tubes with reinfusion). *Remote preoperative donation* and storage is the most commonly practiced type *(684–687)*. By 1992, 8.3% of all blood donated was for this purpose *(684)*. Up to 70% of patients can have their total transfusion needs satisfied by this technique *(687)*. However, although decreasing exposure to allogeneic blood, preoperative autologous donation may lead to increased transfusion of such donors *(688)*. Unfortunately, up to half of autologous units are discarded; they are not used for allogeneic transfusion and the practice is, therefore, wasteful *(684,685)*. Unexpectedly, the safety of autologous donor units is less (12 times the rate of reactions to allogeneic units) and their use has declined since the early 1990s *(9,682,684,685)*.

Immediate preoperative phlebotomy is a similar second option *(9,684,685)*. Potential problems related to such a practice are multiple. The safety of immediate preoperative autologous donations with normovolemic hemodilution has been raised, because patients are generally older with cardiovascular disease *(687)*. Curiously, severe donor reactions have been infrequent and use of allogeneic units is reduced with this practice *(684,685)*.

Overall, the need and extent of serologic testing for autologous donor units have been questioned; it seems prudent not to exempt such donor units and to discard them if they are found to be infected to protect healthcare workers and a potential accidental recipient other than the donor *(687)*. The potential autologous donor can be prohibited if the presence of an infectious agent precludes making donor units safe for handling. There are other logistical problems with such a program, and a residual risk of transfusion reactions exists (hemolysis, sepsis from bacterial contaminants, and pulmonary edema) *(684)*.

Two other forms of autologous transfusions, *intraoperative* and *postoperative salvage* of blood followed by autologous transfusion, have become safer because of methodologic improvements *(684,685,689)*. Concerns remain about such transfusions in patients with infection *(683,684,690)*; the presence of malignancy is generally a contraindication to autologous transfusion after intraoperative salvage *(683,684)*. Bacterial contamination, metabolic complications, and air embolism after use of perioperatively salvaged blood are recognized risks *(685,689)*. The success of perioperative prophylactic antibiotics has been reported recently *(691)*. There is also a question as to whether or not perioperative RBC salvage actually reduces allogeneic transfusion requirements *(684)*. These techniques have been used during vascular, cardiac, and abdominal trauma surgery, in addition to orthopedic procedures *(692–697)*. Normovolemic hemodilution has also been used in the setting of intraoperative salvage *(698)*.

More recent concerns about any form of ABD relate to its cost effectiveness *(682,699–704)*. The cost of a unit of allogeneic RBCs approximates $210 per unit (average) to the administration agency but costs may vary by region. In contrast, a unit after ABD costs approximately 50% more because of the labor-intensive donation process and costs of processing and storage *(704)*. In addition, 9% to 10% of ABD units are used, because they are available only for elective procedures. Few centers allow crossover of ABD units to the allogeneic donor pool of blood for safety reasons *(684,700)*; therefore, most ABD units are discarded. Despite low rates of use, ABD units are associated with higher transfusion rates than for allogeneic blood for the population served (transfusion criteria are not as stringently applied by surgeons) and thereby costs of administration accrue *(688)*. Despite utilization successfully, ABD has been judged not to be cost effective for total hip and knee replacement *(700)* and for coronary artery bypass surgery and transurethral prostate resection *(701,704)*. These findings have probably contributed to the reported decline of ABD *(9,682)*. Despite large cost disadvantages, some knowledgeable physicians still present an argument for continuing ABD because of the fewer noninfectious complications and the recipient's peace of mind *(705)*; however, Medicare and some private insurers will not cover ABD *(684,705,706)*.

The development of safe and effective blood substitutes has been disappointing despite the reduction of infection risk *(684)*. Perfluorocarbons have been ineffective for oxygen delivery and are toxic to leukocytes (1,*684*,*685*). RBC stroma-free hemoglobin solutions are used only in emergency situations because of their short half-life after transfusion (1,*94*). Furthermore, these products are associated with organ toxicity and hypertension *(707,708)*. Hemoglobin encapsulated in liposomes has a longer half-life, but there is concern about compromise of the organs with tissue monocytes/macrophages where it is cleared *(707,708)*. Polymerized hemoglobin was less toxic to organs but hypertensive reactions persisted *(707,708)*. During a multicenter trial for treatment of hemorrhage, use of human polymerized hemoglobin produced similar outcomes to allogeneic blood but adverse events were more frequent; in other analyses mortality was actually increased *(709,710)*.

Preoperative use of recombinant erythropoietin has resulted in reduced need for allogeneic transfusions *(685)*, but has been associated with an increased risk of thrombotic events *(711–713)*. Phlebotomy has been recently re-emphasized as an important cause of blood loss in hospitalized patients, especially in the critical care setting *(714–716)*. Despite recognition that a lower hemoglobin (7 g/dL) should serve as a target for transfusion and that transfusion quantity is directly related to hospital length of stay and mortality, overuse of phlebotomy is perpetuating transfusion ill effects.

Approximately 15 million units of blood are donated annually and 29 million products transfused in the United States, at an average cost of $210 per unit (or more to the patient or the insurance carrier) (2,*678*,*704*). Of this cost, approximately 37% is attributed to acquisition charges from blood donation centers, 13% to handling by the hospital blood bank, 43% to laboratory tests for cross matching, and 7% to blood administration charges *(704)*. In addition to these costs, only about one per 1 million to 8 million units transfused resulted in a serious or fatal infectious complication of transfusion, perhaps necessitating a more prolonged hospitalization or additional laboratory charges to the patient *(9,717)*. Because much of the present cost of a unit of transfused blood is related to screening for transmissible diseases (up to 20% of blood donation center charges), any further reduction of infection risk is

least expensively accomplished through prudent use of transfusions according to suggested guidelines *(9,79,685)*. Furthermore, transfusion related infections today pose less risks and are secondary to those following sometimes unpredictable (and unavoidable) noninfections transfusion reactions (3). It is estimated that 13% to 50% of transfusions are unneeded *(79)*. Most recent studies have documented the lack of benefit of overzealous transfusion thresholds. In intensive care patients, the use of a threshold of <7.0 g of hemoglobin was associated with a lower 30-day mortality compared with a 10-g threshold in multiple studies *(718)*. The exception to this policy appears possibly to be patients older than 55 years and those with cardiac disease *(719,720)*. However, in the patient group with cardiac disease undergoing interventions, unnecessary transfusions have also led to additional costs and potential morbidity *(718)*. The case for a moderate position has been summarized by Valeri et al. *(721)*.

A review of the management of a severely anemic patient who refused transfusion (a Jehovah's Witness) provides perspective for the management of many patients *(722)*. At this time, there is no functional substitute for blood when it is required. Clinicians must continue to strive to make an exceedingly low infection risk product even safer, while practicing cost-effective medicine by reducing reliance on overused blood products. Furthermore, given the results of the SHOT initiative indicating that most transfusion-related morbidity and mortality in Great Britain today is related to noninfectious complications of transfusion, as is true in the United States, one should give considerable attention in the United States to quality improvement initiatives to improve further the safety of utilization of blood products *(723)*.

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CHAPTER 68

Healthcare-Associated Infections Related to Procedures Performed in Radiology

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The radiology department has traditionally been considered a low-risk environment for healthcare-associated infections. However, major advances in the field of radiology over the past few decades, with the introduction of isotope scanning, ultrasound, computed tomography, magnetic resonance imaging, and the development of interventional radiology, have increased the potential for the transmission of infectious pathogens to both patients and healthcare workers. Unfortunately, an appreciation for the occurrence of healthcare-associated infections associated with these radiologic procedures has not kept pace with this technology (*1*,2). Few radiology texts address healthcare-associated infections associated with radiologic procedures. In addition, most invasive radiologic procedures introduced over the past few decades have not been prospectively analyzed for measures that could decrease the occurrence of healthcare-associated infections resulting from them. This is due, in part, to the rather limited time during which the radiologist interacts with the patient, and the resulting difficulty in achieving the long-term follow-up required to identify healthcare-associated infections.

This chapter summarizes the infectious complications associated with radiologic procedures and the infection control practices that might decrease the occurrence of these infections. As conclusive data regarding the prevention of healthcare-associated infections are lacking for many of these procedures, reliance is placed largely on related procedures performed in other specialties of medicine in which interventions that reduce the healthcare-associated transmission of infectious pathogens have been identified.

INFECTION CONTROL POLICY

The radiology suite experiences a steady stream of a wide variety of patients each day. Patients referred from the ambulatory care and emergency areas are intermixed with inpatients requiring diagnostic procedures. All of these patients can contaminate the environment of the radiology service with infectious pathogens. Chin supports and chest racks used in obtaining chest radiographs *(3)*, radiography tables *(3)*, radiographic film markers *(4)*, barium enema equipment *(5)*, x-ray tubes *(6)*, and x-ray film and developing solutions *(7)* may all become contaminated with multiple microorganisms from patients. In addition, the ease with which *Clostridium difficile* contaminates the environment of the patient colonized with this microorganism *(8)* makes it likely that contamination of the radiology area with *C. difficile* occurs as well. This environmental contamination may result in the subsequent spread of pathogenic microorganisms from these objects to other patients. In addition to fomite transmission, potential pathogens may be spread to patients visiting the radiology area via the airborne route. Hopkins et al. *(9)* traced an outbreak of invasive aspergillosis in their hospital due to construction activity in the radiology suite. Patients visiting the radiology suite for diagnostic procedures were infected when there was inadequate containment of aspergillus spores generated during renovation. Similarly, investigations of hospital outbreaks of multidrug-resistant tuberculosis have revealed that most cases were acquired within the facilities via the airborne route. A major factor in most of these outbreaks was a delay in initiating the isolation of patients infected with pulmonary tuberculosis *(10)*. Many of these patients had made multiple visits to the radiology department, with no precautions taken to prevent the transmission of respiratory pathogens, making it likely that some transmission occurred within the radiology department.

Given the large numbers of both diagnosed and undiagnosed infected patients presenting to the radiology department, and the potential for these patients to contaminate both objects and the air with pathogenic microorganisms, the foundation of any program for the prevention of healthcare-associated infections in the radiology department must begin by establishing good infection control policies. Among other issues, these policies must address the effective disinfection of environmental surfaces likely to act as fomites. The cleaning of these surfaces must be performed with an Environmental Protection Agency (EPA)-registered germicide (see also Chapter 80) between all patients, with more rigorous cleaning protocols at periodic intervals (11) (see also Chapter 71). A material that can be either discarded or easily disinfected between patients should cover surfaces that may be difficult to disinfect, such as switches and control panels. Policies should ensure that all disposable items are discarded after a single patient use, as such items are not designed for reprocessing and reuse on multiple patients (11). Attention must also be given to the appropriate cleaning and disinfection of all reusable

equipment, with the level of disinfection determined by the intended use of the item (see also Chapter 80). Items that enter tissues or vascular spaces require sterilization. Items that contact mucous membranes or nonintact skin require high-level disinfection. Items that contact intact skin require only low-level disinfection.

The radiology department must also establish good communication with the clinical areas referring patients to the department so as to identify patients who may require Transmission-Based Precautions. Patients requiring Transmission-Based Precautions must have those precautions continued in the radiology department. When possible, patients on Transmission-Based Precautions should undergo their procedures late in the day when traffic in the department is light and more attention can be given to environmental cleaning. These patients should also spend the minimum time possible in the radiology department so as to limit the potential exposure of susceptible patients and staff.

Due to concern about the healthcare-associated transmission of tuberculosis in the radiology suite (see also Chapter 38), the Centers for Disease Control and Prevention (CDC) has published specific recommendations for precautions to be followed in radiology departments *(10)*. Patients with known or suspected tuberculosis should wear a properly fitted surgical mask when in the department. When possible, an area in the department should be specially ventilated for Airborne Infection Isolation Precautions. This requires a net negative air pressure in relation to surrounding areas, sufficient air changes to remove droplet nuclei between patients, and either direct exhausting of all air to the outside (preferred) or filtration of air through high-efficiency particulate air (HEPA) filters before it is recirculated. In facilities with a high incidence of tuberculosis, ventilation in waiting areas should also be designed and maintained to reduce the risk of tuberculosis transmission. This should include provisions for direct exhausting of all air to the outside (preferred) or HEPA filtration of all air before it is recirculated. A goal of 12 to 15 air changes per hour for such waiting areas has been established (12,*13*).

STANDARD PRECAUTIONS

The infection control measures discussed above protect employees and patients from the transmission of most potential pathogens. However, attention to the transmission of blood-borne pathogens in the workplace increased in the 1980s. Hepatitis B virus (HBV) and the human immunodeficiency virus (HIV) are the blood-borne pathogens that have attracted the most attention from healthcare workers and regulatory agencies *(14)*.

Personnel working in radiology departments historically have not been considered a group at high risk for infection with blood-borne pathogens *(14–17)*. However, radiology personnel are increasingly performing procedures that can result in exposure to blood and other potentially infectious materials (materials epidemiologically linked with the transmission of blood-borne pathogens) *(18)*. Because a high percentage of patients infected with HBV *(19)* or HIV *(20)* are unidentified during their encounter with the healthcare system, it is essential that all patients be approached as though they are infected with blood-borne pathogens. This concept of using Universal Precautions (see also Chapter 89) for blood and other potentially infectious materials of all patients was first suggested by the CDC in 1987 *(21)*. These precautions were subsequently mandated by the Occupational Safety and Health Administration for all healthcare workers *(14)*. In 1996, the CDC recommended replacement of Universal Precautions with Standard Precautions, a change aimed at focusing more attention on pathogens that are not primarily blood-borne (22). Reports have detailed how these precautions can be applied to the radiology department (*18*,22,*23–25*). In general, these recommendations mirror those for other areas of the hospital in which similar procedures are performed (Table 68-1).

SPECIFIC PROCEDURES

Radiographic Studies of the Gastrointestinal Tract

The spread of enteric pathogens during radiologic procedures of the gastrointestinal tract has been a matter of concern for a number of years. Meyers *(5)* and Steinbach et al. *(26)* demonstrated retrograde contamination

TABLE 68-1

Standard Precautions as Applied to Radiology

- Wash hands promptly and thoroughly after patient contact or contact with blood, body fluids, excretions, or secretions.
- All personnel who could be exposed to blood or other potentially infectious material must receive training on these risks and on ways to minimize these risks.
- Employees must be offered hepatitis B immunization free of charge within 10 d of being assigned to tasks that pose a risk of exposure to blood or other potentially infectious materials.
- Disposable sharps, such as needles and scalpels, must be discarded immediately after use into puncture-resistant containers located as close as practical to the point of use. Sharps should not be recapped, bent, or otherwise manipulated before being discarded.
- All personnel who are present at procedures that could involve contact with blood, body fluids, secretions, excretions, mucous membranes, or nonintact skin of patients must use appropriate barrier precautions. This may involve use of gloves, gowns, masks, goggles, or face shields, depending on the degree of potential exposure. Interventional radiologists may need to consider the length of the procedure when establishing gloving policies. Hansen et al. *(25)* found that 23% of the gloves worn for more than 2 h during interventional radiology procedures were perforated by the end of the procedure. Few of these perforations were noted by the wearer. Similar data from other studies could support double-glove policies or the routine changing of gloves during prolonged interventional procedures.

(Data from Centers for Disease Control and Prevention, American Dental Association, American Academy of Oral and Maxillofacial Radiology.)

of the apparatus used for administering barium during the performance of barium enemas. This equipment became heavily contaminated with fecal contents by the end of the procedure. Hervey *(27)* reported an outbreak of typhoid fever traced to an apparatus that resembles the equipment used to administer barium during a barium enema. In his investigation, as in those by Meyers and by Steinbach et al., it was noted that fecal contents could contaminate the apparatus and its tubing via retrograde flow during the procedure. Although the apparatus was cleaned between patients, sufficient microorganisms remained in the apparatus to infect patients on whom it was subsequently used. Similarly, Meyers and Richards *(28)* were able to demonstrate that six of seven patients who underwent barium enemas after contamination of the bag contents with poliovirus became infected with the polio virus, as documented by rises in serum neutralization antibodies to the virus. In a related report, 36 cases of amebiasis were traced to a contaminated colonic irrigation machine in an outpatient chiropractic clinic *(29)*. Although the irrigation equipment was cleaned after each patient use, cultures of the machine immediately after cleaning revealed heavy contamination with fecal coliforms. The ease with which *C. difficile* contaminates the environment of colonized and infected patients *(8)* makes it likely that this bacterium is also present where gastrointestinal procedures are performed.

Given this potential for the transmission of enteric pathogens, all equipment used in barium enema procedures either must be subjected to high-level disinfection or must be disposable. In fact, disposable kits have replaced reusable equipment in most facilities *(30,31)*.

Several investigators have documented bacteremia associated with radiologic studies of the gastrointestinal tract. In two large studies, 11% *(32)* and 23% *(33)* of patients undergoing barium enemas had bacteremia. In both reports, the bacteremia could be detected within 1 minute of the start of the procedure. This bacteremia was transient and could be documented only for 30 minutes. Radiologic findings and colonic pathology did not influence the likelihood of the occurrence of bacteremia. Bacteremia was most likely to occur during the maximal distention of the colon. In evaluating the patients in these studies, no adverse effects of the bacteremia could be documented. However, one episode of *Clostridium perfringens* sepsis has been reported in a patient with acute leukemia who underwent a barium enema *(34)*. Although the transient bacteremia associated with the barium enema is unlikely to adversely affect most patients, bacterial endocarditis after a barium enema has been reported in one patient *(35)*. This has, in turn, raised the question of antibiotic prophylaxis for the prevention of infective endocarditis (*36*,37). However, barium enemas have not been found to be a risk factor in studies evaluating the epidemiology of bacterial endocarditis. Although a definitive answer is probably not possible, the current consensus is to avoid the use of prophylactic antibiotics for patients undergoing barium enemas *(34)*.

Ultrasound Procedures in Radiology

Ultrasonography has become an increasingly popular mode of evaluating a wide range of tissues. It is estimated that the average ultrasound machine may be used on as many as 30 patients a day, giving this equipment the potential to serve as an important fomite for the transmission of pathogens between patients *(38)*. Although many of these procedures restrict the ultrasound probe to contact with intact skin, probes are also being utilized for procedures in which they come into contact with mucous membranes and normally sterile tissues, occasionally in the operating room. Several studies have documented heavy contamination of the ultrasound probe, especially after contact with a mucous membrane *(38–40)*.

The standard manufacturer's recommendation for disinfection of the ultrasound probe is to soak the probe in a dilute sodium hypochlorite solution or an EPA-registered germicide for the time specified by the germicide's manufacturer, frequently 20 minutes. Unfortunately, the multiple procedures scheduled for these probes frequently preclude such long soak times. In addition, the probes may be damaged by total immersion in these solutions due to leakage around the seals or deterioration of the acoustic lens or rubber seals *(38,41)*. In practice, routine cleaning of the probe followed by low-level disinfection with an alcohol wipe seems appropriate when procedures involve contact only with intact skin. For procedures where the probe comes into contact with mucous membranes or nonintact skin, thorough cleaning followed by high-level disinfection with an EPA-registered germicide is recommended (11,42). Because of the difficulty in achieving high-level disinfection, it is recommended that a new sheath, such as a condom, cover probes that will be in contact with mucous membranes or sterile tissues for each such procedure (11,42). In general, condoms have been shown to be less prone to leakage than commercial probe covers and have a sixfold enhanced acceptable quality level when compared to standard examination gloves.

Endoscopic Procedures in Radiology

Other subspecialists such as gastroenterologists, pulmonologists, and surgeons perform endoscopic procedures much more frequently than they are performed by radiologists. Often, endoscopy is not performed in the radiology suite but rather in patient care areas, in the operating room, or in other dedicated areas such as laboratories within the hospital or ambulatory center. To the extent that endoscopy is performed in areas outside of radiology, general infection control policies similar to those recommended for the radiology suite need to be implemented.

Endoscopic procedures of the pulmonary tract *(43–45)*, upper gastrointestinal tract *(35,45–47)*, lower gastrointestinal tract *(35,45)*, and biliary tract *(45,48)* have all been associated with healthcare-associated bacteremia and infections. *Salmonella* species and *Pseudomonas aeruginosa* are the most common pathogens isolated in infections after gastrointestinal endoscopy, whereas *Mycobacterium tuberculosis*, nontuberculous mycobacteria, and *P. aeruginosa* are the most common isolates in infections after bronchoscopy *(45)*. In general, *P. aeruginosa* and nontuberculous mycobacteria tend to come from environmental contamination of the equipment, whereas *Salmonella* and *M. tuberculosis* originate in patients previously studied with the endoscopes.

Risk factors for healthcare-associated infections after endoscopy tend to fall into two categories. The major patient risk factor that increases the likelihood of bacteremia and

infection following endoscopic gastrointestinal procedures is the inability to establish adequate drainage of the biliary tract after endoscopic retrograde cholangiopancreatography (ERCP) *(36,48–50)*. In a recent guideline *(51)*, it was suggested that antibiotic prophylaxis should be considered before an ERCP in patients with known or suspected biliary obstruction, in whom there is a possibility that complete drainage may not be achieved at the ERCP, such as in patients with a hilar stricture and primary sclerosing cholangitis. When biliary drainage is incomplete despite an ERCP, continuation of antibiotics after the procedure is recommended.

As in the case of the barium enema, the question of antibiotic prophylaxis for the prevention of infective endocarditis after ERCP has been raised *(35,36,50)*. However, in two recent guidelines (37,*51*), it was recommended that prophylactic antibiotics no longer be given to any patients undergoing gastrointestinal endoscopy for the prevention of endocarditis.

Failure to adequately disinfect the endoscope and associated equipment appears to be another major risk factor for bacteremia and sepsis associated with endoscopic procedures. Contaminated water bottles *(52)*, inappropriate disinfectants *(43)*, scope designs that make adequate disinfection of the endoscope difficult *(53)*, and inadequate quality control over cleaning procedures for the endoscopes *(54)* have all contributed to healthcare-associated infections. In 2003, a guideline was published for the reprocessing of flexible gastrointestinal endoscopes (55). A recent review (56) was unable to document any episodes of patient-to-patient transmission of pathogens when these guidelines were followed (for a detailed discussion on cleaning and disinfection of endoscopes, see also Chapter 62).

Myelography

Myelography is associated with an extremely low rate of healthcare-associated infections. Given the anatomic location of these infections, however, they can be catastrophic. Twenty-nine cases of meningitis after myelography have been reported *(57–60)*. Oropharyngeal streptococci have caused most of these infections. The presumed source of these bacteria has been the oropharynx of the individual performing the procedure. This has been attributed to the fact that those performing the myelography frequently do not wear masks. The low incidence of this infectious complication has impeded the implementation of more stringent infection control measures *(59)*. Nonetheless, the wearing of masks would appear to be a logical low-cost precaution for the prevention of this potentially lethal infection. At the October 2005 meeting of the Healthcare Infection Control Practices Advisory Committee (HICPAC), the committee voted unanimously to recommend that surgical face masks be worn during myelogram procedures and during placement of epidural catheters *(60)*.

Vascular Radiology

Vascular radiology covers a wide range of procedures performed both by radiologists and cardiologists. As such, these procedures may be carried out both in the radiology suite and in designated catheterization laboratories outside of the radiology suite (see also Chapter 61).

Simple angiography procedures generally have a very low rate of infectious complications. Although endocarditis after coronary angiography has been reported *(61)*, prospective studies have found low rates of bacteremia and infectious intravascular complications associated with angiography. Sande et al. *(62)* found that none of 106 patients undergoing cardiac catheterization had detectable bacteremia or postprocedural intravascular infections. Shawker et al. *(63)* were able to detect bacteremia in 4 of 100 patients undergoing angiography of various vessels. Three of the four episodes were caused by inadequate sterilization of the catheter before the procedure. None of these patients developed any infectious sequelae. Infections at the insertion site of the catheter also appear to be quite infrequent. Laslett and Sabin *(64)* found no evidence of insertion site infection in 504 percutaneous left-sided heart catheterizations. Leaman and Zelis *(65)* were able to collect data on 107,203 cardiac catheterization procedures through a survey of 250 facilities. Only 0.06% of catheterizations performed by percutaneous insertion were reported to lead to insertion site infections. Catheterizations performed by cut down had an insertion site infection rate of 0.62%. Although low, this was 10 times the rate of site infection that occurred after percutaneous insertions. In a recent analysis of patients undergoing diagnostic angiography and angioplasty, Biancari et al. *(66)* found that patients undergoing procedures where manual/mechanical compression was used after the procedure had a 0.2% groin infection rate, while the use of a vascular closure device was associated with a 0.6% groin infection rate—this difference was statistically significant.

In formulating infection control standards for simple angiography, it is generally agreed that the preparation of the insertion site should involve the same disinfection techniques as are used for other intravascular devices. Individuals performing the procedure should wash their hands with an antiseptic-containing hand washing agent before donning sterile gloves. Strict attention must be given to proper cleaning and sterilization of guidewires and catheters that are reused. For angiography performed via the percutaneous insertion technique, it would appear that the remaining elements of the environment may be less critical in preventing insertion site infections. Laslett and Sabin *(64)* and Leaman and Zelis *(65)* could demonstrate no benefit from the use of caps and masks by personnel performing the angiography in preventing site infections. Unfortunately, they did not address the issue of gowns for personnel involved in performing the procedure. Given the potential for inadvertent contact of the catheter with the body or arms of the personnel directly involved in the procedure, gowns for these individuals would seem appropriate, although there is no documentation that they are necessary. Leaman and Zelis's observations indicate that gowns do not appear to be necessary for ancillary personnel and observers.

The 10-fold increase in insertion site infections associated with angiography performed via the cutdown approach would argue for avoiding this technique whenever possible. When the cutdown approach was required, Leaman and Zelis *(65)* found that the use of masks, caps, and gowns for all personnel and observers significantly decreased the rate of site infections. They also demonstrated a significant correlation between the number of cutdown procedures performed by a laboratory per year and the rate

of insertion site infections. Laboratories performing more than 150 cutdown procedures per year had an insertion site infection rate of 0.49%. In contrast, laboratories performing fewer than 150 such procedures per year had an insertion site infection rate nearly three times greater (1.43%). This difference was statistically significant. This observation would argue for the importance of the learning curve in preventing healthcare-associated site infections associated with angiography. While the use of vascular closure devices leads to more rapid hemostasis, the associated complications may outweigh this advantage *(66)*.

Standard Precautions require the consideration of attire not only to protect the patient from infection but also to protect the healthcare worker from exposure to blood and other potentially infectious materials. Thus, although the wearing of masks, caps, and gowns by personnel may not have been documented to prevent infections in patients undergoing percutaneous angiography, the potential for blood exposure during these procedures requires the use of this attire to protect the healthcare worker from exposures (see Chapters 73 and 74). In addition, eye protection, such as goggles or face shields, is essential.

Interventional vascular radiology has moved substantially beyond simple angiography. Angioplasty, arthrectomy, the placement of intravascular stents, and embolotherapy are procedures that were introduced into the modern radiology suite and catheterization laboratory during the 1980s. Most of these procedures have been associated with low rates of healthcare-associated infection. Gardiner et al. *(67)* recorded no infectious complications in 453 transluminal angioplasties. However, Frazee and Flaherty *(68)* were able to identify 10 patients with septic endarteritis of the femoral artery after percutaneous transluminal coronary angioplasty. Zollikofer et al. *(69)* noted no healthcare-associated infections after the placement of intravascular arterial stents in 21 vessels, but Gordon et al. *(70)* documented an episode of renal artery arteritis after placement of a renal artery stent and were able to find reports of four other cases of iliac artery arteritis after stent placement. Both Frazee and Flaherty and Gordon et al. found that reuse of an indwelling catheter or sheath left in a groin for more than 24 hours, repeated procedures, local hematoma formation, and increased procedure time increased the risk of arteritis.

Percutaneous transcatheter embolization is defined as the intravascular deposition of particulate, liquid, or mechanical agents, or autologous blood clot to produce intentional vessel occlusion. *(71)*. This procedure has been associated with a high number of postprocedural infections in certain settings. Whereas Higashida et al. *(72)* detected no infectious complications after the balloon embolization of 215 intracranial neurovascular aneurysms, Hemingway *(73)* recorded seven deaths from sepsis among 410 embolization procedures involving a variety of arteries. All seven patients who died had embolization of hepatic lesions. Although the patients who died were all extremely ill at the time of the procedure, it is of note that all deaths occurred among the early cases performed by their group. A decrease in sepsis as a complication of embolization was observed as the group gained experience with the procedure and as prophylactic antibiotics were introduced into their protocol. Shibata et al. *(74)* reported on 358 patients with 455 liver tumors who underwent a total of 683 ablation procedures. Cholangitis and/or liver abscess occurred in 10 patients. Both cholangitis and liver abscess were noted in seven patients, cholangitis was noted in two, and liver abscess was noted in one. One patient died of septic shock associated with cholangitis.

Embolization of the spleen has also been associated with a high rate of infectious complications. Initial reports cited the almost universal occurrence of splenic abscesses and sepsis after splenic embolization *(75,76)*. After modification of this procedure, with a change to partial rather than total splenic embolization, the introduction of strict sterile technique, and the introduction of antibiotic prophylaxis, Spigos et al. *(77)* were able to perform splenic embolization on 13 patients without any postprocedural infectious complications. Since these modifications were introduced together, it is impossible to evaluate the efficacy of each intervention separately. Although not explicitly stated, the improvement in patient outcome occurred, as noted in Hemingway's series, as the author gained experience with the procedure.

Infection control guidelines in these newer forms of interventional vascular radiology should parallel those used for standard angiography. Strict attention to the disinfection of the insertion site and careful hand washing with an antiseptic-containing agent before donning sterile gloves are important. In angioplasty, arthrectomy, stent placement, and embolization of intracranial vessels, infectious risks appear to be small. However, adherence to Standard Precautions requires the use of masks, gowns, gloves, and goggles or face shields. The Society of Cardiovascular and Interventional Radiology has developed quality improvement guidelines for percutaneous transcatheter embolization *(71)*. Antibiotic prophylaxis is recommended for embolization of the spleen and for other body sites where bacterial contamination is likely, such as the colon, open trauma, and liver. In the embolization of hepatic and splenic vessels, the potential for severe infectious complications appears to be great. Pending more detailed studies, strict attention to sterile technique, the use of prophylactic antibiotics, and performance of the procedure by those with the most experience would seem to offer the greatest benefit in preventing healthcare-associated infections.

Nonvascular Interventional Radiology

Nonvascular interventional radiology has evolved since the 1970s to include percutaneous biopsies, diagnostic and therapeutic aspiration of fluid, treatment of strictures, and removal of stones. Of these, the image-guided percutaneous biopsy has become the most frequently performed interventional radiologic procedure *(78)*. Infections after such biopsies are uncommon. The Society of Interventional Radiology has set a performance standard for infectious complications of 1% for all biopsies and 3% for prostate biopsies *(79)*.

The ability to drain visceral abscesses and collections of fluid, often in lieu of a surgical procedure, has become an increasingly important radiologic intervention. As might be expected, these drainage procedures are associated with a higher rate of infectious complications than are percutaneous biopsies. vanSonnenberg et al. *(80)* summarized the outcomes of 250 percutaneous abscess and fluid

drainage procedures. Two patients experienced sepsis with hypotension, and five others had bacteremia with fever after the procedure. One patient had secondary infection of a noninfected lymphocele after percutaneous drainage. An additional six patients were noted to have infections at the catheter insertion site. Again, as in other interventional radiologic procedures, the authors emphasized that most infectious complications occurred early in the group's experience with the technique. It is also worth noting that although the infectious complication rate approached 6%, it was lower than the rate observed in an equivalent population undergoing surgical procedures to drain fluid collections *(81)*. The Society of Interventional Radiology has set a threshold of 1% to 2% for septic shock, 2% to 5% for bacteremia, and 1% for local superinfection associated with all abscess and fluid drainage procedures *(82)*.

Percutaneous transhepatic drainage of the biliary tract for acute relief of obstruction is an extension of the percutaneous drainage procedure. Drainage in most such patients is either palliative, when the obstruction is secondary to malignancy, or a preoperative measure to decrease the degree of patient illness when obstruction is secondary to cholelithiasis, stricture, or malignancy *(83–86)*. Most of these patients have evidence of cholangitis with multiple bacterial pathogens before the procedure, often with bacteremia. Given the degree of preexisting illness in many of these patients, it is not surprising that some series have reported high rates of infectious complications. Thus, Hamlin et al. *(84)* noted sepsis in 1% of the patients undergoing percutaneous transhepatic drainage. Kadir et al. *(83)* and Joseph et al. *(86)* noted sepsis in 27% and 33%, respectively, of the patients on whom they performed this procedure. Joseph et al. were able to decrease this rate by 50% through the administration of prophylactic antibiotics. Again, the surgical literature suggests that equivalent patients undergoing surgical decompression would experience sepsis over 50% of the time *(83)*.

Related procedures performed increasingly on the biliary tract include transhepatic cholangiography, placement of endoprostheses through a blocked duct, balloon dilation of strictures, and removal of stones. In general, the infectious complications associated with these procedures occur at approximately the same rate as those associated with percutaneous transhepatic drainage *(78,87,88)*. The Society of Interventional Radiology has set a performance standard that 2% of transhepatic cholangiograms should have an infectious complication *(89)*.

Percutaneous genitourinary procedures are most commonly performed to relieve obstruction secondary to neoplasms, stones, or strictures *(78)*. These procedures have fewer infectious complications than do the analogous procedures performed on the biliary tract. Yoder et al. *(90)* reported that 5 of 65 patients undergoing nephrostomy placement for pyonephrosis had septic complications, but none died. Similarly, Stables et al. *(91)* summarized the results of nephrostomy placement in 516 patients. Ten (2%) developed healthcare-associated infections, most commonly pyelonephritis or the exacerbation of pyonephrosis. There were no deaths, as compared with a 6% mortality rate in equivalent patients undergoing surgical drainage procedures. Cochran et al. *(92)* retrospectively reviewed 56 percutaneous nephrostomy procedures. Existence of struvite stones, abnormal urinalysis (not defined by authors), and positive urine cultures (criteria not given by authors) were believed to increase the likelihood of sepsis. Patients with one or more of these risk factors (the high-risk group) had a 50% chance of developing sepsis after percutaneous nephrostomy, as compared with a 14% likelihood of developing sepsis if none of these risk factors (low-risk group) were present. Antibiotic administration did not alter the rate of infection in the low-risk group but decreased the occurrence of sepsis by 80% in the high-risk group.

Although there are few prospective data evaluating interventions for the prevention of healthcare-associated infections after nonvascular interventional radiology *(87)*, a consensus appears to have emerged as to which infection control measures may help to reduce the rate of infectious complications associated with these procedures. With the exception of the percutaneous biopsy, many of these procedures are associated with a high rate of infectious complications with substantial morbidity and mortality. It is generally accepted that these procedures must be performed in an environment approaching that used for the equivalent surgical procedures. Strict adherence to sterile technique with the creation of a sterile field appears to be appropriate *(81)*. All personnel involved in the procedure should wear caps, masks, gowns, and gloves. The simplest procedure required to establish drainage and decompression should be performed with a minimum of manipulation and distention during the initial procedure *(81,91,93)*. Although prophylactic antibiotics have clearly been found to reduce the risk of healthcare-associated infections in a few studies, their exact role has not been determined (*87*,94). Antibiotic prophylaxis is unlikely to be of benefit in percutaneous biopsy procedures given the low rate of infectious complications associated with these procedures. Transhepatic and genitourinary procedures are followed by much higher rates of infectious complications, many of which will likely benefit from prophylactic antibiotics. Other drainage procedures are associated with much lower rates of infection. Further research is required to determine which, if any, of these procedures will benefit from prophylactic antibiotics. If prophylactic antibiotics are used, they should be administered no sooner than 1 hour before commencing the procedure. For most procedures, prophylactic antibiotics should not be continued after the procedure. However, for certain percutaneous drainage procedures, continuing antibiotics for 24 to 48 hours after the procedure may be appropriate *(87)*. Specific agents to be used depend on the body site involved and local susceptibility patterns.

As with vascular interventional procedures, experience is important; rates of healthcare-associated infections are reduced as groups gain experience *(80)*. As in vascular interventional radiology, all personnel must observe Standard Precautions.

Radiolabeled Imaging Studies

Radiolabeled imaging studies appear to be associated with a low rate of infectious complications. Proper attention to technique, as is required in all intravascular access procedures, is essential. In addition, because materials are removed from the patient, processed in another area, and then reinjected into the patient, strict protocols must be developed to prevent the contamination of the material to be reinjected. A

TABLE 68-2

Recommended Policies for Institutions or Clinics in Which Nuclear Medicine Procedures are Performed

- All healthcare providers should receive training on infection control procedures.
- Written infection control policies and procedures for nuclear medicine should be promulgated and disseminated. These should include procedures to follow in the event of a potential emergency, such as an administration error.
- All doses and syringes should be checked for identification and radioassayed before injection.
- All syringes should be labeled with appropriate identifying information, including the patient's name and the pharmaceutical. A unique identification number should also be used.
- Consideration should be given to the implementation of a system when administering biologic products that requires that two persons cross-check all labeling of product to be injected, the prescription, and patient identification.
- Contaminated and used syringes should be disposed of safely and appropriately.
- An administration error should be immediately reported to supervisory personnel. Patients involved should be managed according to policies established for blood exposures.

(From Centers for Disease Control. Patient exposures to HIV during nuclear medicine procedures. *MMWR* 1992;41:575–579, with permission.)

reminder of the care required in dealing with these materials is provided by the report of three patients who received intravenous injections of blood or other materials from patients infected with HIV while undergoing nuclear medicine procedures *(95)*. All three episodes occurred as a result of preventable administration errors. At the time of the report, two of three patients had developed infection with HIV. As a result of these errors, the CDC published recommendations to be followed when nuclear medicine procedures are performed *(95)*. These are summarized in Table 68-2.

Oral Radiology

The dental profession has a long tradition of concern for infection control issues (see also Chapter 54). Dentists were one of the first groups identified as being at high risk for occupational HBV infection *(96)*. In addition, dental personnel have been recognized as being potentially exposed to a wide variety of other pathogens, including *M. tuberculosis*, staphylococci, streptococci, cytomegalovirus, herpes simplex virus, HIV, and viral respiratory pathogens (97). The documented transmission of HBV *(98)*, staphylococci, streptococci *(6)*, and other infectious pathogens (97) to patients has further reinforced interest in infection control in dentistry. Further, dentistry remains one of only two professions in which transmission of HIV from a healthcare worker to patients has been documented *(99)*.

TABLE 68-3

Infection Control Guidelines for Dental Radiology

- Use standard precautions for all patients.
- Set out all necessary supplies and adjust patient chair and head position before beginning.
- The exposure switch and cone should be covered with paper backed by an impervious material, aluminum foil, or clear plastic wrap. These should be changed between patients. If covering is not possible, the switch and cone must be disinfected between patients.
- Operators should avoid touching environmental surfaces with contaminated gloves.
- All materials and instruments used during patient care should be kept on work surfaces that are covered. If this is not possible, work surfaces should be disinfected with an EPA-registered and ADA-accepted disinfectant between patients.
- Wear gloves when exposing radiographs and handling contaminated film packets. Use other PPE (e.g., protective eyewear, mask, and gown) as appropriate if spattering of blood or other body fluids is likely.
- Wash hands before and after wearing gloves.
- Use heat-tolerant or disposable intraoral devices whenever possible (e.g., film-holding and positioning devices).
- Barrier-protected film should be used whenever possible.
- Clean and heat-sterilize heat-tolerant devices between patients. At a minimum, high-level disinfect semi critical heat-sensitive devices, according to manufacturer's instructions.
- Dry film packet after film is exposed.
- If a protective film barrier is used, remove carefully to avoid contamination of the film.
- If a barrier is not used, gloves should be worn when the contaminated film packet is opened and the film allowed to fall out of the packet.
- Transport and handle exposed radiographs in an aseptic manner to prevent contamination of developing equipment.
- All darkroom surfaces that are contaminated by film packets must be disinfected regularly.
- Contaminated packets and gloves should be discarded before film processing.
- The following apply for digital radiography sensors:
  1. Use FDA-cleared barriers.
  2. Clean and heat-sterilize, or high-level disinfect, between patients, barrier-protected semicritical items. If the item cannot tolerate these procedures then, at a minimum, protect with an FDA-cleared barrier and clean and disinfect with an EPA-registered hospital disinfectant with intermediate-level (i.e., tuberculocidal claim) activity, between patients. Consult with the manufacturer for methods of disinfection and sterilization of digital radiology sensors and for protection of associated computer hardware.

(Data from Environmental Protection Agency; American Dental Association.)

Although many procedures within dentistry can lead to the transmission of infectious pathogens, dental radiology has been clearly associated with contamination of the office environment and transmission of microorganisms between

patients. The radiographic equipment, dental chair, headrest, adjacent horizontal surfaces *(100)*, radiographic film, film developer, and darkroom *(7)* may all become contaminated with oropharyngeal pathogens during the course of oral radiology. These pathogens, in turn, may be transmitted to healthcare workers or patients. Design features frequently contribute to this potential for the transmission of microorganisms. The control panel for radiology equipment in the dental operatory is frequently not designed for effective disinfection *(100)*, and it is difficult to aseptically remove the film from a film packet contaminated with oral secretions *(7)*.

In response to these concerns regarding the potential for spread of infectious pathogens between patients and between patients and healthcare workers in dentistry, the CDC (97) and several dental organizations (101,*102*,*103*) have published infection control guidelines for dental radiology (Table 68-3).

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CHAPTER 69

Infection Control in Gene Therapy

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The first gene therapy protocol in the United States was begun in 1990 for the treatment of severe combined immunodeficiency *(1)*. Overall, gene transfer has been used most commonly to treat cancer, followed by monogenetic, infectious, cardiovascular, neurological, and ocular diseases (Table 69-1). Recent success has been reported in treating patients with severe combined immunodeficiency *(2)*, a fatal demyelinating disease of the central nervous system (*3*,4), and an inherited retinal disease causing congenital blindness *(5)*. As of 2009, 1,579 gene transfer protocols have been initiated worldwide (6). Of these, approximately 60% are in Phase I trials, 35% in Phase I/II or II trials, and the remainder in Phase III or IV trials. Only two gene therapy products have been marketed, and these are in China.

Clinical gene transfer trials reflect our developing understanding of the genetic basis of many diseases and rapid advances in molecular biology including the ability to produce vectors capable of transferring genetic material into somatic cells. However, the need for careful assessment of the potential benefits and risks of all gene therapy trials has been highlighted by the unexpected death of a young patient that was directly attributable to the gene transfer trial *(7)* and the development of leukemia in several patients who underwent retrovirus-mediated gene transfer to correct X-linked severe combined immunodeficiency syndrome (8,*9*).

Several live pathogenic viruses have been modified to transfer genes of interest. The ability of these vectors to infect patients (and potentially other unintended persons) raises considerations for infection control. This chapter provides an overview of gene transfer technology and regulatory requirements for research in the United States and discusses the infection control aspects of clinical trials using gene transfer.

Recommendations for infection control of gene therapy/transfer have been discussed in an editorial (10), consensus conference (11), and a review article (12).

BACKGROUND

Gene transfer is a term that can be applied to any clinical therapeutic procedure in which genes are intentionally introduced into human somatic cells *(13)*. Prior to considering gene transfer, several requirements must be fulfilled. First, the gene(s) in question must be identified, and the nature of the defect characterized. Genetic diseases can be defined by the aberrant, specific gene expression that differs from the disease-free state. This variance may be due to a gene product that is absent or deficient (e.g., the cystic fibrosis transmembrane regulator (CFTR) protein) *(14,15)*, one that is abnormally present (e.g., Epstein-Barr virus nuclear antigen-1 in Hodgkin's disease) *(16)*, or abnormal regulation or expression of normal cellular products (i.e., downregulation of human leukocyte antigens by adenovirus). Second, it is important to understand which tissues express the defect and how accessible they are to manipulation. For example, while hemophilia B is caused by inadequate production of factor IX by the liver, factor IX does not require precise metabolic regulation, and even small amounts of production of factor IX by any cell line can prevent disease manifestations. Thus, hemophilia B is potentially amenable to *ex vivo* manipulation of hematopoietic cells or fibroblasts *(17)*. The key technologies that have facilitated the utilization of gene transfer include new methods by which cellular genes can be isolated (cloned), manipulated (engineered), and transferred into human cells. To obtain a therapeutic effect, there are basically three options for somatic gene therapy: (a) replacement of defective or missing genes for the treatment of inherited diseases, (b) augmentation of normal gene function or introduction of additional genetic information that interferes with proliferative diseases, and (c) blocking disease triggering or supporting genes like oncogenes on the deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) level (Table 69-2). In brief, these three options could be thought of as gene replacement, gene addition, or gene correction *(18)*.

Human gene transfer is currently limited to manipulations affecting somatic, differentiated cells. Germline gene transfer, where reproductive cells are treated for the correction of a genetic disease being transferred to the patient's descendants, is not likely to become acceptable as a feasible strategy in the near future. Due to the potential risks and unpredictable results, germline gene transfer has never been authorized in humans.

There are two main approaches to gene transfer: *in vivo* gene transfer, in which genes are delivered directly to target cells in the body, and *ex vivo* gene transfer, in which

TABLE 69-1

Approved Gene Therapy Protocols Through 2009

Trial Division	*Subdivision*	*Number of Protocols (%)*
Country of origin	United States	989 (63%)
	Other	590 (37%)
Clinical phase	I	952 (60%)
	I/II	299 (19%)
	II	258 (16%)
	III	53 (3%)
	IV	2 (0.1%)
Diseases addressed	Cancer	1019 (65%)
	Monogenic diseases	125 (8%)
	Infectious diseases	127 (8%)
	Cardiovascular diseases	138 (9%)
	Neurological diseases	30 (2%)
	Ocular diseases	18 (1%)
Vector	Retrovirus	336 (21%)
	Adenovirus	387 (24%)
	Lipofection	109 (7%)
	Naked/plasmid DNA	287 (7%)
	Pox and vaccinia viruses	222 (14%)
	Adeno-associated virus	71 (4%)
	Herpes simplex virus	55 (3%)
	RNA transfer	23 (1%)
	Others/unknown	128 (8%)

(Adapted from Gene therapy clinical trials. Available from http://www.wiley.com/legacy/wileychi/genmed/clinical/. John Wiley & Sons Ltd., 2009.)

target cells are genetically manipulated outside the body and then reimplanted *(13)*. To carry out gene transfer, the exogenous gene(s) is transferred in an expression cassette, including the promoter, which regulates expression of the new gene, often in the form of a complement DNA (cDNA), and stops signals to terminate translation *(19)*. The exogenous or therapeutic gene can be isolated from the genome of a human, another animal, a plant, a bacterium, or a virus and may code for any type of protein *(13)*. Depending on the choice of the regulatory element, which controls the expression of the therapeutic gene, gene expression can be high or low level, specific to certain cell types, or even continuously variable, and can respond to local environmental factors such as the partial pressure oxygen or the concentration of a drug *(13)*.

The expression cassette is transferred to target cells using a vector. The most commonly used vector systems include retroviruses, lentiviruses, adenovirus, adeno-associated virus, poxviruses such as vaccinia, and herpes simplex virus (Table 69-3). Each delivers the expression cassette via distinct mechanisms and each has unique advantages and disadvantages (Table 69-4). Although viral vectors have been most commonly used, nonviral vector systems are of increasing scientific interest. Nonviral vector systems include plasmid–liposome complexes, newer kinds of vectors that sheath DNA in nonlipid coats, and naked DNA *(20–22)*.

To date, the many obstacles to successful gene therapy/transfer have not been overcome. The ideal gene delivery vehicle would efficiently and specifically transfer the gene to target cells and subsequently obtain high, regulatable, and durable levels of gene expression *(19)*. In addition, an ideal vector should not evoke an immune response (unless designed to do so), should be nontoxic to the recipient and easily purified in high concentration, and there should be no risk of recombination or replication (unless desired). Current obstacles to successful gene therapy include low efficiency of gene transfer to the target cell, inadequate regulation of the therapeutic gene in the transduced cell, and maintaining long-term, stable gene expression at an appropriate level.

COMMONLY USED VECTORS

Adenoviruses

Adenoviruses are the most commonly used vectors for gene transfer (6). They are icosahedral, large, nonenveloped, double-stranded DNA viruses. Adenoviral vectors are widely used because of several advantages (Table 69-4) *(23–25)*. There are four adenovirus gene regions, designated E1 through E4, that encode proteins necessary for viral replication. Early gene transfer trials utilized vectors that were constructed by deleting portions of E1 and inserting the transgene. Although the goal of this method was to develop a replication incompetent vector, it was subsequently demonstrated that cytokines (e.g., interleukin-6) could supply the function of the E1 region and permit low-level vector replication. In addition, E1-deleted adenovirus could replicate in the

TABLE 69-2

Strategies for Use of Gene Transfer

Strategy	*Method*	*Example*
Supplementation	Transfer a functional gene into cells that have a defective gene	Cure severe immunodeficiency by replacing a defective adenosine deaminase gene with the normal gene by means of a retroviral vector
Immunotherapy	Deliver a gene that will elicit an immune response when the gene product is expressed	Infect with vaccinia containing prostate-specific antigen gene
Cancer therapy	Deliver a therapeutic gene into cancer cells	Infect cancer cells with adenovirus containing the gene for tumor necrosis factor
Chemoprotection	Transfer a gene for drug resistance into normal cells to protect them from chemotherapy	Transfer a multidrug resistance gene into normal bone marrow cells; transplant the cells and administer chemotherapy to kill unprotected tumor cells
Ablative therapy	Deliver a gene that will allow activation of a prodrug leading to cell death	Insert the herpes simplex virus thymidine kinase gene into tumor cells and administer ganciclovir
Antiviral therapy	Deliver a gene into infected cells that interferes with viral replication	Transfer the gene for hairpin ribozyme, which cleaves HIV-1 RNA, into HIV-infected cells
Marking	Insert a gene into cells to identify them when the gene is expressed	Infect harvested bone marrow cells with a retrovirus containing neomycin phosphotranferase gene; after transplantation, look for cells producing the enzyme as evidence for engraftment

(Adapted from Evans ME, Lesnaw JA. Infection control for gene therapy: a busy physician's primer. *Clin Infect Dis* 2002;35:597–605.)

presence of coinfection with other DNA viruses, such as papillomavirus or cytomegalovirus. For this reason, modern vectors have deletions in additional regions of E2, E3, and/or E4. Growth of adenovirus vectors in the HEK 293 packaging cell line has led to recombination between the vector and viral gene sequences present in the packaging cell line with the generation of replication-competent adenovirus. The use of alternative cell lines may minimize this problem *(26)*.

Retroviruses

Retroviruses (e.g., murine leukemia virus) and lentiviruses (e.g., HIV) are the second most commonly used vectors for gene transfer. When murine leukemia virus or other retroviral vectors are used for gene therapy, the genes required for retrovirus replication such as *gag, pol,* and/or *env* are deleted and the therapeutic gene is inserted in their place *(27–31)*. As a result of these deletions, the vector is unable to replicate. Lentiviruses are increasingly

TABLE 69-3

Vectors Used for Gene Therapy

Vector	*Genome Size (kbp)*	*Gene(s) Deleted or Inserted*	*Packaging Cell Line*
Adenoviruses	36–38	E1a, E2, E3, E4, or all genes leaving signal sequences	HEK 293
Murine retroviruses	7–11	*gag, pol*, and *env*	HEK 293
Lentiviruses	7–11	All except *gag*, *pol*, and *rev*; additional deletions in long terminal repeats to produce self-inactivating vectors	HEK 293
Adeno-associated viruses	4.7	*cap* and *rep*	HEK 293 with plasmid-bearing adenovirus helper functions
Vaccinia	130–380	No deletions; therapeutic gene inserted into silent regions of the genome or into nonessential genes (e.g., the thymidine kinase gene)	Not applicable
Herpesviruses	120–240	Immediate-early genes	
Plasmids and virus-like particles		Not applicable	Not applicable

(Adapted from Evans ME, Lesnaw JA. Infection control for gene therapy: a busy physician's primer. *Clin Infect Dis* 2002;35:597–605.)

TABLE 69-4

Advantages, Disadvantages, and Infection Control Concerns by Vector

Vector	*Advantages*	*Disadvantages*	*Infection Control Concerns*
Murine retroviruses	Little immune response; potential for stable integration into host chromosome; amphotropic viruses for a wide variety of tissues	Inefficient *ex vivo* transfer; genes insert randomly and therefore have risk of insertional mutagenesis; inactivated by complement; only infect actively dividing cells; size of transgene limited	Minimal hazard when they are incubated with host cells *ex vivo*; secondary infections via accidental inoculation unlikely
Lentiviruses	Little immune response; potential for stable integration into host chromosome (lifelong gene expression); can be administered *in vivo* because they are complement resistant	Insertional mutagenesis; limited to CD4+ cells unless pseudotyped with vesicular stomatitis or Ebola virus surface glycoprotein	Secondary infections via accidental inoculation possible
Adenoviruses	High titers can be grown; not integrated into host genome; large capacity for transgenes; infect dividing and nondividing cells; very stable virus; can be administered *in vivo*	Systemic infection possible; elicits an immune response that may limit repeated use; genes may function transiently	Stable in the environment; potential transmission via contaminated fomites, close personal contact, or droplets; relatively resistant to some disinfectants
Adeno-associated viruses	Integrates into host chromosome; infects dividing and nondividing cells, can be administered *in vivo*; does not elicit an immune response; requires helper virus for expression	Small capacity for transgenes; risk of insertional mutagenesis; association with male infertility; problems with expansion of production capacity	Prudent to use same precautions as for adenovirus
Vaccinia	Can accommodate large transgenes; can be lyophilized; does not integrate into host chromosome	Replication-competent vector with many adverse reactions; immune response may limit usefulness	Infection can be transmitted via contact or droplet routes; may cause severe disease in immunocompromised contacts or contacts with underlying skin disorders; vaccinators should receive vaccinia vaccine
Herpesviruses	Produced at high levels; targets nondividing nerve cells; can accommodate large transgene; latency	Latency	If cutaneous infection present, transmission may occur via direct contact
Plasmids and virus-like particles	Safe; gene expression can be regulated	Low gene transfer efficiency; unstable in most body tissues	None

(Adapted from Evans ME, Lesnaw JA. Infection control for gene therapy: a busy physician's primer. *Clin Infect Dis* 2002;35:597–605.)

used because they overcome some of the limitations of the murine leukemia virus vectors. Multiple gene deletions in the lentivirus vectors make it extremely unlikely that the vector could be reactivated. In addition, the vectors are engineered to be replication incompetent by deleting sequences in the terminal signal (i.e., long terminal repeats) that are essential for gene expression. Unlike murine leukemia viruses, these vectors are resistant to complement and can be infused directly into the circulation, where they infect quiescent or dividing cells expressing CD4 on their surface *(32)*.

Retroviruses are advantageous because they elicit little immune response and because they integrate into the host genome. They offer the potential for stable long-term gene expression. A major concern is that these viruses may induce insertional mutations and transform target cells into cancer cells *(33)*.

Adeno-Associated Viruses

Adeno-associated virus is a single-stranded DNA virus. The virus is usually found as a provirus integrated into chromosome 19 of the host cell genome, where it remains inert until

helper viruses supply the missing proteins or genes needed for replication. Helper viruses include herpesviruses, adenoviruses, or vaccinia virus. Replication-defective vectors can be constructed by removing all internal viral coding sequences of the wild-type strain and inserting the transgene. The use of adeno-associated viral vectors including their advantages and disadvantages has been reviewed elsewhere *(34,35)*.

Poxviruses

Vaccinia virus, the vaccine agent used in the eradication of smallpox, is being used as a gene therapy vector. Unlike other vectors, it has not been engineered to be replication incompetent. Instead, transgenes are inserted into silent regions of the vaccinia genome *(36)*.

Herpesviruses

Herpes simplex is an enveloped double-stranded DNA virus that infects sensory neural cells where it remains in a latent state. Replication-incompetent virus can be produced by mutations in the required immediate-early genes *(37)*. Transgenes can be inserted into these replication-incompetent vectors. The use of herpes virus vectors has been reviewed *(38,39)*.

INFECTION CONTROL

Key aspects of infection control include protection of researchers and healthcare workers administering the gene therapy vector and caring for subjects of gene therapy research, environmental and equipment disinfection, and laboratory safety. Institutional guidelines should be based on the vector used.

Protection of Healthcare Workers

Currently, there are no National Institutes of Health (NIH), Food and Drug Administration (FDA), or Centers for Disease Control and Prevention (CDC) infection control guidelines for minimizing the hazards to healthcare personnel caring for patients on gene transfer protocols or for preventing person-to-person transmission of gene transfer vectors. For protocols that are conducted at, or sponsored by, institutions that receive NIH funding for recombinant DNA research, the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (http://oba.od.nih.gov/rdna/nih_guidelines_oba.html) requires that the submission of the gene transfer protocol to NIH include a description of the hazards of the proposed transfer to persons other than the patients being treated (40). Specifically, the investigator must describe the following:

1. On what basis are potential public health benefits or hazards postulated?
2. Is there a significant possibility that the added DNA will spread from the patient to other persons or the environment?
3. What precautions will be taken against such spread (e.g., patient sharing a room, healthcare workers, or family members)?
4. What measures will be undertaken to mitigate the risks, if any, to public health?
5. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to patients? Are such concerns applicable to healthcare personnel?

However, *NIH Guidelines* do not discuss how to assess the level of risk, what level of risk is acceptable, or measures to minimize such risks.

The goal of the infection control policies should be to minimize the risk of transmission of the gene vector to healthcare providers and visitors. For protocols that involve removal of the target cell with *in vitro* alteration followed by reinfusion, environmental controls should be adequate to prevent hazardous exposure of healthcare personnel. For protocols that involve administration of vectors that could result in potentially transmittable diseases (e.g., vaccinia, adenovirus), use of appropriate personnel protective equipment as recommended in the isolation guidelines (41) of the CDC should be sufficient to protect healthcare workers (Table 69-5). Special precautions may be advised for use of certain vectors. For example, persons administering vaccinia-based products should be screened and, if no contraindications are present, immunized with vaccinia.

For directly administered gene vectors, prevention should focus on the known modes of transmission of the vector. Standard Precautions, as described by the CDC, should form the basis for rational infection control measures. At our current stage of knowledge, the use of Contact and Droplet Precautions (gloving and masking before entering the room) for vectors transmitted by the contact or droplet routes appears warranted. For vectors infused directly into the patient, Standard Precautions should be adequate.

All gene transfer protocols should include guidance on the management of healthcare workers accidentally exposed to a gene therapy vector.

Disinfection

Proper disinfection of work areas, instruments, and spills is critical to prevent person-to-person transmission of pathogens via contaminated hands. The environmental stability and susceptibility of microorganisms varies. Among gene transfer vectors, adenoviruses are likely to be the most environmentally stable. Healthcare-associated outbreaks have been reported with both poxviruses and adeno viruses. Although most transmission is likely via droplets, contaminated fomites have also played an important role. CDC guidelines for the disinfection of environmental surfaces and equipment should be scrupulously followed *(42)*. In general, an EPA-registered hospital disinfectant should be used for cleaning environmental surfaces. A 1:10 diluted preparation of household bleach (sodium hypochlorite) would be effective against all currently used vectors. Infection control personnel should consult with the manufacturer of the gene transfer vector for their recommendations on the most effective surface disinfectant. EPA-approved high-level disinfectants would be adequate for patient equipment. However, care must be taken (appropriate use of personal protective equipment [PPE]) during the cleaning steps to protect healthcare workers from accidental infection. When possible, initial decontamination followed by cleaning and then high-level disinfection should be undertaken.

Laboratory Safety

Gene transfer vectors may represent a laboratory hazard during their construction. The U.S. Public Health Service

TABLE 69-5

Recommended Biosafety Levels for Pharmacy and Transmission Precautions Used for Patients Undergoing Gene Therapy

Vector	*Recommended Biosafety Level*	*Intravenous*	*Intramuscular or Intratumoral*	*Aerosol*	*Intradermal*
Murine retroviruses	2	S	NA	NA	NA
Lentiviruses	3	S	NA	NA	NA
Adenoviruses					
At $\leq 10^{13}$ pfu/dose	2	S	S	C, D	NA
At $>10^{13}$ pfu/dose	2	D, S	D, S	A, D, C	NA
Adeno-associated viruses	1	S	S	C, D	NA
Vaccinia	2	NA	NA	NA	S
Herpesviruses	2	S	S	NA	NA
Plasmids and virus-like particles	1	S	S	S	NA

A, airborne precautions; C, contact precautions; D, droplet precautions; NA, not applicable; S, standard precautions
(Adapted from Evans ME, Lesnaw JA. Infection control for gene therapy: a busy physician's primer. *Clin Infect Dis* 2002;35:597–605).

has provided an excellent guideline for assuring the safe handling of microbes (41). Strict adherence to this guideline is recommended for all microbiological and biomedical laboratories (Table 69-5). The key principle of biosafety ensconced in the guidelines is "containment," a collection of engineering controls designed to allow the safe handling of infectious materials in the laboratory environment. *Primary containment*, the protection of personnel and the immediate laboratory environment from exposure to infectious agents, is provided by good microbiologic techniques and the use of appropriate safety equipment (e.g., biological safety cabinets, enclosed containers). Preexposure immunization may be available and recommended (e.g., vaccinia vaccine for personnel working with this agent as gene therapy vector). *Secondary containment*, the protection of the environment external to the laboratory from exposure to infectious material, is provided by a combination of facility design and operational practices (e.g., specialized ventilation systems to ensure directional airflow, controlled access zone).

The U.S. Public Health Guideline groups all microbes into four categories depending on several factors including pathogen virulence, modes of transmission, and availability of vaccine and treatment. The pathogen group then defines four levels of recommended biosafety levels (BSLs) that require increasingly elaborate primary and secondary containment:

- BSL-1 practices, safety equipment, and facility design and construction are appropriate for undergraduate and secondary educational training and teaching laboratories, for other laboratories in which work is done with defined and characterized strains of viable microorganisms not known to consistently cause disease in healthy adult humans (e.g., adeno-associated virus).
- BSL-2 practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with the broad spectrum of indigenous moderate-risk agents that are present in the community and associated with human disease of varying severity (e.g., adenovirus). Primary hazards to personnel working with these agents relate to accidental percutaneous or mucous membrane exposures, or ingestion of contaminated materials.
- BSL-3 practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents with a potential for respiratory transmission, and which may also cause serious and potentially lethal infection (e.g., lentiviruses). Primary hazards to personnel working with these agents relate to autoinoculation, ingestion, and exposure to infectious aerosols.
- BSL-4 practices, safety equipment, and facility design and construction are applicable for work with dangerous and exotic agents that pose a high individual risk of life-threatening disease, which may be transmitted via the aerosol route and for which there is no available vaccine or therapy (e.g., Ebola virus). Currently, no gene therapy vectors fall into this class. The primary hazards to personnel working with BSL-4 agents are respiratory exposure to infectious aerosols, mucous membranes or nonintact skin exposure to infectious droplets, and autoinoculation.

Management of Research Subjects

It would be ideal to either use or engineer live vectors that have a self-limited life span. In this case, research volunteers should be maintained on precautions until proven vector-free. Informed consent should include agreement to consent to isolation requirements. Prior agreement with state or local health departments can be sought to allow the use of a limited, legally enforced quarantine for patients who seek to leave the hospital and who may endanger the community. Quarantine measures should be individually reviewed by a biosafety

committee whenever instituted. Should volunteers exposed to live vectors decide to leave containment prior to the end of their quarantine period, they should be contacted by appropriate county or state health department personnel.

Adenoviruses

In persons with normal host defenses, adenoviruses cause minor illnesses such as conjunctivitis, respiratory tract disease, and gastroenteritis. In persons with abnormal host defenses, adenoviruses may cause serious illnesses including pneumonia, gastrointestinal hemorrhage, cystitis, and hepatic necrosis. The mortality rate has been reported to be as high as 60% among stem cell transplant patients and as high as 20% among renal or liver transplant patients with adenoviral infections. Currently, there is no effective prophylactic vaccine or therapy.

Initially, the use of adenoviral vectors generated two concerns. First, that the vector might recombine with wild-type virus and become replication competent. Second, that replication-competent adenovirus reactivants in the treatment inoculum might be shed by patients who had undergone gene transfer leading to transmission of infection to healthcare workers, visitors, family members, or other patients. For this reason, elaborate infection control measures were initially employed. However, published trials in which inocula $<10^{13}$ virus particles were used have not demonstrated either shedding or significant numbers of replication-competent recombinants. It is still not known if therapy with higher titers of virus would present a hazard.

Because of concerns that complementation by wild-type adenoviruses could lead to the development of replication-competent virus, it may be prudent to screen prospective gene transfer patients and healthcare workers for clinical signs of adenovirus infection. Subjects with possible active infection should be deferred from entering the trial; healthcare workers with possible infection should be reassigned to care for other patients. Pharmacy staff preparing adenoviral vectors should work in a level 2 biosafety cabinet and wear appropriate PPE (gloves, gowns). The vector should be transferred in a container clearly marked with a biohazard label. Air in syringes or tubing should be expressed in the pharmacy, not at the bedside.

Adenoviruses are extremely hardy and can survive on surfaces for an extended period of time. Surface disinfection should be performed after the subject has left his/her room. Only disposable equipment should be used, or equipment should be disinfected following patient use. Because of the theoretical risk of aerosol transmission if high-titer vector is provided, it would be reasonable to manage such patients on Droplet Precautions.

Retrovirus

Murine retroviral gene transfer is usually performed *ex vivo* in a laboratory under carefully controlled conditions. Since there is no evidence that wild-type murine retroviruses cause human disease, these vectors probably do not represent a risk even if directly inoculated into the bloodstream. Newer murine-based vectors that have been engineered to be complement resistant and lentiviral vectors are theoretically capable of causing human disease. However, replication-competent lentivirus vectors have not been reported and hence infection, while theoretically possible, is highly unlikely.

Standard Precautions as used to prevent HIV transmission should be effective in preventing transmission of retroviral vectors. Whenever possible, needleless devices should be used to minimize the likelihood of accidental percutaneous injury. There is no need to isolate patients, use dedicated equipment, restrict visitors, use special precautions for waste disposal, or require special handling of linens or eating utensils.

Adeno-Associated Virus

Only limited data are available on the frequency of vector shedding or reactivant shedding. Theoretically, adeno-associated virus vectors could be transmitted by the respiratory or fecal–oral route as is adenovirus. In the absence of specific guidelines, it seems reasonable to use the same guidelines for adeno-associated viral vectors as are recommended for adenoviral vectors.

Poxviruses

Vaccinia is administered most commonly by intradermal scarification or intradermal injection. The virus is likely to be shed from the immunization site until the lesion completely scabs and heals over. Administration of vaccinia vectors should be done using aseptic technique (gloves) in a private room. Because vaccinia vectors are not designed to be replication defective, the risk of cross-infection with this vector is greater than for other gene therapy vectors. The risk of contact transmission can be minimized by keeping the vaccination site covered with a semipermeable or gauze dressing. An occlusive dressing should not be used. Contaminated dressing should be managed and disposed of as regulated medical waste. All personnel working with vaccinia vectors should be screened and provided vaccinia immunization unless contraindicated. Personnel with a contraindication to vaccinia immunization should be prohibited from working with vaccinia vectors. Vaccinia vaccine should be provided only with informed consent. Vaccinated healthcare personnel should be managed as recommended by the CDC during the postvaccination period.

Vaccinated subjects may be managed using Standard Precautions. If they develop generalized vaccinia, progressive vaccinia, or eczema vaccinatum, they should be placed on Contact and Airborne Precautions. In some cases, use of vaccinia immune globulin may be indicated. There are no special recommendations for the handling of eating utensils. Potentially contaminated clothes and bed linens should be managed appropriately during transport and washed with either hot water followed by drying or washed with bleach.

Herpesviruses

Only limited information is available on the shedding of herpesvirus vectors. Transmission is possible with direct contact with lesions. However, the use of Standard Precautions should prevent transmission. Although, herpes simplex virus can survive on fomites for up to 4 hours, fomite-mediated transmission has not been reported.

REGULATION

The institutions with major regulatory responsibility over human gene therapy are the NIH and the FDA, which have overlapping jurisdiction in the United States. Within the NIH, the Office of Biotechnology Activities (OBA) is responsible for reviewing and coordinating all activities related to gene therapy (43). The Recombinant DNA Advisory Committee (RAC), administered by OBA, is a public advisory committee that advises the NIH Director on recombinant DNA research. Within the FDA, gene transfer oversight falls within the Center for Biologics Evaluation and Research (CBER) (44). Experiments involving the deliberate transfer of recombinant DNA or DNA- or RNA-derived recombinant DNA into human subjects (human gene transfer) cannot be initiated without review by both NIH/OBA and the FDA if the trial is conducted at, or sponsored by, an institution that receives any NIH funding for recombinant DNA research. For studies subject to NIH oversight, the local Institutional Biosafety Committee (IBC) must review these and other studies involving recombinant DNA and the IBC is responsible for insuring that the principal investigator carries out the requirements outlined in the *NIH Guidelines*. In addition, the local Institutional Review Board (IRB) must approve human studies.

PRODUCT PREPARATION AND MONITORING

Key regulatory and safety aspects of product preparation include (a) an adequate rationale for efficacy of therapy; (b) vector source materials, which should be characterized and documented thoroughly, and viral vectors or plasmids, which should be generated from cloned and characterized constructs and subjected to confirmatory identity tests; (c) a detailed understanding and description of the procedure for selection of the final gene construct, method of transfer of the gene construct into the host cell, and selection and characterization of the recombinant host cell clone including vector copy number and physical state of the final vector construct inside the host cell (i.e., integrated or extra chromosomal); (d) a master viral bank, which should be created when a virus, with or without a therapeutic gene, is used as a seed in the manufacture of a therapeutic vector; and (e) demonstration of lot-to-lot reproducibility.

Additional important factors in the preparation of material for human gene transfer include the following: (a) sterility of the final product must be maintained (e.g., freedom from bacteria, fungi, *Mycoplasma,* and adventitious viruses); (b) in the case of replication-defective or replication-selective vectors, master viral banks should be demonstrated to be free of replication-competent viruses, which may arise as a result of contamination or recombination during the generation of the master viral bank; (c) products made by cells and required for therapeutic activity should be shown to be biologically active, and this activity must be quantified and shown adequate to produce the desired effect *in vivo*; (d) for genetically altered *in vitro* cells, evidence should be available as to whether cells survive and continue to function *in vivo*; and (e) for directly administered vectors, a highly sensitive assay should be available for detecting infection with the vector. In addition to being highly sensitive, the assay should also be specific for detection of the genetically altered vector.

This last point has been a concern since the inception of the RAC in 1974 and is a critical issue in infection control. There are many viral-like sequences endogenous in mammalian genomes, and the possibility exists that a vector could recombine with endogenous sequences or with a coincident superinfecting virus. Consequently, vectors have been designed that would require multiple recombination events, each one unlikely to produce a replication-competent virus (45).

DEVELOPING AN INFECTION CONTROL POLICY

Infection control recommendations are based on the microbiology and epidemiology of the vector used in the gene therapy protocol. Infection control policies should be altered after scientific studies provide data to liberalize or alter the recommendations. Unfortunately, there are only limited data on which to base our current recommendation because data on transmissibility of vectors (e.g., shedding) and production of replication-competent vectors have often been considered proprietary. The development of infection control guidelines should gene therapy enter general medical use will be imprecise because data on which to base recommendations are limited by the small size of current trials, multitude of vectors in current use, highly selected patient populations,

TABLE 69-6

Components of an Infection Control Policy Regarding Gene Therapy

- Basis of infection control policy
  - Vector employed
  - Method of vector administration
  - Ability of vector to cause disease in the patient
  - Mode of transmission of the vector (i.e., contact, droplet, airborne)
  - Infectivity (i.e., transmissibility)
  - Ability of vector to cause disease in healthcare personnel
  - Potential for development of replication-competent vector
  - Environmental stability (i.e., survival)
  - Susceptibility to disinfectants
- Hospital care issues
  - Isolation precautions
  - Visitor guidelines
  - Restrictions on patient travel outside hospital room
  - Disinfection: surface, equipment
  - Restrictions on healthcare personnel allowed to care for patient
  - Laboratory risks: via percutaneous injury, via aerosolization
  - Monitoring: research subject, medical staff, environment, visitors

and handling of vectors by highly skilled researchers. Further, the limited number and small size of trials makes it impossible to assess the possibility of rare adverse events.

The issues to be assessed in developing infection control policies are described in Table 69-6. In general, patients should be placed on isolation precautions based on the vector, mode of transmission, and risk of transmission. All patients should be managed using Standard Precautions. Other CDC Precaution categories should be used as previously described. Measures should be in place to prevent sharps injuries.

Gene transfer vectors should be managed in the laboratory using NIH biosafety guidelines. Research personnel should be trained in the proper use of PPE. Vectors should be disposed of as regulated medical waste. Surface decontamination should be performed using EPA-registered hospital disinfectants unless the vector requires other agents to ensure inactivation. In general, the pharmacy should adhere to similar safety guidelines such as preparing vectors for administration in an appropriate biosafety cabinet and use of appropriate PPE.

The infection control policy should also address the screening and potential exclusion of personnel (e.g., workers with potential adenovirus infection), need for immunizations (e.g., vaccinia immunization), and management of personnel with accidental exposure to the vector (e.g., sharps injury).

Gene transfer studies have been conducted in the United States for more than 20 years. To date, such studies have not resulted in demonstrated illness or infection in healthcare personnel. Thus, healthcare personnel should be reassured that the recommendations described in this chapter can protect their safety.

CONCLUSIONS

Gene therapy is at the cutting edge of science. Appropriate infection control practices will need to be based on technologic advancements within the field of gene therapy, scientific assessment of the adequacy of current containment practices, and ongoing evaluation of risks to patients and healthcare personnel.

ACKNOWLEDGMENT

The authors wish to thank Jacqueline Corrigan-Curay, J.D., M.D., Acting Director, Office of Biotechnology Activities, National Institutes of Health, for her careful, thoughtful, and constructive review of this chapter.

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SECTION IX

Prevention of Healthcare-Associated Infections Related to the Hospital Environment

CHAPTER 70

Central Sterile Supply

Lynne M. Sehulster

Reliable sterilization of surgical instruments, textiles, utensils, and innumerable other items essential to medical care is one of the oldest and most basic measures for the prevention of healthcare-associated infection (HAI), dating back to the studies of Louis Pasteur and Robert Koch over a century ago *(1)*. The central sterile supply (CSS) unit, or sterile processing department, is a specialized service area of virtually all hospitals and an increasing number of nonhospital healthcare settings (e.g., ambulatory surgical centers). This service area is responsible for collecting and receiving reusable patient-care items (e.g., instruments and devices) used during the provision of healthcare and for cleaning, reprocessing, and distributing these items back to appropriate patient-care areas in the healthcare facility (e.g., operating rooms [ORs], intensive care units). CSS units are often called upon to manage the receipt and distribution of sterile, single-use, disposable patient-care items and other consumables as well. Patient safety is the overriding objective for all aspects of CSS activities.

The delivery of safe products for use in patient care, however, depends not only on the efficacy of the microbial inactivation processes (e.g., sterilization, high-level disinfection) and a thorough understanding of these processes and instrument cleaning, but also on a well-designed facility, good infection prevention practices, effective quality control, and use of proven device management procedures before, during, and after device reprocessing *(2)*. The CSS unit should have in place policies and procedures governing all aspects of activity within the unit. Key elements in these documents include but are not limited to (a) engineering and facilities management requirements; (b) infection prevention; (c) quality assurance and process management; (d) occupational safety and health; (e) employee training and competency demonstration; and (f) traffic control *(3)*. Furthermore, the CSS unit should develop policies that address oversight of instrument reprocessing located elsewhere in the facility.

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names and/or proprietary product names is for identification purposes only and does not constitute an endorsement by CDC or the U.S. Public Health Service.

GENERAL CSS UNIT DESIGN, ENVIRONMENT, AND INFRASTRUCTURE

CSS Unit Design, Configuration, Function

A CSS unit is divided generally into distinct areas based on unique functions (4,5). These areas should be partitioned into separate units whenever possible; separation of soiled and clean work areas is especially important to minimize spread of contamination. The receiving, decontamination, and cleaning area has work tables, sinks, and equipment to facilitate sorting, initial decontamination of, and thorough cleaning of devices and reusable items. Some washer–decontamination equipment units are designed with pass-through doors to allow items to move from the soiled area to a clean area in a single pass, thereby avoiding recontamination (4). The clean side of a CSS unit encompasses several functions. These include a preparation and packaging/tray

assembly, the sterilization area where the various sterilizers are located, an area for ethylene oxide (ETO) sterilization and aeration (if such a sterilizer is present), and a storage space for sterilized packs. If the hospital has a laundry on site, the surgical pack room where clean textiles are prepared for surgical packs to be sterilized may be located on the clean side as well (6). Other function-specific areas within the CSS unit include (a) a materiel management area (if assigned to the CSS unit) for incoming new, packaged manufactured supplies; (b) an equipment and cart holding area for sterilized packages awaiting distribution within the hospital; (c) an equipment storage area; (d) housekeeping and a housekeeping equipment storage room; (e) the personnel support area; and (f) the administrative area.

The design of a CSS unit takes into account the flow of the work load and the type of material distribution system. Distribution may be accomplished by automation (e.g., vertical or horizontal conveyor, pneumatic tube systems), powered delivery carts, or manual pickup and delivery. Hand washing facilities should be conveniently located throughout all areas within the CSS unit (4,5). Emergency eye wash stations and showers should be available in areas where chemicals are used (5). The layout of the CSS unit should allow for adequate space for personnel and equipment/cart movement. Clean areas should have adequate space for work tables and appropriate equipment and sterilization supplies support to facilitate the assembly of instrument trays and packages for sterilization. Equipment and cart areas should be readily accessible from the clean areas. CSS units may or may not serve as materiel management operations for the facility. If this function is assigned to CSS, the decasing/breakout area is used to accommodate the unpacking and distribution of manufactured clean supplies to locations elsewhere in the hospital. Alternatively, some of the purchased items may be sent to the preparation/assembly area to be packaged for sterilization. The material management area is usually located near the clean area but not in it (4,5). This helps to prevent introduction of environmental contamination often associated with packaging materials such as corrugated cardboard. The personnel support area provides space for toilet, shower, and locker facilities for employees. If the surgical pack room functions are assigned to the CSS unit, this is usually a room where clean textiles are inspected, repaired as needed, folded, and assembled into wrapped packs to be sterilized (6). If the hospital's laundry service, including surgical pack assembly, is provided by an outside contractor, the CSS unit must develop policies and procedures to have those packs delivered to the CSS unit for sterilization.

Climate Control and Ventilation Requirements

Adequate humidity, ventilation, and temperature control are important for prevention of environmental contamination of reprocessed items, provision of appropriate storage of sterile goods, and maintenance of a safe workplace. Temperatures in CSS areas vary, but it is common to find the temperature in general work areas, administrative areas, and personnel support areas set at 75°F (24°C). The main exception is for the cleaning/decontamination area where temperatures are in the range of 60°F to 68°F (15.6°C–20°C) as recommended by the Association for the Advancement of Medical Instrumentation (AAMI) (5). This provides an adequate comfort range for the workers who must wear substantial protective attire throughout the day. Humidity levels in CSS areas should be set generally in the range of 30% to 60% (4,5). The ventilation system should be designed so that air flows from clean areas into soiled areas and is exhausted to the outside or, if recirculated, passed through an appropriate bank of filters (e.g., a high-efficiency particulate air [HEPA] filter) for return to the system (4,5). Depending on which standards organization's benchmarks are used for reference, 4 to 10 air changes per hour (ACH) are specified for CSS ventilation, with a minimum of 6 to 10 ACH in the cleaning/decontamination area and a minimum of 10 ACH in the area where the sterilizer equipment is located (4,5). The areas under negative pressure (i.e., cleaning/decontamination, sterilizer loading area, and restrooms/housekeeping) are vented directly to the outside, whereas air from the other areas of CSS can be recirculated. Table 70-1 depicts the ventilation benchmarks set by two major standards resources.

The Joint Commission has updated the hospital accreditation standards for 2011 to reflect adoption of the Facility Guidelines Institute (FGI) *2010 Guidelines for Design and Construction of Health Care Facilities* (4,*7,8*). According to the Joint Commission, architects and design engineers for any new hospital construction or major renovation projects (including those in the CSS unit) initiated after January 1, 2011, need to use the 2010 edition of the FGI guidelines or look to relevant state rules and regulations pertaining to hospital construction.

Utilities Infrastructure

The availability and configuration of systems that provide steam, hot and cold water (or water of a temperature specified by reprocessing equipment manufacturers), distilled or demineralized water, compressed air, nitrogen, vacuum sources, electrical power, air exhaust, and drainage of sewage are important to consider when designing the CSS unit and installing equipment (*3*,4,5). The electrical system in the unit should allow for the safe and efficient operation of equipment and provide for adequate lighting. Availability of a source of uninterrupted power is recommended in the event of an emergency (5).

Moist heat sterilization methods (i.e., saturated steam under pressure) remain the primary choice for terminal reprocessing of heat-stable instruments and devices. The quality of the steam is critical to the efficient operation of these sterilizers, and there should be sufficient steam capacity engineered into the system to accommodate this demand. Hospital boiler systems may not be capable of providing steam of sufficient quality; self-contained packaged steam generators are another option. If a boiler is used, the equipment must be serviced and maintained by trained personnel. Additionally, the steam distribution system and piping should be insulated to prevent steam condensation to water while en route to the sterilizer *(9)*. Steam delivered to the steam sterilizers should be saturated steam with a steam quality between 97% and 100% (5,10). The purity of the steam should meet or exceed International Standards Organization (ISO) recommendations for limits on heavy metals, conductivity, pH, appearance, hardness, chlorine, phosphate, and evaporate residue (5,*11*).

TABLE 70-1

CSS Unit Ventilation/Climate Control Requirements

	Air Flow/Pressure		*Minimum Outdoor ACH*	*ACH*		*Exhaust to Outside*		*Recirculated*		*Temperature*		*Relative Humidity*	
Area	*FGI*	*AAMI*	*FGI*	*FGI*	*AAMI*	*FGI*	*AAMI*	*FGI*	*AAMI*	*FGI*	*AAMI*	*FGI*	*AAMI*
Endoscope cleaning area	Neg (In)	—	2	10	—	Yes	—	No	—	NR	—	NR	—
Soiled/decontamination room	Neg (In)	Neg (In)	2	6	10	Yes	Yes	No	—	72–78°F 22–26°C	60–65°F 16–18°C	NR	30–60%
Clean workroom (preparation and packaging)	Pos (Out)	Pos (Out)	2	4	10 (down draft type)	NR	No	NR	—	72–78°F 22–26°C	68–73°F 20–23°C	≤60%	30–60%
Sterilizer equipment room	Neg (In)	Neg (In)	NR	10	10	Yes	Yes	No	—	NR	75–85°F 24–29°C	NR	30–60%
Sterilizer loading/unloading area	—	Pos (Out)	—	—	10	—	Yes	—	—	—	≤75°F ≤24°C	NR	30–60%
Textile pack room	—	Pos (Out)	—	—	4 (down draft type)	—	No	—	—	—	68–73°F 20–23°C	—	30–60%
Clean/sterile storage	Pos (Out)	Pos (Out)	2	4	10 (down draft type)	NR	No	—	—	72–78°F 22–26°C	≤75°F ≤24°C	≤60%	≤70%
Restrooms, housekeeping	Neg (In)	Neg (In)	NR	10	10	Yes	Yes	No	—	NR	≤75°F ≤24°C	NR	30–60%

ACH, Air changes per hour; FGI, Facility Guidelines Institute; AAMI, Association for the Advancement of Medical Instrumentation; Neg, Negative pressure, air flows into the space; NR, No requirement; Pos, Positive pressure, air flows from the space into adjacent areas.

KEY ELEMENTS OF INSTRUMENT AND DEVICE REPROCESSING

Effective sterilization of items depends not only on reliable operation of the gas, steam, or low-temperature sterilizers, but also on correct methods of cleaning, packaging, arrangement of items in the sterilizer, and storage of these items. Likewise, if it is appropriate for a device to receive high-level disinfection, the success of this process depends on thorough precleaning, adherence to disinfectant use conditions, followed by thorough rinsing and drying.

Cleaning and Decontamination

The essential first step to any terminal reprocessing strategy for reusable medical instruments and devices is the reduction of bioburden. Debris such as blood, mucus, oil, or other foreign matter interferes with the sterilization process by acting as a barrier to the sterilizing agent (5,*12*,13). Additionally, cleaning and decontamination of used instruments render those instruments safe for CSS unit staff to handle during further reprocessing *(14)*. Retained debris can also affect the functionality of a device at the point of use, resulting in additional patient safety concerns *(15)*.

A process definition of cleaning is the removal of all adherent visible soil from the surfaces, crevices, joints, and lumens of instruments. Decontamination is the physical or chemical process that renders a potentially contaminated, inanimate object safe for further handling (5,*15–18*). The techniques for instrument cleaning and decontamination are manual scrubbing with brushes, ultrasonic cleaning, and processing with a washer–sterilizer or washer–decontaminator *(15)*.

Initial Considerations Instruments in general should be kept moist prior to cleaning. Dried-on debris is more difficult to remove. Disinfection or sterilization cannot be accomplished if gross contamination is present on the instruments at the time when the final reprocessing steps are initiated (12,*15,16,18,19*). Instruments should be covered with a wet cloth and then contained for transport to the CSS unit. Soaking instruments in water or other fluid during transport is discouraged because of the risk of spills and the danger of injury to workers in lifting heavy basins or containers. Once in the CSS area, instruments contaminated with organic matter may be immersed in an enzyme detergent solution to enhance manual or mechanical cleaning effectiveness. Enzyme soaks keep debris suspended in solution, preventing its deposition and drying onto the surface of instruments. When employing this method, care should be taken to use the appropriate use-dilution, water temperature, and soak times as provided by the specific manufacturer of the enzyme detergent. Additionally, workers may get a false sense of security about the safety of handling the instruments immersed in a presoaking solution. These instruments are not yet safe to handle without personal protective equipment (PPE).

The use of an appropriate detergent avoids damage to instruments, prolongs their use life, and prevents the creation of crevices in which debris can collect *(20,21)*. One inadvertent result of the implementation of Standard Precautions has been the increasing use of disinfectant/detergent agents for presoaking or manually cleaning medical instruments. Agents that contain chlorinated compounds (e.g., bleach) or that are highly acidic or alkaline can damage the surface layer of stainless steel instruments, resulting in corrosion and weakening. It is important to use only those detergent and disinfectant products specifically labeled for instrument cleaning. Hard surface disinfectant/detergents registered by the U.S. Environmental Protection Agency (EPA) are generally intended for cleaning and disinfecting large environmental surfaces (e.g., floors, walls, and table tops) and are not appropriate for general use on instruments.

Manual Cleaning Manual cleaning of instruments at the sink is still done and may be necessary for powered equipment and some extremely delicate items or to apply direct water pressure to contaminated lumens. Cleaning agents commonly used in manual cleaning contain surfactants, and some mechanical cleaning action (i.e., scrubbing, brushing) is needed for the effective removal of organic matter. During the cleaning and decontamination process, personnel must wear appropriate protective apparel (e.g., fluid-impervious gown or apron with full sleeves, latex or vinyl gloves that resist puncture or tearing during the process, face shield or surgical mask and goggles, a hair covering, and impervious shoe covers) (22). Such items provide the worker with protection from wetness and exposure to body fluids and tissues *(23)*. Splatter or aerosols generated during hand scrubbing should be kept to a minimum through appropriate cleaning techniques (e.g., keeping brushes under water during scrubbing) (5).

Whenever possible, scrubbing the devices by hand should be avoided, because it increases the worker's contact with contaminated surfaces and involves the added danger of handling sharp and pointed objects, thereby increasing the risk of sustaining percutaneous injuries. Sharp instruments should not be cleaned by hand when they can be effectively washed in a machine. Furthermore, contaminated, reusable sharps must not be stored or reprocessed such that the worker would have to reach into a container to retrieve the item *(20)*. Alternatives that can help prevent these injuries include using forceps retrieval or a perforated tray so that the devices can be cleaned *in situ* (22).

Ultrasonic Cleaning Ultrasonic cleaning is a method that reduces the need for hand scrubbing. The ultrasonic washer cleans by cavitation, a process whereby sound waves produce vigorous microscopic implosions of tiny vapor bubbles on the surface of objects immersed in the cleaning chamber (5,13). This agitation causes a vacuum-scrubbing action, pulling out fine debris particles from manually inaccessible surfaces (e.g., box-lock joints and serrations). Ultrasonic cleaning is not suitable for all devices. Refrain from using ultrasonic technology on chrome-plated instruments; powered instruments; endoscope lenses; or items made of rubber, silicone, or plastic (24). Items should be rinsed to remove gross soil before being placed in the ultrasonic washer. When grossly soiled items are placed into the ultrasonic washer, the process is less effective because the debris absorbs the sound waves. The water needs to be changed more frequently as well to minimize the amount of tissue and gross soil, but also to minimize the buildup of gram-negative bacteria, biofilm,

and endotoxin. Ultrasonic technology produces aerosols that reflect the fluid contents of the chamber; operation of the ultrasonic cleaner unit without a chamber cover allows these aerosols to escape. Because of this, the ultrasonic washer should be located in the decontamination area of the CSS unit. The potential hazards to personnel from aerosolization of such contaminated fluids should be considered when planning CSS worker safety programs. Exposure to such fluids should be prevented by use of engineering controls, changes in work practices, or use of PPE. The unit's chamber should be disinfected, rinsed, and dried at the end of the day. The manufacturer's directions should be followed for optimal results (5,*17,18,20*,24,*25*).

Automated Reprocessing Systems Washer–sterilizers use one of two methods to wash chamber contents. The first is a flooding technique, in which the chamber partially fills with water to which detergent has been added and then is agitated by blowing steam into the chamber through the water. These units generally operate at 270°F (132°C). This is an inefficient cleaning method that should not be relied on when there are lumened or complex devices in the load. The second method is generally used in larger, tunnel-type units. In these, rotating spray arms create water jets that clean by impingement. In this second category, most machines reach a temperature of 285°F (141°C) *(17)*.

Washer–decontaminator or washer–disinfector machines easily remove excessive amounts of debris from instruments by using spraying water aimed to cover all parts of the load. The numerous water jets allow excellent cleaning even if instruments are grossly soiled. The agitation of the water is such that it cleans instruments thoroughly without tossing them about, thereby reducing the risk of damage to delicate items. The operating water temperature is generally around 140°F (60°C), below the level at which protein rapidly coagulates, making removal easier than at higher temperatures *(15,25)*. Appropriate soap and disinfectant should be used in accordance with the manufacturer's instructions *(17)*.

Automated cleaning/decontamination equipment must be loaded, operated, unloaded, and serviced in accordance with manufacturer instructions (22). Washer racks should never be overloaded, and the placement of loaded racks in the equipment chamber should allow sufficient clearance for the water jet arm to move freely. Instruments in the racks and trays should be open and disassembled if appropriate to allow maximum contact with water and cleaning agent. Routine service typically includes visual inspection for mineral deposits that should be removed.

It is important that these automated systems are cleaned and maintained regularly in accordance with the manufacturer's instructions to prevent the colonization of the equipment with bacteria (e.g., *Pseudomonas aeruginosa* or nontuberculous mycobacteria [NTM]). Outbreaks of HAIs and episodes of pseudoinfections related to endoscopy and bronchoscopy have been attributed to contaminated washer–disinfectors through molecular epidemiology and strain identification techniques *(26–29)*. Bacteria, particularly those microorganisms commonly found in tap water (e.g., *Pseudomonas* species), can become resident in poorly maintained equipment through the formation of biofilms that may help protect the bacteria from inactivation with liquid chemical germicides *(29–34)*. This phenomenon has led some to explore ways to enhance quality assurance of the process in the interest of patient safety. A recent issue of debate is the sampling of the automated endoscope reprocessing system (AER) rinse water to help verify that in-line bacteriologic filters are performing according to specifications *(33)*. This position, however, is still not widely embraced by the endoscopy community at present, although debate continues (13,*35*).

Automated cleaning/decontamination processing is not indicated for all instruments and devices. This processing is not appropriate for washing electrical devices, battery-operated devices, or pneumatic operated equipment and devices (22). Instruments and devices with such features must be cleaned manually. However, the use of automated cleaning/decontaminating systems offers some advantages over manual cleaning. The process is controllable and minimizes worker contact with contaminated items *(14,36)*. Automation can enhance the quality assurance for the cleaning portion of the overall instrument reprocessing strategy. A wide variety of mechanical washer–cleaners from a number of manufacturers is available, and new technology continues to be developed. New innovations that increase worker safety and protection are especially in demand *(37)*. No single approach to decontamination and cleaning is effective for all instruments and degrees of contamination. Risks and benefits are associated with each method, and it is the responsibility of the CSS unit director to become familiar with relevant standards, guidelines, and information from the medical literature to determine best practices for decontamination and cleaning.

Endoscope Reprocessing The cleaning and terminal reprocessing of flexible fiberoptic and video endoscopes and bronchoscopes are often performed by specially trained technicians in the care units where these instruments are used. Nevertheless, CSS managers should have some oversight of the policies and procedures in these satellite reprocessing areas. Briefly, endoscopes (categorized as semi-critical devices according to the Spaulding Classification) are cleaned and subjected to either sterilization or high-level disinfection (13,38). From a practical perspective, high-level disinfection is chosen because these devices are heat sensitive (thereby precluding use of steam sterilization), but also for effectiveness of this disinfection process and its reasonably rapid turnaround time *(39)*. At present, the only sterilization process available for endoscope reprocessing is that of ETO sterilization. However, this process may not be suitable or appropriate for makes and models of endoscopes, and the required aeration time is very long (e.g., ~18 hours), which makes this an impractical choice (13,*40–42*). Immersion in a liquid chemical sterilant is also an impractical method due to the lengthy contact time periods (e.g., 10 hours). The practical alternative (i.e., liquid chemical sterilization using peracetic acid as the active ingredient in a proprietary system [Steris System 1, S20 sterilant]) is not an option at present due to recent regulatory action by the U.S. Food and Drug Administration (FDA). FDA has determined that this equipment and its proprietary chemical agent are adulterated and misbranded products *(43)*. Consequently, this chemical sterilizing system has been withdrawn from the market (44).

Effective reprocessing of these instruments begins the moment they are removed from the patient (13,38). All surfaces of the endoscope or bronchoscope should be kept moist until cleaning and further reprocessing can be performed. Although endoscopes can be cleaned with manual scrubbing and disinfected using immersion into liquid sterilant (with a short contact time validated for disinfection) or high-level disinfectant, AERs for washing and disinfection are the predominant choice for the reprocessing of these instruments primarily for the effectiveness of the process, but also because of space limitations in the care unit. One critical point to remember is that all AERs on the market today require that the endoscope or bronchoscope be manually rinsed so that gross soil is removed before placing the instrument in the AER. Some units also require the use of special connection devices that may be specific to a type or model of instrument *(26)*. Use of appropriate connectors helps to ensure that the liquid chemical sterilant or high-level disinfectant can effectively reach the interior surfaces of the instrument's channels (13,*45*) Thorough rinsing with sterile water, or tap water if sterile water is unavailable, is necessary to remove disinfectant residues that could lead to adverse patient reactions (13,38). An alcohol rinse is used primarily as a drying agent to help eliminate any residual moisture in the lumen of the device. Reprocessed endoscopes should be hung vertically in a designated cabinet to drain and dry until next use (13,38). A reprocessed endoscope should never be stored until next use in its original case (with the original protective padding). This practice prevents the internal channels of the instrument from drying in a timely manner, but more importantly the padding in the case usually becomes wet, leading to a buildup of bacterial contamination of the padding that in turn will contaminate the endoscope (13,38).

Packaging

Materials used for hospital instrument wrapping and packaging should provide a cost-effective means of containment to maintain the sterility of the contents (5,22,46). An intact wrapper impervious to extraneous microbes, moisture, dust, and soil, and strong enough to resist punctures and tears during normal handling, theoretically should protect properly sterilized material indefinitely. However, such materials may also impede the passage of steam, ETO, or the sterilants in low-temperature sterilizing systems, thus interfering with the sterilization process. Therefore, compromises from this ideal must be made for items processed in healthcare facilities because of the limited choices available for terminal sterilization. Additionally, wrapping materials should (a) provide a seal of proven integrity, (b) be resistant to delamination when the pack is opened, (c) be free of pinholes, (d) allow suitable printing or labeling, (e) minimize the generation of nonviable particles, (f) provide evidence of tampering, and (g) produce minimal or no lint if fabric is used *(47–49)*.

Packaging materials should be compatible with the sterilization process. When the steam sterilization process is used, the materials should allow adequate air removal, steam penetration, and drying (5,46). When ETO sterilization is used, materials should allow adequate penetration and release of the gaseous sterilant and moisture, a function that is especially important during aeration. Packaging materials for use with hydrogen peroxide gas plasma sterilizers and ozone sterilizers should be made from materials that are compatible with those processes to allow effective sterilant penetration and will not interact with the contents of the pack (46). Manufacturers of sterilizer equipment should provide the user with some indication of which packaging materials are suitable for their units.

Packaging materials should also be inexpensive, impervious to bacteria, sealable before sterilization, and flexible enough to permit swift wrapping and unwrapping (46,*50,51*). Materials should be evaluated and selected according to their performance properties rather than according to whether they are woven, nonwoven, reusable, or disposable *(52)*.

Muslin (i.e., 140 thread count, 100% cotton fabric) was the standard for many years in packaging for healthcare facilities, and some healthcare facilities continue to use textile packaging. Other fabrics have been used for packaging, including duck cloth, twills, barrier cloth, and treated barrier fabrics (22). Textile packaging is generally a reusable product, but this means that the textile needs to be laundered and inspected for fabric integrity. Patching of reusable fabrics is acceptable as long as the patches are applied with adhesive and not sewn in place. The critical factor is the amount of nonoccluded surface left after patching and folding (6). It is also important that textile packaging be stored at room temperature and humidity for at least 2 hours before use. This approach minimizes moisture buildup in the textile, thereby preventing superheating of the pack contents during steam sterilization (22).

Before a textile wrapper can be marketed, the product must be cleared by the FDA for use as a sterilization wrapper. In addition, consideration should be given to requiring that the material pass the American Society for Testing and Materials (ASTM) standard test method for resistance of protective clothing materials to synthetic blood (53).

Durable containment for instruments and devices is another option. FDA-cleared rigid containers, instrument cases, instrument cassettes, and organizer trays are commonly used (46). Regardless of what type of packaging is used to prepare packs for sterilization, packs should not exceed 25 lb in weight (46). This includes both the contents of the pack and the wrapper or containment.

Policies and procedures for in-house packaging should be written, reviewed annually, and readily available within the institution (46,*47–52*,53,*54–58*).

Activities Associated with the Sterilization Processes

General Principles The first thing that must be considered before subjecting a cleaned, reusable device or patient-care item to a sterilizing process is whether or not the materials are compatible with that process. Saturated steam sterilization is the most commonly available processing method in healthcare facilities, and it should be used whenever the device or instrument can tolerate moist heat because of the inherent reliability and robustness of the process and its low cost relative to other methods. However, heat-sensitive materials are being incorporated increasingly into modern medical devices and patient-care items. A number of modern, low-temperature sterilizing

systems provide alternatives for the sterilization of heat-sensitive materials. When making the decision to purchase a low-temperature sterilizing system/equipment, it's important to have a clear sense of what types of instruments and medical devices will be reprocessed in this equipment and to carefully consider the manufacturer's equipment information and advisories for use. Some device materials may be incompatible with some of these newer processes, and such interactions may physically degrade the item, destroy its material, or leave toxic residuals on or in the treated item *(58,59)*.

Currently, the FDA-cleared sterilization processes/technologies used in CSS units are: (a) saturated steam under pressure (steam sterilization); (b) ETO sterilization; (c) hydrogen peroxide gas plasma sterilization; (d) dry heat ovens; and (e) ozone sterilization. A detailed description of each of these processes can be found in Chapter 81 in this text.

It is important to remember, however, that all sterilizing systems have inherent limitations and that no single system can be used effectively for all instruments and devices *(60)*. A common problem with any sterilizing system is the ability of the sterilizing agent (e.g., steam, gas, gas plasma) to diffuse throughout the chamber and the load so that the agent makes contact with all surfaces (both exterior and interior) of the items undergoing sterilization. In steam autoclaves, trapped air, either in the chamber or within an instrument or container, can prevent effective penetration of the steam to all surfaces in the load. Instrument design (e.g., a long, narrow lumen) can pose significant challenges both for effectiveness of the cleaning procedures and sterilant diffusion. Load configuration and density must be carefully controlled to allow air removal, sterilant penetration, and drying in steam sterilization cycles. This is especially critical if the sterilizer relies on gravity displacement to remove air (5,22). For steam sterilizers that have mechanisms to assist in air removal (e.g., dynamic-air removal using pulsing steam or vacuum conditioning phases), the configuration and density issues are not as great, but drying may still be a problem if the sterilizer is overloaded (5,22). The performance of low-temperature systems, including ETO and gas plasma, is particularly affected by the presence of residual organic matter, salt, and moisture *(61)*.

Loading the Sterilizer Chamber: Key Considerations

All articles to be sterilized should be arranged so that all surfaces are directly exposed to the sterilizing agent for the prescribed time and at the prescribed temperature and humidity as appropriate. All hinged instruments should be open and/or unlocked. Reliable sterilization depends on both the sterilant's contact with all surfaces of the item and the duration of that contact. All articles should be aligned on sterilization carriers or in the sterilizer so as not to interfere with air removal and introduction of sterilant. Instrument sets should be placed in perforated wire mesh bottom trays or in instrument container systems (5,22). They should not be tilted on edge, as this results in the concentration of metal mass at the bottom of the tray. This arrangement interferes with drying *(15)*. Wrapped trays should not be stacked, as instrument damage can result. Rigid, reusable, sterilization container systems may be horizontally stacked if the container design permits adequate penetration of the sterilant. The container manufacturer's written instructions on this point should be followed.

When items are nested in one package, they should be separated by absorbent towels or other moisture-absorbent material. This enhances the passage of steam to all surfaces during sterilization and facilitates drying by preventing the pooling of condensate. Nested items should be positioned in the same direction so that (a) air pockets are not created, (b) condensate can drain out, and (c) sterilant can circulate freely *(62)*.

Sterilization Cycle Parameters Sterilizer equipment manufacturers are required to develop validated sterilization cycle parameters in order to obtain FDA clearance of said equipment. Depending on the sterilizing technology, the parameters may include but are not limited to time, temperature, humidity, pressure, concentration of the sterilant, aeration time, dry time. Standard cycles are typically used to sterilize the majority of surgical instruments and devices that are fairly simple in design and materials (e.g., heat-stable metal, manual instruments). Table 70-2 depicts sterilization cycle parameters for routine loads for steam sterilizers as compiled by AAMI (5). Sterilizer manufacturers will typically program these standard cycles into the equipment.

More recently, manufacturers of complex instruments (e.g., instruments with complex design, increased weight, powered instruments) are indicating in their reprocessing instructions that extended sterilization cycles (i.e., longer contact time with the sterilant, increased dry time) are necessary for the successful terminal reprocessing of these instruments (63). It is important to consider both the sterilizer equipment operating instructions and the instrument reprocessing instructions to determine the appropriate cycle parameters. When there are differences between these two instructions, the instrument instructions should take priority *(64)*. Invariably, this means that extended cycle instruments cannot be autoclaved with standard cycle instruments in the same load (63). Furthermore, not all extended cycle instruments have the same validated cycle requirements. The result of this is that it may be necessary to process a few instruments at a time rather than in a full load (63). In addition to sterilizer operating instructions, CSS units should ensure that there are written reprocessing instructions for all instruments, but it's especially important for all extended cycle instruments *(64)*.

Performance records for all sterilizers should be maintained for each cycle, including load contents and retained for the period indicated by the individual healthcare facility and/or the state's statute of limitations. Records for implantable devices should allow for tracking from the sterilizer to the point of use. These records may be used as documentation for product recall and quality assurance (5,10,22). All packages should have internal and external chemical indicators appropriate for the sterilizing system used (i.e., steam or low-temperature systems using ETO, gas plasma, or ozone).

Methods to Monitor the Sterilization Process Monitoring the sterilization process is an important quality assessment procedure for infection control and patient safety. The three forms of monitoring are (a) physical monitoring (observing and recording the parameters of

TABLE 70-2

Minimum Parameters for Steam Sterilization Cycles Used in Healthcare Facilities

Cycle Times for Gravity-Displacement Steam Sterilization Cycles

Item	*Exposure Time at 121°C (250°F) (min)*	*Exposure Time at 132°C (270°F) (min)*	*Exposure Time at 135°C (275°F) (min)*	*Drying Times (min)*
Wrapped instruments	30	15		15–30
			10	30
Textile packs	30	25		15
			10	30
Wrapped utensils	30	15		15–30
			10	30
Unwrapped nonporous items (e.g., instruments)		3	3	0–1
Unwrapped nonporous and porous items in a mixed load		10	10	0–1

Cycle Times for Dynamic-Air Removal Steam Sterilization Cycles

Item	*Exposure Time at 132°C (270°F) (min)*	*Exposure Time at 135°C (275°F) (min)*	*Drying Times (min)*
Wrapped instruments	4		20–30
		3	16
Textile packs	4		5–20
		3	3
Wrapped utensils	4		20
		3	16
Unwrapped nonporous items (e.g., instruments)	3	3	NA[a]
Unwrapped nonporous and porous items in a mixed load	4	3	NA

Check the instructions for your sterilizer to ascertain the manufacturer's cycle specifications.
[a]NA, not applicable.
(Adapted from ANSI/AAMI ST79:2010 & A1:2010 with permission of Association for the Advancement of Medical Instrumentation, Inc. © 2010 AAMI www.aami.org. All rights reserved. Further reproduction or distribution prohibited.)

sterilizer functioning, such as time, temperature, pressure, or gas concentration); (b) chemical monitoring (color- or physical-change indicators that detect exposure to sterilizing agents or conditions); and (c) biologic monitoring (spore testing, the most important check on sterilizer function). Additional information about sterilization process monitoring can be found in Chapter 81.

Physical Monitoring Physical data (e.g., physical parameters information for time, temperature) are usually the first indications of whether or not the sterilization process is consistent with manufacturer recommended cycle parameters. For each sterilization cycle, the mechanical readings should be checked on the printout at the conclusion of the cycle. Sterilizers without such printouts (either in digital or chart form) are not appropriate for modern acute care facilities and other healthcare venues and should be phased out of use as soon as economically feasible. Any deviation from the expected normal readings of the various parameters (e.g., time or temperature) should alert the operator to potential problems (5,22).

For steam sterilizers that use a vacuum assist to remove air at the beginning of the cycle (dynamic-air removal steam sterilizers), a Bowie-Dick–type test should be run daily at the beginning of the day to ensure that this key operation in the system is working properly (5,22). If this test indicates that air is not effectively removed from the sterilizer chamber, the sterilizer needs to be taken out of service for maintenance/repair. Prior to the sterilizer being returned to service, a repeat Bowie-Dick test is run on the sterilizer to confirm that the air removal problem has been corrected.

Chemical Indicators Chemical indicators are devices to provide information relative to the achievement of one or several of the conditions necessary to destroy microorganisms by a sterilization process. Some chemical indicators can indicate that a device has been exposed to a sterilization process (e.g., a throughput or process indicator), while others may provide more detailed information on the exposure conditions endured by the device. They can be useful for (a) monitoring product flow, to make sure that unprocessed product is not mistaken for that which has been sterilized; (b) ensuring the use of proper packing and sterilizer load configurations; and (c) ensuring the proper functioning of the processing equipment (5,22,*65*).

Chemical indicators are intended for use in conjunction with other process monitoring systems. The AAMI and the International Organization for Standardization (ISO) have designated six classes of chemical indicators available in the United States (5,22,*66*,67,68,*69*,70). These classes are (a) Class 1—process or throughput indicators, typically affixed to the external surface of the pack or rigid containment; (b) Class 2—specific test indicators, of which the air removal indicator (Bowie-Dick tests) is the prototype; (c) Class 3—single parameter indicators, designed to react to one aspect of the sterilization process (e.g., temperature); (d) Class 4—multiparametric indicators, designed to react to two or more parameters of the sterilization process; (e) Class 5—integrating indicators that are designed to react to all of the critical parameters over a specified range of sterilization cycles; and (f) Class 6—emulating indicators that are designed to react to all of the critical variables of specified sterilization cycles, with stated values having been generated from the critical values of the specified sterilization process (5,22,*66*,67,68,*69*,70). Class 3, 4, 5, and 6 indicators are all designed to be inserted into a pack to demonstrate that the target parameter(s) of the sterilization process has been achieved. When a Class 5 integrator chemical indicator is used according to manufacturer instructions, it can provide very accurate information about the sterilization process. Class 6 chemical indicators (emulating indicators) must be specific for each sterilization cycle and sterilization technology. Consequently, the CSS unit must have a different Class 6 emulating chemical indicator for each sterilizer time/temperature combination used (5,22). As the availability of Class 5 and Class 6 chemical indicators is a recent event in the US healthcare market, readers should consult AAMI standards for more detailed information regarding use of these devices (5,*66*,67,68,*69*,70). When used properly, the performance of the Class 5 and Class 6 chemical indicators has been correlated to the performance of a biological indicator (BI), but it should be emphasized that these chemical indicators are not intended to replace or be used to the exclusion of a BI. Class 1 to 6 chemical indicators are available to monitor steam sterilization processes. Class 1, 3 to 6 chemical indicators can be used with dry heat sterilizers and ETO sterilizers. Consult the sterilizer manufacturers for ozone and hydrogen peroxide gas plasma sterilizers for their recommendations regarding selection of appropriate chemical indicators.

Biological Indicators In the early 20th century, microbiologists and clinicians began to seek further assurances of sterility of reprocessed items beyond monitoring the physical variables, and suspensions of bacterial spores came into use as a biologic means of monitoring steam sterilization. The earliest culture control used was garden soil to which had been added a number of sporulating cultures of known resistant laboratory strains. In the late 1950s, commercially manufactured BIs began to be used in US hospitals *(1,71)*. These consisted of standardized preparations of *Geobacillus stearothermophilus* (formerly known as *Bacillus stearothermophilus*) spores with defined heat-kill characteristics.

BIs are defined in the AAMI standard as a calibration of microorganisms in or on a carrier put up in a package that maintains the integrity of the inoculated carrier while allowing exposure to the sterilant, is convenient to the user, and serves to demonstrate whether the conditions were adequate to achieve sterilization (5,*65*). BIs are standardized bacterial spore populations known to be resistant to the particular sterilant and physical methods of sterilization to be monitored. Thus, no single BI can be used reliably to monitor all of the various physical methods of sterilization. There are three basic types of BIs: (a) paper strips inoculated with bacterial spores; (b) self-contained BIs, in which the spores are enclosed in a carrier; and (c) enzyme-based BIs *(72)*. Of these, only the enzyme-based BIs are capable of providing rapid readout of results, generally in a matter of hours, as opposed to the 48 hours incubation required for determining growth. There are two types of enzyme-based indicators. One such product contains only the enzyme itself and is regarded by the FDA as a chemical indicator (either Class 4 or 5, depending on data submitted to the FDA). Another type relies on the reaction of an enzyme that is actually in the spore coat of a microorganism known to be resistant to the method of sterilization. This second type can be used either as an early readout indicator when only the enzyme reaction is assessed or as a typical BI if the spores are actually incubated in growth media.

At present, the Joint Commission, AAMI, and the Association of periOperative Registered Nurses (AORN) recommend using *G. stearothermophilus* spores for steam sterilizers, ozone sterilizers, and hydrogen peroxide gas plasma sterilizers; and *Bacillus atrophaeus* (formerly known as *Bacillus subtilis* var. *niger*) spores for ETO sterilizers and dry heat ovens (*8*,73,*74,75*). The Centers for Disease Control and Prevention (CDC) concurs with the use of gram-positive bacterial spores for BIs (13). Manufacturers of low-temperature sterilizer equipment should provide the user with information on the proper selection of an indicator system for use with their equipment. All hospital steam autoclaves should be monitored at least weekly with BIs, although many CSS units are monitoring their equipment daily. The Joint Commission, AORN, and AAMI also recommend monitoring every load sterilized by ETO. Each load containing implantable objects should be monitored with a spore test. The Joint Commission, AORN, and CDC further recommend that sterilizer loads containing implantable devices or intravascular devices should not be released until the spore test has been reported as negative. It is recognized, however, that in an emergency situation it may not be possible to quarantine implantable items for the 48 hours necessary for BI incubation (culture assay), especially if the assay of the indicator is dependent on growth of survivors. Rapid BIs (e.g., enzyme-based indicators) may alleviate this situation. The enzyme-based indicator measures a spore-specific enzyme, α-D-glucosidase, which is inactivated proportionally with the inactivation of the spore population. The assay of this enzyme-based indicator can be accomplished in a matter of minutes, and it has been shown that this BI is equivalent in sensitivity to the more conventional BIs (13,*76*). The availability of this type of BI may encourage more healthcare facilities to incorporate this quality assurance process into their services. A questionnaire survey of US hospitals in the late 1980s showed that 30% of 120 hospitals used a spore test with all loads containing implants. Furthermore, few hospitals using spore tests in the late 1980s quarantined the items until results were available *(77)*. The AAMI has recently endorsed the routine

release of all steam-sterilized loads, including implantable devices, based on the results of the enzyme readout only for the enzyme/spore combination BI *(74)*.

The BI pack should be placed in the area of the sterilizer that will present the most challenge to all sterilization parameters. For steam sterilizers, the BI should be placed at the front on the bottom and near the door in a routinely loaded sterilizer. For ETO sterilization, the BI should be in the center of the load. Each manufacturer of a sterilizer should provide instructions on test pack placement for that sterilizer, since these may differ based on design and cycle considerations.

BIs are designed such that the inoculum size should reflect the expected degree of contamination plus a margin of safety. Currently, commercially available BIs fall in the range of 10^4 to 10^6 spores for *G. stearothermophilus* and at 10^6 spores for *B. atrophaeus*. Additionally, the resistance of these cultivated spores is generally higher than that found in native species of the same type. Because the BIs have 10^4 to 10^6 spores per unit (which is far in excess of the expected bioburden remaining on thoroughly cleaned instruments and patient-care items), and the resistance is considered to be greater than the microorganisms on the healthcare items undergoing sterilization, the probability of nonsterility of the items in the load is considered to be <1 in 1,000,000 after a 12-log reduction of the BI *(78)*. This provides for a sterility assurance level of 10^{-6}.

Since their development, commercial BIs have shown significant variability *(79,80)*, but manufacturers in the industry have reduced this variability, increasing the reliability of their product. Still, problems with sporadically false-positive BIs continue to occur *(81,82)*. There are several factors that may influence the occurrence of a false-positive BI, many of which relate to human error. Use of a self-contained BI can minimize handling and the inadvertent introduction of contamination. If a BI is used without spore strip containment, the extra handling and open transfer for assay may produce false-positive BIs more often *(83)*. At present, use of a bare spore strip is not a general practice.

A single positive test does not necessarily indicate sterilizer failure (13). If available, a presumptive identification of the growing microorganism should be performed. This can be done by Gram stain and microscopic examination to ascertain that the microorganism is of the *Bacillus* species (i.e., gram-positive rods). While this is occurring, equipment failure should be ruled out. Immediate service should be requested to detect any sterilizer malfunction. If a sterilizer malfunction is identified, the equipment should be taken out of service and all items processed in that load should be recalled, cleaned, and reprocessed (13). Once a sterilizer is repaired, it is necessary to challenge the unit to confirm proper operation. This approach is also used when it becomes necessary to switch steam sterilizers over to an auxiliary supply of steam. The unit should be operated until two consecutive runs return negative BI results before the unit is returned fully to service. Ordinarily, this will mean that steam sterilizers may be down for several hours after repair, whereas ETO sterilizers and gas plasma units may be off-line for at least 7 days *(83)*. It is important to recognize that the use of a BI does not guarantee sterility but rather provides an additional mechanism for monitoring the sterilizer cycle beyond the graphic temperature–pressure record and chemical indicators. A negative BI test offers further assurance that the sterilizer variables and exposure time were what was intended. It can be inferred that there is a very high probability that all viable microorganisms remaining on the cleaned items contained in the load were killed *(1,84–86)*.

Indicators are validated for standard, programmed cycles. Therefore, the cycle parameters specified on the indicator should be matched to the cycle used for the load. Extended cycles should be monitored with a BI validated for the specific extended cycle and a Class 5 integrating indicator placed in the least accessible location in the tray or load *(64)*.

Storage

The sterile storage area should be adjacent to the sterilizing area, preferably in a separate, enclosed, limited-access, and well-ventilated area to provide protection against dust, moisture, and temperature and humidity extremes (4,5). The maintenance of optimal environmental conditions in the storage area minimizes the potential for contamination of sterile supplies. There should be a minimum of 4 to 10 total ACH, and the relative humidity should be <70% (4,5). The area should also be free of insects and other vermin that seek the warmth of reprocessed packages for habitat.

Sterile materials should be stored at least 8 to 10 in. from the floor, at least 18 in. from the ceiling, and at least 2 in. from outside walls (5,6). The items should be positioned so that packaging is not crushed, bent, compressed, or punctured, all of which will compromise the sterility of the contents. The contents of any sterilized package should be considered contaminated if the packaging is damaged. All wrapped sterilized packages should be handled and stored in a manner that minimizes stress and pressure *(54)*. Storage of supplies on floors, windowsills, and areas other than designated shelving counters or carts should be avoided (5,10). Open shelves, cupboards, or drawers are acceptable, but articles stored in drawers may need special protection against physical damage *(57)*. Some hospitals have utilized movable shelves to maximize storage capacity when space is limited *(87)*.

Every package that has been sterilized within the facility should be imprinted or labeled with a load control number that indicates the sterilizer used, the cycle or load number, the date of sterilization, and an expiration date. The term *shelf life*, as used with respect to a sterilized product, is defined as the period during which sterility can be maintained. Shelf life considerations create more misconceptions, confusion, and misleading information than any other facet of the preparation and use of sterilized products *(47–50,54)*. There are reports in the technical literature describing the length of time sterile goods can be stored and still be considered sterile, with safe storage times reported to range from as short as 1 week to indefinitely (13,*50*). To add to the confusion, some reports discuss neither the wrapping material used nor conditions for storage in relation to the safe storage periods *(54,88)*. Some studies suggested that safe storage times ranged from 2 days to 9 months depending on the wrapper/storage combination. The problem related to most studies is that the conclusions became a standard for all hospitals regardless of the barrier properties of the wrappers used or the hospital's

control over the environmental factors that really affect shelf life. No trend toward increased probability of contamination over time was observed for any pack type studied. The studies were not ready to call any storage time safe or unsafe. They observed, however, that storage periods up to 50 weeks did not increase the probability of contamination regardless of the wrapping material used (nonbarrier woven, barrier nonwoven, or polypropylene peel pouches), storage location, or dust cover use (13,*47,48,62*).

Loss of sterility of package contents is considered event-related, not time-related, and depends in part on the type of packaging used *(89)*. Event-related factors include (a) frequency and method of handling; (b) storage area conditions such as location, space, open/closed shelving, temperature, humidity; and (c) the presence of dust, insects, flooding, and vermin (46). Sterility of package contents is considered compromised if packages become wet or are dropped on the floor, or if the packaging is torn, punctured, or otherwise comes apart (22).

Shelf life and expiration dating policies must be decided by each individual healthcare facility. Because of the differences in both packaging materials used and facilities for storage, it is impossible to recommend shelf times that would be universally applicable for sterile items.

Material Management and Inventory of Sterile Supplies

Inventory control means that the correct quantity and quality of supplies is readily available to meet demands. A stock rotation policy and procedure should be developed for all areas of the facility in which sterile supplies are stored. Supplies should be placed on shelves so that expiration dates are readily visible. Correct stock rotation minimizes waste by reducing the number of sterile items that will have to be reprocessed or discarded. This approach helps to ensure that devices that may no longer be sterile are not inadvertently used (46).

More and more material managers within CSS units are automating inventory control through the use of bar coding and radiofrequency technology *(90)*. Each of these approaches to automated inventory control offers innovative ways of tracking trends in usage, availability, product identification, recalls, etc. One inventory system may not be suitable for all purposes. For example, the integrity of information in bar coding can be compromised if the bar code is defaced in some fashion. Radiofrequency identification is accomplished via the affixing to an item a battery-powered tag that emits a radiofrequency, which in turn is detected with a scanner/reader device. Reports have indicated that this tag often becomes damaged when subjected to sterilization processes *(90)*. Nevertheless, use of automated inventory control has improved CSS unit efficiency in managing supplies moving in and out of the unit.

More recently, automated inventory control is being applied to reusable medical devices. This automation not only tracks the shipping, receipt of, and use life of devices, but also there is increasing interest in using this technology to follow the clinical uses of devices and even record the device information into the patient's medical record *(90)*. Although there are no formal studies as yet to examine the use of automated device tracking, there are a few observational reports in which hospital staff indicate that the use of a device tracking system has helped to manage device recalls or to trace device use to specific patients, thereby providing important epidemiologic information during adverse patient event investigations *(91,92)*.

On September 27, 2007, Public Law 110-85 was signed by President George W. Bush. Section 226 of this law amended the Federal Food, Drug, and Cosmetic Act by requiring the establishment of a "unique device identifier" (UDI) system. FDA is at present developing rules to carry out the intent of this law. Research groups who have explored the implications of utilizing a UDI system have reported to the FDA a number of situations for which a UDI may prove to be a beneficial tool to hospitals. These include: (a) recall of devices (e.g., disposable, reusable, implanted, reprocessed); (b) recall of capital equipment; (c) detection of magnetic resonance imaging–incompatible devices; (d) tracking and documenting device use (including tracking those devices associated with an adverse event, or tracking repairs); (e) identifying devices associated with medical errors; and (f) identifying and reducing device counterfeiting (93).

Distribution of Sterile Goods

Packs transported to ORs and other areas within the healthcare facility should be provided with an additional outer dust-protection cover that can be removed before the pack is taken into the clean zone. This can be applied either to the individual packages or to the total cart. The transporting vehicle should be reserved for CSS unit use (5,*55*).

Maintenance

Preventive maintenance of all sterilizers should be performed according to individual policy on a scheduled basis by qualified personnel, using the sterilizer manufacturer's service manual as a reference (24). Sterilizers should be inspected and cleaned daily or at intervals recommended by the manufacturer to prevent the accumulation of residue that may transfer to packaging in the chamber. The time–temperature charting devices and temperature–pressure gauges should be calibrated after any repair affecting sterilizer performance and at least every 6 months or at the interval recommended by the sterilizer manufacturer (5,24).

Reuse of Single-Use Medical Devices and Patient-Care Items

Over the past 20 years or so, there has been a growing interest in reuse of instruments and items clearly labeled and marketed as single-use only. Many of these devices appear to sustain little obvious wear and tear after their one-time use on the patient, and it is tempting to consider cleaning and reprocessing these devices. However, there are a number of factors that should be considered when evaluating whether or not a single-use device can be reused safely (e.g., difficulties in cleaning, presence of long narrow lumens, chemical coatings, integrity and compatibility of materials, and continued performance of the instrument according to specifications) *(94)*.

Most of the reprocessing of single-use medical devices in the United States is now being done by commercial companies commonly known as "third-party reprocessors." These companies decontaminate, clean, inspect/test, package, and sterilize the single-use devices (SUDs) and return them to the healthcare facility client. The FDA

has regulations governing the reuse of SUDs as is presently occurring in US hospitals (95,*96–100*). Although there are little available data on specific incidents of harm caused to patients because of the reuse of these devices, the government has concluded that the potential risks are such that reprocessing entities should be regulated in the same way as original medical device manufacturers. The FDA now considers hospitals that reprocess devices labeled for single use as manufacturers as well. FDA, therefore, expects hospitals to meet either the requirements of the industrial standards for device reprocessing or have an equally rigorous scientific rationale for sterilization procedures used in reprocessing *(101)*. The regulations do not apply to office-based practices, independent ambulatory surgery centers, or clinics at this time. Additionally, the question has been raised as to whether the regulations exclude SUDs that are opened from packaging but not used. To quote the agency's answer to this inquiry: "The FDA's guidance document 'Enforcement Priorities for SUDs Reprocessed by Third Parties and Hospitals' (dated August 14, 2000), defined *opened-but-unused* SUDs as single-use, disposable devices whose sterility has been breached or compromised, or whose sterile package was opened but not been used on a patient, that is, they have not been in contact with blood or bodily fluids." (Appendix B, page 40.) In Section "C. Scope" of the guidance document, it states that the enforcement priorities do not apply to *opened-but-unused* SUDs. This means that at this time, FDA is not requiring third-party or hospital reprocessors of SUDs to submit PMAs (premarket approval applications) or 510(k)s (premarket notification submissions) for *open-but-unused* SUDs. However, FDA's existing policy for *opened-but-unused* SUDs that are reprocessed by third parties remains unchanged: *opened-but-unused* SUDs reprocessed by commercial reprocessors are subject to the Quality System Regulation (QSR)" *(99)*.

Reprocessors must comply with all of the pre- and post-market regulations governing medical device manufacturing, including the need for premarket clearance if required for that specific device, registration and listing as a manufacturer, mandatory reporting of adverse events, medical device tracking (if required for a specific device), corrections and removals, labeling, and compliance with the QSR *(102)*. The FDA maintains a very helpful Web site on reuse issues and regulation *(100)*.

Contract, Off-Site Reprocessing Services

Healthcare facilities are under constant demand to reduce expenditures wherever possible while not compromising the quality of patient care. This discussion often comes up when it is time to replace outdated and old equipment *(103)*. Some healthcare facilities have opted to outsource their reusable instrument reprocessing service to a contractor, based largely on economic assessment. Many off-site contractors provide the instruments, devices, linens, and other durable goods in addition to the reprocessing service. This means that the healthcare facility can reduce its instrument inventory and largely eliminate an in-house service that has potential occupational risks for injury and infection. The disadvantages to utilizing such a service include the possible elimination of the facility infrastructure that would normally support instrument reprocessing, and the lack of "favorite" instruments from the physician/surgeon's perspective (unless arrangements to retain these instruments are built into the contract) *(104)*. Healthcare facilities are often expected to remove gross soil from the instruments before the contractor comes for instrument pickup. Contractors then fully clean and reprocess the instruments accordingly, and transport them back to the facility in a manner that prevents the reprocessed instruments from becoming contaminated prior to use. The frequency of pickup and delivery is dictated by the work volume of the facility. The company should provide CSS staff with full documentation of its operation, including the details of quality assurance and infection control. CSS staff should be confident that all aspects of the terminal reprocessing services provided by an outsourcer would be equal to or better than those provided in-house. Contract services also provide backup instrument reprocessing services on an as-needed basis, such as during emergency shutdown of a hospital's CSS or during construction and renovation of CSS areas *(104)*.

PATIENT SAFETY: ADVERSE OUTCOMES LINKED TO DEFICIENT CSS PROCESSES AND MATERIALS

Although CSS units have a long history of providing quality service to the patients in the hospitals, there are occasions when infections, injuries, and other adverse outcomes associated with CSS processes or materials affect patients and the quality of their medical care.

Strategies for Managing Errors in Reprocessing

Adherence to reprocessing standards and best practices is the basis for consistent quality service in the CSS unit. Briefly, sterilization and high-level disinfection are processes that effectively prevent transmission of potentially infectious material from one patient to the next. However, occasionally, healthcare facilities are made aware of adverse events during the delivery of patient care that may jeopardize patient safety, increasing the potential risk of infection transmission. In some instances, these events may be traced back to some deficiency in device reprocessing. There may be several contributing factors that need investigation: (a) human error (incorrect settings on reprocessing equipment or failure to follow established disinfection procedures); (b) equipment or product failure; or a (c) systemic or organizational failure (using incorrect connectors or reusing contaminated needles and syringes) *(105,106)*. CSS unit supervisors should establish policies and procedures to address human errors and equipment failures in their unit and partner with facility infection preventionists and epidemiologists to determine the root cause of the deficiency and assess the potential for infection transmission to patients. Within the CSS unit, equipment failures/malfunctions should be identified as quickly as possible so the equipment can be taken out of service, repaired or replaced as appropriate, and full function restored. Any unused instruments from affected sterilizer batches should be recalled, cleaned again, and reprocessed (22,*105*). The margin for allowable error implicit in modern

sterilization procedures is sufficiently large for those based on physical methods of microbial inactivation, such that there is minimal risk that items in a load will fail to achieve sterility in the event of a potential sterilizer malfunction, especially if the microbial bioburden on reprocessed items has been reduced before sterilization by proper cleaning. As a consequence, HAI, particularly bacterial infection, traced to mechanical failure of sterilization equipment has been infrequent *(1)* (see also Chapter 81). Nevertheless, it is important for CSS unit supervisors to provide reprocessing assessment information to the healthcare facility's efforts to determine the risk of transmission to patients that may or may not lead to patient notification.

Some adverse events have been attributed to failure to follow best practices when performing high-level disinfection on complex devices (i.e., endoscopes) *(105)*. Other events may be linked to poor infection prevention practices during the delivery of patient care (i.e., reuse of needles and syringes, or using previously contaminated needles and syringes with multidose vials) *(106)*. In these situations, the infection control breach is evaluated to determine the likelihood of pathogen transmission. This information, coupled with affected patient population factors and time line of events, is weighed in the decision whether or not to notify patients for medical assessment and follow-up *(106)*. If a reusable device is involved in a potential adverse event for a patient, the CSS unit supervisor can anticipate that he/she will be called upon to help assess the problem and assist with response strategy development.

Examples of Adverse Events Associated with Device Reprocessing Deficiencies

Several aspects of the instrument reprocessing strategy, however, can be associated with adverse outcomes for patients if recommended practices are not followed. In 1961, three cases of surgical site infection caused by *Clostridium perfringens* were reported as a result of inadequate cleaning of instruments and sterilizer failure *(107)*. Transmission from the index case to the other patients was linked to residual contamination on the surgical instruments. Another episode traced to sterilizer failure in a hospital resulted in six cases of *P. aeruginosa* meningitis or intra-abdominal abscesses *(108)*. Possible failure of flash sterilization processing of implantable neurosurgical devices was epidemiologically implicated in this outbreak. Bacteremias and fungemias have been associated with improperly sterilized pressure transducer domes *(109)*. Improperly sterilized surgical equipment was linked to an outbreak of postsurgical nasal cellulitis in which *Mycobacterium chelonae* was recovered from patients undergoing surgical rhinoplasty *(110)*. Improper packing of surgical linens/drapes prior to autoclaving was associated with an outbreak of polymicrobial ventriculitis in a surgical intensive care unit *(111)*. Tight packaging of the linens prevented the sterilant from penetrating throughout the pack. Additionally, the hospital failed to run routine process indicators (i.e., Bowie-Dick testing, BIs). Another episode resulting in transmission of NTM was linked to deficiencies in disinfection or sterilization practices in the OR and major defects in the autoclave located in the OR *(112)*. Inadequate sterilization and rinsing surgical instruments with tap water, coupled with minimal training in instrument reprocessing strategies, were implicated in an outbreak of *M. chelonae* abscesses after liposuction in a physician's office–based practice *(113)*. These latter two outbreaks illustrate the problems that may occur with instrument reprocessing activities that are based elsewhere in the healthcare facility. Lack of experience with proper instrument reprocessing and attendant quality assurance can be problematic, especially if the workers and the processes in these areas do not have any oversight from infection control or CSS unit personnel.

Proper maintenance of the equipment in CSS is very important in the prevention of healthcare-associated adverse outcomes for patients. One outbreak of diffuse lamellar keratitis (DLK) was attributed to endotoxin exposure from sterilized instruments *(114)*. Biofilms of gram-negative bacteria built up in the sterilizer's water reservoir, presumably diminishing the quality of the steam and thereby resulting in the transfer of endotoxin to the instruments. Biofilm control measures were implemented and a significant reduction in the development of DLK was observed.

Materials compatibility with sterilants has been a problem with the development of new options for sterilization. Therefore, it is important to review fully the advantages and limitations of new sterilization technologies so that it is clearly understood which items and materials can be safely reprocessed. An outbreak of corneal decomposition among patients receiving elective intraocular surgery was associated with residual copper and zinc in lumened, copper, and brass surgical instruments sterilized with the Plazlyte system (AbTox, Mundelein, IL), a sterilizer that is no longer marketed in the United States *(115)*. The contact of the instruments' metals with the sterilant in this system produced toxic by-products that resulted in ocular damage, with some of the cases experiencing irreversible conditions.

Reuse of single-use medical devices has also been debated in the context of potential infectious risks to patients or risk of injury should the reprocessed device malfunction. The medical literature has been mixed on this issue. Some *in vitro* studies lend support to the practice of reusing these items *(116–118)*, whereas others point to definite problems encountered with cleaning and with materials integrity or compatibility *(119–124)*. There is potential for injury, infection, or other adverse outcome to occur. In a Brazilian hospital, several patients undergoing cardiac catheterization with reprocessed catheters experienced pyrogenic reactions. The catheters were sterilized by ETO after being cleaned several times in a CSS unit. Analysis of the water used to reprocess catheters revealed elevated endotoxin levels; endotoxin was also detected in the reprocessed catheters *(125)*.

OCCUPATIONAL RISKS FOR CSS UNIT WORKERS

Occupationally Acquired Infections

CSS workers encounter blood, tissues, body substances, and devices contaminated with these proteinaceous materials on a daily basis. According to Standard Precautions, blood and body substances from all patients should be considered infectious, and used instruments and items

should be considered potentially infective and therefore handled with extraordinary care *(126)*. There is a recognized risk of exposure to blood-borne pathogens (i.e., human immunodeficiency virus, hepatitis B virus, and hepatitis C virus) for CSS unit personnel during the reprocessing of contaminated, reusable medical devices. CSS workers, therefore, are considered appropriate candidates for hepatitis B vaccination and should be offered the vaccine accordingly *(23,127,128)*. Additionally, these workers should be trained on the importance of promptly reporting occupational exposures to blood and body fluids *(23)*. Workers should be encouraged to report to employee health any occupationally acquired cut, puncture wound, or splash to the eyes and mucous membranes so that postexposure evaluation can be initiated and prophylaxis be administered as appropriate.

Although it is accepted that the work activities in a CSS unit can potentially expose the workforce to blood-borne pathogens, there is limited occupational event surveillance information with which to evaluate the extent of the injury problem in this part of the hospital. Cuts from sharp instruments and needle sticks from hollow-bore needles have been reported by CSS unit personnel *(126,129)*. In two reports from the United Kingdom during the late 1980s and early 1990s, the injury prevalence rates annually per 100 staff ranged from 17 to 83 injuries per 100 staff *(130,131)*. In one of these reports, however, it is evident that the actual number of injuries (two injuries) among a small workforce in the CSS unit represents only a very small proportion of the total number of needlesticks occurring in that hospital that year (2 of 64, or 3.4%) *(130)*. In contrast, the nursing staff sustained 29 needlesticks that year, or more than 45.3% of the total number of needlesticks *(130)*. In the past two decades, the healthcare industry has embraced technological improvements in PPE (e.g., fluid-impervious protective attire, gloves to prevent cuts to the hands) and CSS unit equipment to enhance worker safety. More recently, as states in the United States become more engaged in healthcare safety surveillance reporting, CSS unit–specific occupational event data may emerge. Texas, for instance, has conducted statewide surveillance for contaminated sharps incidents from 2001 to 2008 (2008 being the most recent year for data analysis). Reported injuries among CSS unit workers during those years ranged from 0.0% to 0.6% of the total number of sharps incidents reported among the participating healthcare venues during the year *(132)*.

CSS personnel performing decontamination should wear PPE appropriate for the task. For example, an impervious gown and shoe covers, heavy gloves, and eye goggles or face shields would be appropriate for the CSS unit staff that work in the decontamination and/or cleaning area(s). This work area houses the manual device cleaning activities that may produce aerosols and spray mists. Furthermore, automated equipment (e.g., washer–decontaminators, washer–sterilizers, and ultrasonic cleaners) may produce a spray from the fluids contained within, and this should be considered when one is planning programs for protection of workers. Nevertheless, among the benefits these pieces of equipment provide is the opportunity to minimize the amount of contact with contaminated medical devices during cleaning, thereby reducing the risk of exposure to potentially infectious fluids and aerosols *(129,133)*. Proper technique when handling contaminated patient-care items remains an important part of the process when loading the items into the automated equipment for cleaning.

Even though properly attired with PPE, healthcare workers in the CSS unit are still at risk for injuries and infections by puncturing themselves with sharp, contaminated instruments. Disposable sharps need to be discarded in an approved sharps container at the point of use. Reusable instruments should be placed in a puncture-resistant container for safe transport to the decontamination area *(133)*.

Occupational Risks Associated with Ethylene Oxide Sterilization

ETO has been produced commercially and used as a sterilizing agent for many years. ETO is both combustible and flammable, and it was common to find ETO mixed with inert gas to reduce these hazards. However, more recently, ETO is supplied in small canisters of 100% ETO as a result of technological improvements in the sterilizer equipment and the rising costs of gas blends (22). Its use as a sterilant of choice for heat-sensitive devices, however, is limited in healthcare settings mainly because of environmental concerns relating to emissions and inherent health risks for both CSS workers and patients who come in contact with ETO vapors and surface residuals, respectively. ETO has produced tumors, teratogenic effects, and maternal toxicity when injected into mice *(134,135)*. ETO is a known carcinogen for humans; some studies have noted an increase in the incidence of lymphoid tumors and hematopoietic cancer among workers with ETO exposure, but particularly among male workers in those work settings *(136–138)*. Study of spontaneous abortions in hospital staff suggested that exposure to ETO in hospitals may carry a risk of spontaneous abortion among CSS staff *(139,140)*. Items (e.g., prosthetic devices, instruments, or catheters) improperly aerated can cause serious chemical burns or tissue irritation and have been shown to be neurotoxic (*141–143*,144,*145*). Aeration will reduce some of these residuals on the sterilized items, but the extended time needed to accomplish this makes ETO sterilization somewhat impractical in the face of increasing demands for short turnover of instruments. Nevertheless, ETO sterilization still plays an important role among the reprocessing options in a CSS unit.

To use ETO in the safest possible manner, three guidelines need to be followed: (a) provide safe devices that are sterile, unaltered, and with no undesirable residues; (b) protect workers from chronic ETO exposure; and (c) take steps to prevent hazardous episodes of leaks, fires, or explosions (22,*143*).

Aeration of Instruments, Devices, and Items After Ethylene Oxide Sterilization Use of ETO as a sterilant will generate ETO by-products, primarily ethylene glycol and ethylene chlorohydrins. ETO and ethylene chlorohydrin can be removed from items by aeration. It is imperative that all instruments and devices subjected to ETO sterilization are fully aerated to eliminate these residuals prior to handling and use (22). Ethylene glycol, however, is not removed by aeration. Therefore, precautions such as

making certain that no liquid exists in the load, selection of a quality gas source, and routine maintenance of the sterilizer are needed to prevent its formation (22).

Aeration of ETO-reprocessed instruments and patient-care items at ambient conditions in an open, unrestricted area is unacceptable, because it would unnecessarily expose workers to ETO. The basic elements for controlling ETO emissions during aeration are process enclosure, local exhaust ventilation, PPE, and equipment functional design *(146)*. To protect CCS unit workers from ETO exposure, the United States EPA requires as of February 28, 2010, that facilities use a single chamber process (i.e., sterilization and aeration occurring in the same chamber) when using an ETO sterilizer for the terminal reprocessing of heat-sensitive instruments *(147)*. Adequate aeration time must be allowed after sterilization so that residual ETO can be reduced to a level safe for both personnel and patients. Length of aeration depends on many variables, including (a) composition, form, density, and weight of the sterilized item; (b) product packing, loading, and mass; (c) type of ETO sterilization system used; (d) temperature of the aeration chamber; (e) number of filtered ACH and air flow characteristics; and (f) intended use of the item (i.e., external application or implantable device) (24,*143*,144). Polyvinyl chloride is one of the most challenging materials from which ETO residue must be eliminated. No standard times for aeration can be reliably given without consulting the device, sterilizer, and packaging manufacturers. Items can require as short as a few hours or as long as several days in an aeration cabinet to reduce ETO to safe levels.

In 1978, the FDA proposed limits on the amount of residual ETO (30 μg/kg/day for 30 days) that can remain on sterilized medical devices for human patients. These limits were based on histologic and hematologic studies in rodents and dogs *(145)*. The FDA has raised the allowable residual limit of ETO to 250 parts per million (ppm) on devices subjected to ETO sterilization, with the exception of those devices used in donor and patient blood collection (product codes 81GKT and 81KSR). More recently, the ISO and AAMI have adopted a philosophy that the limit should depend on the intended use of the device and the length of contact with human tissue so that the dose to tissue is considered, not just the amount retained in the device (68,*148,149*).

Preventing Occupational Exposure to Ethylene Oxide In the late 1980s/early 1990s, the National Institute for Occupational Safety and Health estimated that 270,000 workers in the United States were potentially exposed to ETO, the majority of which were working in hospitals and other healthcare settings *(150)*. With the development of more effective engineering controls, work practices, and workplace design requirements, the risk of occupational exposure has been minimized over the last two decades. Nevertheless, CSS unit personnel who work with ETO must be informed of the possible health effects of ETO exposure. This information must include an explanation of the requirements of the Occupational Safety and Health Administration (OSHA) standard on occupational exposure to ETO and must identify the areas and tasks in which there is potential exposure to ETO emissions *(151)*.

OSHA published a final ruling on ETO in 1984 that reduced the permissible worker 8-hour time-weighted exposure level of ETO from 50 ppm of air to 1 ppm of air. In 1988, OSHA amended its existing standard by adopting an excursion limit for ETO of 5 ppm of air averaged over a 15-minute sampling period *(58,151)*. Workers who are exposed to ETO emissions at or above the action level (0.5 ppm) for at least 30 days per year, even if an approved respirator is used, must have medical examinations at least annually. Trend data for US hospitals have shown that facility efforts to monitor occupational exposures to ETO increased dramatically after the implementation of the OSHA regulation, but current surveillance is documenting a general decline in adherence to and enforcement of the OSHA ETO standard *(152,153)*. Hospitals should maintain responsible employee and environmental monitoring as part of a comprehensive worker safety program.

Restrictions on ETO use have included the amount permitted to exit the sterilizers to the atmosphere. These restrictions have been imposed by individual states and air pollution control boards *(154)*. These restrictions not only ensure that occupational exposure to ETO is minimized but also prevent the passive exposure of patients, other hospital workers, visitors, and individuals in or near the healthcare facility. All ETO sterilizers and aerators must be directly vented out of the workplace to the outside atmosphere (4). The vent line must not terminate within 25 ft (7.6 m) of any building air intake. A greater distance may be needed in some situations, depending on the direction of prevailing winds and the location of buildings (68,*154*).

Desirable ETO sterilizer safety features include, but are not limited to (a) purge of the system at the end of cycle, (b) door-locking and sealing mechanisms, (c) audible alarm at the end of the ETO cycle, (d) automatic door controls, and (e) audible and/or visual alarms for system failures. Scrubbers that convert ETO to less toxic ethylene glycol have been used successfully to control ETO emissions (68,*143*).

CSS personnel should ask instrument and device manufacturers for written instructions on the proper sterilization and aeration times for their products when ETO is the recommended sterilant for successful reprocessing. CSS personnel also have to develop, implement, and enforce aeration policies and procedures. Aeration recommendations should be carried out in an uninterrupted cycle to prevent unnecessary operator exposure to ETO due to opening the aerator door. Policies regarding early removal of devices that have not been completely aerated must be established through the hospital's infection control committee, legal counsel, and/or risk management committee (144).

For a more in-depth discussion of the safe use of ETO in hospitals and other workplaces, the reader is referred to a recent guide published by OSHA (155).

CONCLUSION

CSS is an example of the person–machine interface that is so visible in the delivery of healthcare. The processes and products coming from a CSS unit impact virtually all of the care activities provided in a healthcare facility, ranging from distributing patient-care supplies to providing sterilized

surgical instruments and sterile textiles. Sterility assurance depends on the performance of both employees and equipment. Several low-temperature sterilization processes are widely available (e.g., ozone, hydrogen peroxide plasma, hydrogen peroxide liquid) and along with ETO provide more options to sterilize heat-sensitive items. Advances in sterilization technology and automation necessitate that CSS unit professionals have a solid scientific understanding of the basic principles of cleaning, decontamination, disinfection and sterilization, and current clinical practices in order to best evaluate innovations and to enhance patient safety *(156)*.

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CHAPTER 71

Healthcare-Associated Infections and the Environment

Andrew J. Streifel

ENVIRONMENTAL RESERVOIRS AND THE EPIDEMIOLOGIC CHAIN

The relationship between the physical environment of healthcare facilities and infection control has long been debated. Continuing advances in medical technology and pharmacology have given physicians many options, unrelated to the physical environment, for preventing healthcare-associated infections. Restrictive and time-consuming barriers and procedures such as laminar-flow rooms with attendant aseptic technique have generally been in disfavor relative to the pharmacologic approach to preserving immune competence. At the same time, passive environmental controls such as filtration and pressurization systems to provide spore-free environments continue to be used in increasingly sophisticated ways. Legitimate questions remain as to the extent to which environmental reservoirs contribute to healthcare-associated infections. An argument can legitimately be made that cleanliness needs no further epidemiologic justification and that all hospitalized patients are entitled to a clean and odor-free environment. However, legitimate questions can also be raised as to allocation of resources to environmental controls that have no epidemiologic basis. An example is the extent to which chemical germicides should be used on environmental surfaces as opposed to nongermicidal cleaning methods that appear to yield equivalent microbiologic reductions *(1)*. With such issues, new technology is adapting to the means of real-time sampling using indicators such as environmental adenosine triphosphate (ATP) *(2)* for determining cleanliness.

One reason for continued disagreement over the importance of environmental reservoirs is failure to consider historical perspective and thus the starting point for measuring significance. People have rightly come to expect a high level of sanitation in medical facilities, a level that has already achieved a major reduction in infection incidence, and are now dealing with a very different set of infection determinants focusing largely on patient susceptibility factors. The writings of Florence Nightingale based on her experiences in the Crimean War in the 1850s reveal the striking contrasts between conditions then and now *(3)*. She devoted whole chapters to pure air, pure water, efficient drainage, cleanliness, and light, which she considered the cornerstones of good health and prevention of mortality. In her detailed journals, she documented survival data in the hospital where she cared for British soldiers of the Crimean War. She documented dramatic changes in mortality from February 1855 (420/1,000) to September 1855 (22/1,000), which she attributed to "nursing care and sanitary measures" *(4)*. Her changes included such basics as scrub brushes, laundry tubs, and clean dressings for wounds, all replacing abominably filthy conditions associated with the pest houses of the time. Thus, the question that should be addressed today is not whether the environment is important—it obviously is—but how best to use available infection control practices most cost effectively to protect patients and healthcare workers from infectious hazards. In this chapter, a variety of environmental reservoirs are reviewed relative to evidence linking these reservoirs to disease and a distinction is made between proven linkage to disease and simple evidence of lower contamination levels (which may or may not be worthwhile, regardless of disease linkage). In this chapter, two developments are emphasized, which are considered the most significant in this ongoing attempt to define the role of the physical environment in healthcare-associated infections. First, as antibiotic resistance problems mount and higher percentages of infections become more difficult to treat, one has little choice but to fall back on environmental cleanliness as a cornerstone preventive component of infection control. The second development is the continuing refinement of DNA fingerprinting technology, which more and more enables identification of specific sources of infection and determines the relatedness of infection clusters. A number of examples are cited and predictions are made that this technology will eventually shed further light on the importance of environmental controls.

LITERATURE REVIEW

Association of Reservoirs with Healthcare-Associated Infections

Although the literature is replete with accounts of microbial contamination in a great variety of hospital settings, most of these articles describe contamination levels, not infection levels, and prescriptions for reducing these contamination levels do not necessarily translate into

reduced incidence of healthcare-associated infection. Even when specific correlation to infection rates is suggested, the evidence is often tenuous, and direct association to an environmental source is difficult to prove. One area where investigators seem to be convinced that environmental sources contribute to infection is that of *Aspergillus* infections in severely immunocompromised patients. Humphries et al. *(5)* attributed two invasive *Aspergillus* infections in an intensive therapy unit to spores accumulating in fibrous insulation material above a perforated metal ceiling. Arnow et al. *(6)* similarly attributed an increase in *Aspergillosis* incidence to growth of microorganisms on filters and claimed that improved environmental maintenance and filter replacement were associated with a fourfold reduction in aspergillosis incidence over a 2-year period. Table 71-1 lists environmental sources of fungi in the hospital (*6*,7,*8–13*,14,*15–19*).

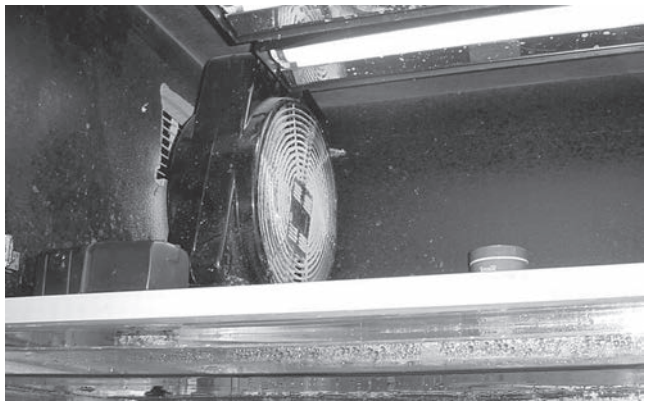

FIGURE 71-1 Aquarium fan lint with *A. fumigatus* contamination due to growth on fish food. This contamination was implicated in burn patient infections (unpublished data).

Air

The controversy over the role of airborne microbes as a source of surgical site infections has gone on for many decades. In theory, a surgical site exposing sterile tissue is susceptible to invading microorganisms from many sources. Certainly, rigid aseptic techniques and the need to sterilize any item entering a surgical site has long been accepted practice. Similarly, the need for filtration and high dilution rates of operating room air has also been accepted. However, proof of airborne infection of surgical sites has been hard to come by, and demonstrated effectiveness of specific controls as a means of reducing infection incidence has similarly been hard to prove. Walter et al. *(20)* claimed to have demonstrated a specific airborne surgical infection, and Hart *(21)* published the results of a 29-year study claiming the significant benefits of ultraviolet installations for limiting surgical site infection. Other investigators, however, have failed to confirm these conclusions. In particular, Ayliffe and Beard *(22)* and Howe and Marston *(23)*, while confirming that good filtration and dilution could reduce airborne contamination levels, could find no association of such reductions with infection prevention. In a general review of indoor microbial aerosols, Spendlove and Fannin (24) made the point that little is known about the true significance of these aerosols relative to human health and that continued research is needed. The sources of mold are many in the biologic world and the indoor environment can be controlled when emphasis is placed on filtration, air exchanges, and pressure management *(25)*. It becomes imperative to control sources close to the patients at risk from opportunistic microbes such as *Aspergillus fumigatus* (see also Chapter 41). Such practice of source management also works for industrial hazards. These settings, however, provide easier identification for source management.

TABLE 71-1

Environmental Fungal Sources in Hospitals

Source	*Reference*	*Patient Infection Claim*
Ventilation system	Fox (7)	Surgical wounds
Fireproofing material	Aisner *(8)*	Yes
Blankets	Noble *(9)*	No
Air conditioner	Lentino *(10)* Wadowsky *(11)*	Yes
Insulation	Arnow *(6)*, Fox (7)	Yes
Construction projects	Krasinski *(12)*	Yes
Demolition	Streifel *(13)*	No
Track dirt (1976)	Arnow (14)	Yes
Road construction	Lentino *(10)*	Yes
Plants	Staib *(15)*	No
Pigeons	Kyriakides *(16)*	Yes
Food	Falken *(17)*	Colonization
Housekeeping	Rhame *(18)*	No
Moldy wood (1981)	Streifel *(19)*	No
Fish Aquarium (2008)	Streifel (Fig. 71-1)	Yes

Water Reservoirs

The literature is replete with reports of improperly disinfected medical devices that are implicated in healthcare-associated infections, particularly devices such as respiratory therapy equipment that are associated with water reservoirs of one kind or another *(26)* or devices that have hard-to-clean channels such as fiberoptic endoscopes *(27)*. Similarly, a number of environmental water reservoirs have quite clearly been associated with infection involving aerosolization from these sources. Examples include faucet aerators associated with *Pseudomonas* infections *(28)* and shower heads associated with legionellosis (29,*30*) (see also Chapter 36). Weber et al. *(31)* recently confirmed by pulsed-field gel electrophoresis that faucet aerators were contaminated with identical strains of *Stenotrophomonas maltophilia* found to colonize a cluster of patients in a surgical intensive care unit. They attributed the problem to low-level contamination of potable water subsequently amplified in the faucet aerators. Jonas et al. *(32)* used three methods of DNA typing to compare environmental and patient isolates of *Legionella pneumophila*. Although all three methods detected one prominent genotype, amplified fragment length polymorphism had better interassay reproducibility and concordance than either macrorestriction analysis (MRA) or arbitrarily primed polymerase chain reaction (AP-PCR). MRA was also cited as an important tool for epidemiologic investigation of healthcare-associated

infections by Luck et al. *(33)* who used that technique to match *Legionella* isolates from four patients with identical strains isolated from the hot water supply of the hospital. Legionellosis is a disease, important in the lexicon of healthcare-associated infections, for which an environmental reservoir has clearly been identified (warm water reservoirs in buildings) and for which specific preventive environmental protocols are recommended and generally accepted. Edelstein *(34)* reviewed some of these recommendations. They include hyperchlorination (6–20 mg/L) followed by long-term continuous chlorination at 1 to 2 mg/L or intermittent elevation of water temperature to 60°C to 70°C with or without chlorination. An additional example of aerosolization from a water reservoir was reported by Grieble et al. *(35)*. They associated a rise in gram-negative septicemias with aerosolization from a waste hydropulping system that had been installed in a new Veterans Administration hospital. They also suggested that closing down the system halted the outbreak.

Hydrotherapy pools and tanks are another water reservoir wherein the combination of organic debris from infected patients and elevated water temperature clearly supports growth of microorganisms; not surprisingly, several investigators have associated these tanks with infections. Examples include McGuckin et al. *(36)* reporting on an outbreak of *Pseudomonas aeruginosa* wound infection and Mayhall et al. *(37)* describing a bacteremia outbreak of *Enterobacter cloacae*. Rutala and Weber *(38)* reviewed the subject of water reservoirs of healthcare-associated pathogens. They listed more than a dozen such reservoirs identified in hospitals, including potable water, sinks, faucet aerators, showers, ice and ice machines, eyewash stations, dental-unit water systems, dialysis water, water baths, ice baths, tub immersion, toilets, and flower vases. All these sources have been specifically shown to harbor healthcare-associated pathogens, and regardless of the uncertain epidemiologic significance of such reservoirs, prudent control measures are available to limit microbial growth and such measures should be used. The authors also pointed out the growing importance of molecular epidemiology for typing pathogens in these reservoirs. DNA fingerprinting by pulsed-field gel electrophoresis is an example of a technique that can be used to match clinical and environmental strains. That technique was used by Buttery et al. *(39)* to link a *P. aeruginosa* outbreak to water-retaining bath toys in a toy box. Finally, Verweij et al. *(40)* used random arbitrary polymorphic DNA PCR analysis to link an infant death from *S. maltophilia* infection to contaminated tap water. They concluded that preterm infants should not be washed using tap water. Water has been implicated as a potential reservoir for filamentous fungi *(41,42)*, and it is logical that spores could become entrapped in water and distributed to susceptible patients. This contamination was not associated with growth in water, but at the interface of water and air (43). Although eliminating all of these microbes seems easy to do with high-efficiency particulate air (HEPA)-quality filters, it would seem more effective to provide sterile water for drinking. The potential pathogenic sources in municipal water include soil, expansion tanks, evaporative pans, or accumulated biofilm within the water distribution system. Water usage is decreasing in healthcare facilities due to sustainable and green building concepts. Use of air-cooled med gas machines, digital radiology processors, and waterless hand cleaning is remarkably reducing water consumption. For example, at the University of Minnesota Medical Center, since 1990 the water usage volume has dropped from 164,000 to 82,000 g/day. This drop in water usage promotes stagnation, which increases bacteria levels in water. Incidents investigated by this author regarding resistant gram-negative bacteria confirm transmission from sink to patient with respiratory therapy equipment and feeding tubes. Inappropriate use of tap water is often the cause of such transmissions.

Infant Formula

As early as 1990, Clark et al. *(44)* used plasmid analysis, chromosomal restriction endonuclease analysis, ribotyping, and multilocus enzyme electrophoresis to match isolates of *Enterobacter sakazakii* from patients with isolates from infant formula, strongly implicating the formula as the source of those infections.

Environmental Surfaces

Environmental surfaces have long been something of an enigma for healthcare facilities. Although no one disputes the desirability of keeping these facilities clean or that esthetic considerations alone justify the cost of routine housekeeping, it is more difficult to justify the routine use of costly disinfectants on hospital floors and furnishings. No one has seriously proposed that such products in themselves can prevent healthcare-associated infections. It was demonstrated in the 1960s by Vesley and Michaelsen *(45)* and by Finegold et al. *(46)* that detergents (or even hot tap water) without chemical disinfectants can achieve microbial reduction equivalent to that of disinfectants. It has also been demonstrated by Vesley et al. (1) that dry cleaning with a chemically treated mop before wet cleaning accounts for most of the microbial load reduction on floor surfaces in hospitals. Dharan et al. *(47)* compared germicidal treatments to detergent only cleaning of floors and furniture in a 4-month trial in Switzerland. They concluded that microbial levels could be reduced but failed to observe any change in healthcare-associated infection rates in more than 1,000 patients. Maki et al. *(48)* performed an elaborate study of microbes on floors, walls, and other surfaces of an old hospital; then, before occupancy, they performed the same study in a new hospital that was replacing it. They reported no change in infection rates in the new hospital despite an absence of the surface pathogens immediately on occupancy. The old surface contamination patterns were reestablished in 6 to 12 months, leading the authors to conclude that the environment was contaminated by the patients rather than the other way around. Similarly, Danfoth et al. *(49)* compared infection rates over a 3-month period on eight acute care nursing units that had been cleaned with either a disinfectant or a detergent. The rates were not significantly different (8.0 per 100 discharges in the units cleaned with disinfectant vs. 7.1 per 100 discharges in the units cleaned with a detergent).

ATP technology is providing real-time analysis of surfaces suspected of being contaminated; while a clean look may be useful as an indicator, verification by testing provides greater sanitation assurances (50,51). Boyce has shown that education plus consistent concern for post clean testing improved outcome when checked with the indicator ATP (52). This method attaches bioluminescent material to

the chemical structure of residual protein or ATP left over from living cells. For situations involving the potential environmental microbes like *C. difficile*, methicillin-resistant *Staphylococcus aureus*, and Norovirus, methodically checking touch points in recently cleaned rooms assures a sanitation standard for respective facilities enlightened by quality audits for infection prevention (53).

The emergence of vancomycin-resistant enterococci (VRE) as a major healthcare-associated pathogen in the 1990s has rekindled some of the arguments about the importance of environmental surfaces. Weber and Rutala *(54)* reviewed this subject and hypothesize that "there is sufficient evidence to state that inanimate surfaces likely play a role in the transmission of VRE." They support this view by citing the survival of VRE on environmental surfaces for hours and claim that such contaminants can colonize hands. They also call into question the adequacy of current terminal room cleaning practices for eliminating VRE from environmental surfaces. The seriousness of the VRE problem and recent confirmation of the first vancomycin-resistant *S. aureus* certainly warrants close surveillance of the role of the environment. However, it remains difficult to determine whether such environmental surfaces play a role in initiating infection or, as others have claimed, merely reflect the presence of a source patient contaminating his or her surroundings.

A relationship was established by Alberti et al. *(55)* between the environmental contamination of a hematology–oncology ward and the incidence of invasive healthcare-associated aspergillosis. The conclusions of such evaluations indicate the importance of environmental control of contamination. In other words, the hospital environment should be kept clean for the sake of infection control (56). These concerns are not always detectable with the real-time monitors yet when evaluating aspergillosis incidents, environmental surface sampling is often forgotten for the less sensitive air sample methods. Surfaces retain spores in dust longer than fluid air retains them in a ventilated space. Focused cleaning with specific attention to water damage locations is required to minimize internal sources for fungal spores.

Soiled Linen

Soiled linen is another source of contaminants that has drawn some attention in hospitals. Again, the need for clean bedding is not at issue. Clearly, every patient is entitled to freshly laundered bedding as a matter of routine practice. However, the manipulation of soiled bedding is recognized as a major contributor to airborne contamination, and the question becomes "Does aerosolization contribute to healthcare-associated infection?" For example, Michaelsen and Vesley *(57)* reported a significant increase in air contamination even on the upper stories of a hospital when soiled linen was pulled from a basement chute closet, but the importance of such an observation relative to infection transmission has not been established. Colbeck *(58)* claimed a reduced incidence of skin boils after disinfection of blankets, but the evidence was purely circumstantial.

In 1988 at the University of Minnesota Hospital, an increase in *Aspergillus flavus* infections was observed after having moved 2 years prior into a new ventilated hospital. Investigation with air sampling showed no airborne *A. flavus*, but after a skin infection was observed, there was suspicion of laundry contamination. Further evaluation showed laundry from the storage areas had *A. flavus* contamination when vacuumed in a class 0 clean room. The laundry transport truck did not have a back door, and while the laundry had plastic covering, it did not prevent the contamination from a dirt road over which the truck was required to travel during a road/sewer construction project between the laundry and the University Hospital. The problem went away after putting a back door on the truck and paving the road. Additional laundry incidents have occurred, mostly due to product contamination after cleaning. This author was involved with three such incidents including the above-mentioned problem. Laundry manufacturing, transport, and storage comprise the focus of the Health Care Laundry Accreditation Council whose mission is to assure clean product management in the healthcare industry.

Construction Projects

One correlation of an environmental source relative to patient colonization that has been documented fairly consistently is that of building construction projects and fungal infection. Arnow et al. (14), Sarubbi et al. *(59)*, and Krasinski et al. *(12)* have all demonstrated recovery of *Aspergillus* from patients, which they traced to specific construction activities. Streifel et al. *(13)* reported that careful control measures during a building demolition project successfully prevented patient fungal colonization despite an enormous increase in fungal air contamination resulting from demolition. In a related finding, Streifel et al. *(19)* associated airborne *Penicillium* spores with leaking pipes in a rotting wood cabinet in a medication room (Fig. 71-2). Thus, special precautions to contain contaminants during ongoing remodeling and new construction projects would appear to be one environmental control situation that is justifiable for infection prevention reasons. Carter and Barr *(60)* reviewed construction-related healthcare-associated infection outbreaks, citing particularly *Aspergillus* and *Legionella* as often construction-related. They make specific recommendations for environmental control during construction including barriers, signs, traffic control, and ventilation suggestions.

Information now is available for construction of effective barriers to prevent dissemination of construction aerosols. Anderson et al. *(61)* published a Temporary

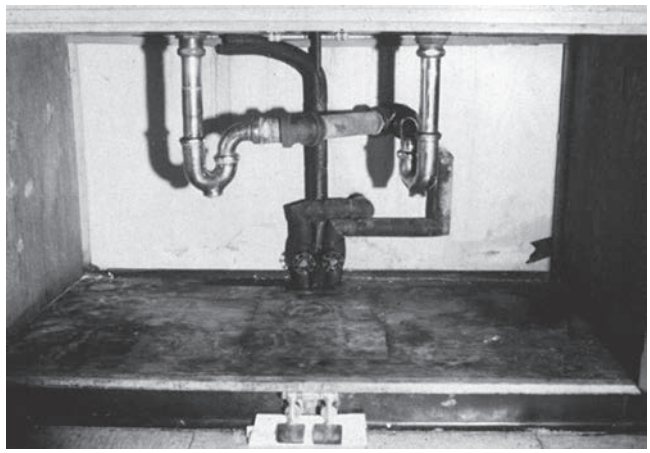

FIGURE 71-2 Mold accumulation in wooden cabinet under hand wash sink.

Negative Pressure for Isolation (TNPI) booklet intended to help show guidance for establishing and monitoring TNPI. Choosing an appropriate barrier for type of job is dependent on length of project or type of disruption. Barriers can be either long-term or short-term. Consideration for the length of a project in a critical space is important for project management. Risk factors that take into account the nature of the healthcare area being remodeled, and what is being disrupted, should be included in the decision making. Streifel *(25)* provided an example of barrier-related differences in microbial counts when a bathroom was dismantled using a substantial barrier and portable HEPA filtration. Also, Rautiala et al. *(62)* provided comparison methods for three types of barriers in controlling microbes during renovation. The study showed that the methods used were effective at preventing movement of microbes to adjacent spaces but did not minimize the exposure to workers in the construction zone. Such efforts demonstrate the effectiveness of barriers when they have negative pressure or airflow from clean areas to dirty areas. The levels of pressurization needed to achieve such control have not been standardized. Levels at or above 2.5 pascal (Pa) would be acceptable for protected environments. Alevantis et al. *(63)* found that a pressure differential of 8 Pa prevented the migration of environmental tobacco smoke. Smoke serves as a good surrogate, so that the barriers where critical control is necessary should be designated as smoke barriers, which is common in healthcare construction because of interim life safety code requirements (64).

Control of internal sources of mold during maintenance and renovation is a challenge, but external construction control is contingent on protecting the external shell of the building from penetration by excavation aerosols. This can be complicated if the building requiring protection is a high rise. The lower portion of a high-rise building has a natural tendency to pull air into the building to satisfy heat rising through the structure. Occupants using close proximity areas for smoking or normal pedestrian traffic may create an opening in the building to enhance the movement of excavation aerosol into the protected clinical structure. Control of entrances to a critical building is essential to protect the building from external projects.

Regardless of the project, a risk assessment is necessary to recognize the status of the clinical areas affected and the type of project impact on those areas. For example, if the windows are to be replaced on a hospital building, efforts to ensure pressure control on the internal connections are critical, and an airlock (ante) egress room may be necessary to ensure air pressure control. Likewise, if work is scheduled on a roof, efforts to protect that roof surface from puncture are critical for water damage control. Water damage control is essential for ensuring minimal mold growth inside of a building. If water damage occurs because of leaks, broken piping, or heavy rainfall, mold growth on modern building material such as gypsum board will occur if drying does not occur within 72 hours. Unprotected elevator shafts have resulted in multistory mold contamination occurring in a university hospital that required removal of the elevator shaft fire–rated gypsum board. A specification in the construction documents stating that the gypsum board was to be installed and protected from weather conditions required that the moldy board be removed at the contractor's expense. This is still cheaper than the litigation potential if the moldy board was left in place while the hospital initiated a program for bone marrow transplantation and a patient developed a mold infection. Under such circumstances, the knowledge that the elevator shafts were moldy and not removed would make them be suspected as the source of infection and thus become the focus of major legal problems. Contract specifications for a construction project should be provided in the bid documents to ensure basic consideration for clean to dirty airflow, construction traffic, roof protection, water damage management, and assurance that the spaces to be occupied by immune-compromised patients (such as bone marrow transplant recipients) have definable protective parameters such as pressure differential, air changes per hour, and filtration (65). The "Guidelines for Environmental Infection Control" (*http://www.cdc.gov/mmwr/pdf/rr/rr5210.pdf*) have certainly added to the coordination of construction management in healthcare facilities as part of the justification involved with the infection control risk assessment (see also Chapter 83). With the abovesaid considerations for construction contract labor in North America, the Carpenter Brotherhood Training Center in Las Vegas has made infection control training available for hospital labor pools. Such efforts have helped ease the risk. In addition, the American Society for Healthcare Engineering (ASHE) has programs for all hospital facility management and contractor supervision as well as programs for contract management in healthcare facilities, including infection prevention. These programs continue to promote quality management principles based on risk factors unique to healthcare facilities.

Food Sources

Another potential environmental source for introduction of opportunistic microorganisms into hospitals is on raw food products. Shooter et al. *(66)* isolated *P. aeruginosa* from salads and other cold foods in London area hospitals and then showed that some patients apparently acquired similar strains. Kominos et al. *(67)* reported on the introduction of *P. aeruginosa* into a hospital via raw vegetables such as carrots, celery, and tomatoes but presented no evidence of direct association with healthcare-associated infection. Sanborn *(68)*, on the other hand, claimed that an outbreak caused by *Salmonella chester* was traced to contamination of a cutting board by a raw turkey, and Levine et al. *(69)* similarly implied that equipment contaminated by egg products was at least partially to blame for numerous cases of salmonellosis reported from nursing homes. Thus, careful attention to the basics of food sanitation can certainly be justified as an infection control practice. This basic food sanitation practice is also provided with real-time quality assurance on the food preparation areas in a hospital food service. The same methods can be used for training purposes, essentially to demonstrate to employees the data as it is developed in the food service area. Employee demonstrations and audits have proved to be an effective learning tool.

Plants and Flowers

Cut flowers, and particularly the vase water in which they are displayed, have been well established as a source of opportunistic pathogens. Taplin and Merz *(70)* detected gentamicin-resistant gram-negative rods in 23 of 75 vases tested in a burn unit and associated the removal of these flowers with a decrease in wound colonization. Schoroth

and Cho *(71)* and Rosenzweig *(72)* also detected gram-negative microorganisms on flowers or in flower water but did not implicate these microorganisms in patient infection. Potted plants have been reported by Staib et al. *(15)*, Burge et al. *(73)*, and Smith et al. *(74)* as potential sources of aerosolized fungal spores, but none of these authors presented evidence of epidemiologic significance for their findings.

Solid Waste

In recent years, most of the attention related to hospital solid wastes has focused on infectious waste issues, particularly on treatment and disposal of these wastes after they leave the hospital. A 1997 report indicated that 3 active cases of tuberculosis and 13 additional conversions resulted from clogged filters in a shredder at a commercial infectious waste treatment facility in Washington *(75)*. The lesson learned is that decontamination must precede shredding to prevent such incidents from occurring. The effect of such wastes within the hospital has received very little attention in recent years, undoubtedly because of the lack of evidence linking such wastes to healthcare-associated infections. An elaborate survey of hospital waste handling and its contribution to microbial contamination of air and surfaces was described by Bond and Michaelsen *(76)*. They concluded that contamination emanating from solid wastes was relatively insignificant and was greatly overshadowed by contamination levels resulting from the handling of soiled laundry. The quantitative and qualitative aspects of that study were detailed by Greene et al. (77,78).

DISCUSSION AND RECOMMENDATIONS

The role of the environment in healthcare-associated infections has been studied and debated for many years. Looking objectively at the evidence, it seems that much of the confusion relates to semantics rather than to scientific differences of opinion. Identification of reservoirs, issues of survival and infectivity of microorganisms, the relative importance of immune suppression, the role of autogenous versus exogenous sources, and the identification of transmission paths and portals of entry are now well understood. The previous sections have identified specific reports wherein environmental reservoirs have been cited (with varying degrees of evidence) as the source of cases or outbreaks of healthcare-associated illness, of colonization without illness, or, even more frequently, simply as reservoirs or hiding places for opportunistic microorganisms without epidemiologic association of any kind. Depending on the definition of environment and particularly of the interface between people, instruments, and equipment and the traditional air, water, or surfaces (floors, walls, and furniture), all of which can conceivably be lumped together as environment, one can conclude a greater or lesser role for environmental transmission. For example, everyone agrees on the importance of hand washing in preventing healthcare-associated infection, but is hand washing an environmental issue (involving products and methods) or is it simply a personal practice issue?

In a 1981 review, McGowan *(79)* suggested that the interest in the role of environmental factors in healthcare-associated infections is that they appear more amenable to control than do other facets of the problem. He argued against the routine monitoring of such environments as being of limited value, a position now shared by almost all practitioners in this field, and argued for selective monitoring only for clearly defined objectives, such as to support epidemiologic investigations or to monitor sterilization processes. Rhame *(18)* reviewed the role of the inanimate environment in healthcare-associated infections and differentiated types of evidence related to environmental involvement. He made the point that many reports merely indicate that a particular microorganism was cultured from a particular fomite with or without proliferation, the implication being that the environment becomes contaminated from infected or colonized patients not the other way around. He correctly downplayed these reports relative to the fewer case-control or prospective epidemiologic studies.

Thus, it is not possible to generalize meaningfully about environmental transmission. Instead, specific items and areas of the institutional environment must be considered separate entities, and environmental manipulation must be consistent with efficient operation and productive infection control practice. For example, there is sufficient evidence for the potential of hot water reservoirs to harbor *Legionella* microorganisms and to transmit those microorganisms to patients to warrant environmental intervention to prevent that problem. Conversely, there is insufficient evidence linking floor contamination to disease transmission to justify the use of expensive disinfectants for routine cleaning. Instead, esthetic cleanliness based on effective soil removal and odor control is clearly justifiable as the expectation of all patients. Recent concepts focus on controlling risk at those critical points of potential transmission. Of course, hand washing before touching the patient plays into the concept of controlling the environment through intervention in human behavior once that control point has been recognized. Such evidence-based concepts are being validated for prevention.

Recommendations for Environmental Control

One is left with having to design, construct, and maintain a complex physical environment for the care of increasingly susceptible hospital patients. Although one may quibble over the epidemiologic significance of this environment, we believe that current knowledge should enable clinicians to proceed with this task in a sensible, science-based, and cost-effective manner, confident that they are enhancing infection control practice and doing their duty for the patients that they are charged with protecting. In the following section, some of these approaches are proposed without apology. Again, "Guidelines for Environmental Infection Control" (*http://www.cdc.gov/mmwr/pdf/rr/rr5210.pdf*) is followed as part of the environment of care, especially as it relates to The Joint Commission's accreditation/certification stipulations mandated by Medicare funding protocols. Such "carrot sticks" will certainly help to define the cost-effective measures necessary to maintain a healthcare facility as a safe environment of care. And with recent rulings tying infection rates to reimbursements, policy changes are beginning to include patient safety priorities relating to infection prevention.

General Considerations A modern healthcare facility should be designed for efficient traffic flow, with particular attention to separation of dirty and clean areas. Among the clean areas, operating rooms and bone marrow transplantation facilities should be considered at the cleanest end

of the spectrum. Unnecessary traffic should be effectively excluded from any critical care area. Such concepts are being formalized into Lean Management principles for efficient patient care. Air-handling systems should be designed flexibly to allow higher volume air circulation in critical areas. Higher air volumes are needed to accommodate varying temperature and humidity conditions but should never be allowed to compromise contamination control airflow patterns. Air should move generally from cleaner to dirtier locations. Air intakes should be well separated from dirty air discharges and located away from loading docks subject to diesel fumes (see also Chapter 84). Redundant systems are necessary due to outages planned and unplanned. Such systems will avoid short-term exposure potentials, often occurring at times when most hospital occupants are unaware of these utility outages. Such short-term environment issues are critical points that beckon careful consideration for vulnerable patient populations. It is amazing to note, from past investigations into clusters of environmental infections such as aspergillosis, how many incidents of probable cause go unreported within the institution and, unfortunately, unreported to the public at large who may well sense the need for more systematic disease control efforts.

Maintenance of Ventilation Systems Duct and fan systems should be subject to routine maintenance and cleaning practices, including regular filter changes. It is important to remove dust and lint accumulations periodically. However, protocols should be developed to ensure that such maintenance does not release accumulated buildup of lint or other debris that could aerosolize opportunistic fungal spores. Figure 71-3 presents an example of heavy lint buildup on a bathroom exhaust grill. Particular attention must also be paid to avoiding high moisture conditions with resultant mold growth in ducts or on insulating materials (Fig. 71-4). Moisture content of >25% water content and 95% relative humidity promote rapid mold growth. Such local conditions should be altered immediately to avoid germination and subsequent sporulation of opportunistic spore forming filamentous fungi. Rapid removal of wet material, proper drying methods, and preservative application will manage spore formation in a critical environment. Rapid response is critical for moisture removal as sporulation can occur under ideal conditions within 96 hours.

FIGURE 71-3 Bathroom exhaust debris.

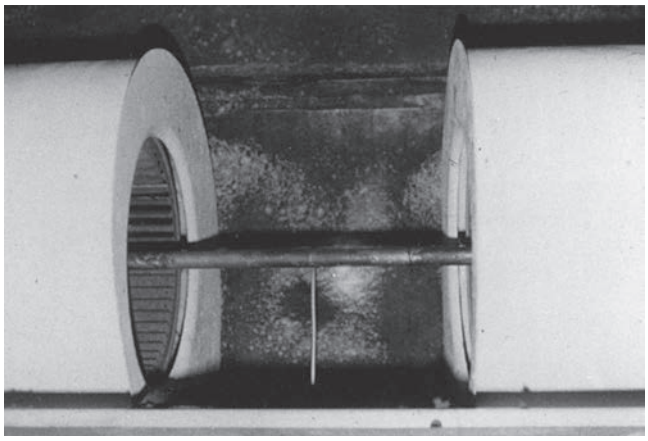

FIGURE 71-4 Fan coil with mold on wet insulation.

Control During Construction Projects The large number of ongoing renovation projects in healthcare facilities requires particular attention to detail to avoid outbursts of airborne fungi or bacteria. Written procedures should be in place to ensure consistency of these efforts, particularly as they pertain to the most critical areas of the facility. Erection of physical barriers to isolate renovation projects may often be necessary. Ventilation systems may need to be shut down temporarily or airflow may need to be rerouted to protect sensitive areas. Control over elevators to facilitate removal of debris or supply of building materials; without mingling workers with patients and staff members, may be necessary. Finally, traffic flow patterns for construction personnel *vis-à-vis* patients and healthcare workers should be defined and monitored. Table 71-2 lists some of the considerations for external project planning. Water damage management, external and internal, can potentially be an important factor for preventing mold colonization of a building. Prolonged wetting of modern building materials such as gypsum board and ceiling tiles can establish

TABLE 71-2

External Construction Planning

Project notification process
Pest management
Building seal
Windows and doors
Employee access
Ventilation assurance for protected hospital areas
Filtration integrity
Appropriate airflow
Air changes per hour
Pressurization
Water damage plan
Roof protection
Water damage–resistant gypsum board
Emergent response for water damage
Outage planning
Ventilation
Plumbing
Electricity
Infection control commissioning

significant mold reservoirs in a building that could be problematic later. Bid specification should address such incidents with a plan for delegating responsibility for drying or removal of the materials before mold contaminates the internal clinical areas of a healthcare facility. New York City Guidelines on assessment and remediation of indoor fungi (*http://www.nyc.gov/html/doh/downloads/pdf/epi/epi-mold-guidelines.pdf*) are helpful for management of mold guidance and for determination of the limit of cleanup by relatively untrained personnel. Careful consideration of cleanup includes realization that when spores dry they "fly." Wetting with surfactant and careful cleanup will help mitigate uncontrolled release of spores. A more common incident than most realize (see also Chapter 83).

General Housekeeping Housekeeping protocols should take into account the need for continuous surveillance over potential buildup of moisture conditions and subsequent fungal proliferation. Dust suppression practices should be emphasized, and cleaning of vents and air conditioners should be routine. Any use of vacuum cleaners should incorporate exhaust filters. Specific spill cleanup procedures should be in place with clear designation of responsibility for such cleanups. Attention should also be paid to ongoing availability of all supplies needed for emergency spill cleanup. Types of chemical disinfectants should be carefully chosen and should follow Centers for Disease Control and Prevention guidelines. Frequently, nongermicidal cleaning products are sufficient at lower cost than sanitizers or disinfectants and have the added benefit of a lower probability of causing chemical sensitivity problems (see also Chapter 80).

Maintenance of Water Reservoirs Specific measures for ensuring the absence of water contaminants such as *Legionella* have been discussed. Control of temperature, periodic superheating, maintenance of chlorine residuals, routine cleaning of storage tanks and other reservoirs, and avoidance of dead-ends or other promoters of stagnation are all important features of preventive maintenance of water reservoirs (see also Chapter 36). In special systems, such as renal dialysis units, ultraviolet light and/or bacterial filters may be appropriate to ensure consistent control. It is remarkable to realize that most buildings under construction, including hospitals, have their pipes filled up to a year before occupancy. Anecdotal experiences have seen high concentrations of gram-negative bacteria, often hard to eliminate if a biofilm has formed (80).

Methods to flush and disinfect water supplies are becoming an important disease control factor due to increasingly resistant strains of bacteria, which occasionally find their way to patient hosts. We must endeavor to better understand plumbing utility management, especially since water usage has begun to shrink in volume used.

CONCLUSIONS

Since this chapter was first drafted about 15 years ago, hundreds of additional articles have been published detailing contamination problems in healthcare facilities. This revision has endeavored to update the original chapter to reflect any significant new developments in the field. The looming threat of antibiotic resistance overcoming pharmacologic innovation clouds the future but brings us again to emphasize the basics of microbial contamination control. Although medical practice, facilities, and equipment for patient care have become more sophisticated and automated, the basic premise of the original chapter has not changed: controlling and minimizing levels of conventional and opportunistic microbial pathogens in healthcare environments is an integral and important aspect of healthcare-associated infection control.

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CHAPTER 72

Microbiologic Sampling of the Environment in Healthcare Facilities

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In the world of medicine, three developments occurring in the second half of the 20th century have served to increase the complexity of infectious diseases epidemiology—opportunistic pathogens, sophisticated lifesaving medical therapies (e.g., solid organ transplants, bone marrow transplants), and the rapidly increasing diversity and magnitude of antibiotic resistance among bacteria. The experiences gained in dealing with each of these have heightened our awareness of man's interaction with the environment, and the indoor environment in particular. Exposures to environmental pathogens can result in life-threatening infections among the most severely immunosuppressed patients. The identification of antibiotic-resistant bacteria in healthcare environments has drawn scrutiny to care-giving procedures as healthcare personnel move among patients from one area to another; the resistance pattern in one sense becomes a marker to help with the epidemiologic investigation to identify the source(s) of transmission. In the end, there is a renewed interest to understand how the indoor environment influences and/or facilitates transmission of infection. This necessitates the need to sample the environment in a way that is both practical and meaningful. Microbiologic sampling is the approach that most healthcare professionals often choose first when an epidemiologic investigation indicates some evaluation of the environment is needed, but this is not the only method, and it may not be the most appropriate method depending on the circumstances. Furthermore, environmental sampling methods are distinctly different from clinical microbiology methods, and clinical microbiology laboratories are often poorly equipped to carry out environmental sample analyses. This chapter addresses the basic principles and microbiologic methods of sampling indoor environmental surfaces and other environmental sources for microorganisms (1,2). Detailed methods for microbiologic sampling of the environment are included in this chapter since such sampling is frequently used during infectious disease outbreaks (2). Microbiologic sampling in response to a bioterrorism event is beyond the scope of this chapter; the reader is referred to other sources for more specific information about the unique sampling concerns for this endeavor (2).

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Any use or mention of trade names in this chapter is for identification purposes only and does not represent any endorsement by either the CDC or the U.S. Public Health Service.

GENERAL PRINCIPLES: MICROBIOLOGIC SAMPLING OF THE ENVIRONMENT

Before 1970, US hospitals conducted regularly scheduled culturing of the air and environmental surfaces (e.g., floors, walls, and table tops) *(3)*. By 1970, the Centers for Disease Control and Prevention (CDC) and the American Hospital Association (AHA) were advocating the discontinuation of routine environmental culturing because rates of healthcare-associated infection had not been associated with levels of general microbial contamination of air or environmental surfaces, and because meaningful standards for permissible levels of microbial contamination of environmental surfaces or air did not exist *(4–6)*. During 1970 to 1975, 25% of US hospitals reduced the extent of such routine environmental culturing—a trend that has continued *(7,8)*.

Random, undirected sampling (referred to as "routine" in previous guidelines) differs from the current practice of targeted sampling for defined purposes *(5,9)*. Previous recommendations against routine sampling were not intended to discourage the use of sampling in which sample collection, culture, and interpretation are conducted in accordance with defined protocols *(9)*. In this chapter, targeted microbiologic sampling connotes a monitoring process that includes (a) a written, defined, multidisciplinary protocol for sample collection and culturing; (b) analysis and interpretation of results using scientifically determined or anticipatory baseline values for comparison; and (c) expected actions based on the results obtained. Infection control, in conjunction with laboratorians, should assess the healthcare facility's capability to conduct sampling and determine when expert consultation and/or services are needed.

Microbiologic sampling of air, water, and inanimate surfaces (i.e., environmental sampling) is an expensive and time-consuming process that is complicated by many variables in protocol, analysis, and interpretation. It is therefore indicated for only four situations *(10)*. The first is to support an investigation of an outbreak of disease

or infections when environmental reservoirs or fomites are implicated epidemiologically in disease transmission *(11–13)*. It is important that such culturing be supported by epidemiologic data. Environmental sampling, as with all laboratory testing, should not be conducted if there is no plan for interpreting and acting on the results obtained *(14–16)*. Linking microorganisms from environmental samples with clinical isolates by molecular epidemiology is crucial whenever it is possible to do so.

The second situation for which environmental sampling may be warranted is in research. Well-designed and controlled experimental methods and approaches can provide new information about the spread of healthcare-associated diseases *(17,18)*. A classic example is the study of environmental microbial contamination that compared healthcare-associated infection rates in an old hospital and a new facility before and shortly after occupancy *(19)*.

The third indication for sampling is to monitor a potentially hazardous environmental condition, confirm the presence of a hazardous chemical or biological agent, and validate the successful abatement of the hazard. This type of sampling can be used to (a) detect bioaerosols released from the operation of healthcare equipment (e.g., an ultrasonic cleaner) and determine the success of repairs in containing the hazard *(20)*; (b) detect the release of an agent of bioterrorism in an indoor environmental setting and determine its successful removal or inactivation; and (c) sample for industrial hygiene or safety purposes (e.g., monitoring a "sick building").

The fourth indication is for quality assurance to evaluate the effects of a change in infection-control practice or to ensure that equipment or systems perform according to specifications and expected outcomes. Currently, much of the environmental assessment of practice in healthcare settings involves nonmicrobiologic methods such as covert visual inspection, use of ultraviolet (UV) fluorescent chemical markers, and adenosine triphosphate measurements of bioburden using relative light units recorded with a luminometer device (21,*22*). Nevertheless, any sampling for quality-assurance (QA) purposes (microbiologic sampling or any nonculture method) must follow sound sampling protocols. Microbiologic sampling in particular must address confounding factors through the use of properly selected controls. Results from a single environmental sample are difficult to interpret in the absence of a frame of reference or perspective. Evaluations of a change in infection-control practice are based on the assumption that the effect will be measured over a finite period, usually of short duration. Conducting QA microbiologic sampling on an extended basis, especially in the absence of an adverse outcome, is usually unjustified. A possible exception might be the use of air sampling during major construction periods to qualitatively detect breaks in environmental infection-control measures. In one study, which began as part of an investigation of an outbreak of healthcare-associated aspergillosis, airborne concentrations of *Aspergillus* spores were measured in efforts to evaluate the effectiveness of sealing hospital doors and windows during a period of construction of a nearby building *(23)*. However, the only types of routine environmental microbiologic sampling recommended as part of a QA program are (a) the biological monitoring of sterilization processes by using bacterial spores (24) and (b) the monthly culturing of water used in hemodialysis applications and for the final dialysate use dilution (see Chapter 63 for more information on sampling in dialysis settings).

Microbiologic sampling of the environment involves selecting a representative sample of that environment and collecting microbial contaminants with appropriate sampling devices. The interpretation of results should be based on the understanding of the recovery efficiencies of the materials and the limitations of the processing method (2).

Air Sampling

Biological contaminants occur in the air as aerosols and may include bacteria, fungi, viruses, and pollens *(25,26)*. Aerosols are characterized as solid or liquid particles suspended in air. Talking for 5 minutes and coughing each can produce 3,000 droplet nuclei; sneezing can generate approximately 40,000 droplets that then evaporate to particles in the size range of 0.5 to 12 μm *(27,28)*. Particles in a biological aerosol usually vary in size from <1 to >50 μm. These particles may consist of a single, unattached microorganism or may occur in the form of clumps composed of a number of bacteria. Clumps can also include dust and dried organic or inorganic material. Vegetative forms of bacterial cells and viruses may be present in the air in a lesser number than bacterial spores or fungal spores. Factors that determine the survival of microorganisms within a bioaerosol include (a) the suspending medium; (b) temperature; (c) relative humidity; (d) oxygen sensitivity; and (e) exposure to UV or electromagnetic radiation *(25)*. Many vegetative cells will not survive for lengthy periods of time in the air unless the relative humidity and other factors are favorable for survival and the microorganism is enclosed within some protective cover (e.g., dried organic or inorganic matter) *(26)*. Pathogens that resist drying (e.g., *Staphylococcus* spp., *Streptococcus* spp., and fungal spores) can survive for long periods and can be carried considerable distances via air and still remain viable. They may also settle on surfaces and become airborne again as secondary aerosols during certain activities (e.g., sweeping and bed making) (*26*,29).

Microbiologic air sampling is used to determine the numbers and types of microorganisms, or particulates, in indoor air (30). Air sampling for quality control is, however, problematic because of lack of uniform air-quality standards. Although airborne spores of *Aspergillus* spp. can pose a risk for neutropenic patients, the critical number (i.e., action level) of these spores above which outbreaks of aspergillosis would be expected to occur has not been defined. Healthcare professionals considering the use of air sampling should keep in mind that the results represent indoor air quality at singular points in time, and these may be affected by a variety of factors including (a) indoor traffic; (b) visitors entering the facility; (c) temperature; (d) time of day or year; (e) relative humidity; (f) relative concentration of particles or microorganisms; and (g) the performance of the air-handling system components. To be meaningful, air-sampling results must be compared with those obtained from other defined areas, conditions, or time periods and outside air samples.

Several preliminary concerns must be addressed when designing a microbiologic air-sampling strategy (Box 72-1).

BOX 72-1

Preliminary Concerns for Conducting Air Sampling

- Consider the possible characteristics and conditions of the aerosol, including size range of particles, relative amount of inert material, concentration of microorganisms, and environmental factors.
- Determine the type of sampling instruments, sampling time, and duration of the sampling program.
- Determine the number of samples to be taken.
- Ensure that adequate equipment and supplies are available.
- Determine the method of assay that will ensure optimal recovery of microorganisms.
- Select a laboratory that will provide proper microbiologic support.
- Ensure that samples can be refrigerated if they cannot be assayed in the laboratory promptly.

Because the amount of particulate material and bacteria retained in the respiratory system is largely dependent on the size of the inhaled particles, particle size should be determined when studying airborne microorganisms and their relation to respiratory infections. Particles >5 μm are efficiently trapped in the upper respiratory tract and are removed primarily by ciliary action *(31)*. Particles <5 μm in diameter reach the lung, but the greatest retention in the alveoli is of particles 1 to 2 μm in diameter *(32–34)*.

Bacteria, fungi, and particulates in air can be identified and quantified with the same methods and equipment (Table 72-1). The basic methods include (a) impingement in liquids; (b) impaction on solid surfaces; (c) sedimentation; (d) filtration; (e) centrifugation; (f) electrostatic precipitation; and (g) thermal precipitation (29). Of these, impingement in liquids, impaction on solid surfaces, and sedimentation (on settle plates) have been used for various air-sampling purposes in healthcare settings (30).

Several instruments are available for sampling airborne bacteria and fungi (Box 72-2). Some of the samplers are self-contained units requiring only a power supply and the appropriate collecting medium, but most require additional auxiliary equipment (e.g., a vacuum pump and an airflow measuring device [i.e., a flow meter or anemometer]). Sedimentation or depositional methods use settle plates (Petri plates with agar media) and therefore need no special instruments or equipment. Selection of an instrument for air sampling requires a clear understanding of the type of information desired and the particular determinations that must be made (Box 72-2). Information may be needed regarding: (a) one particular microorganism or all microorganisms that may be present in the air; (b) the concentration of viable particles or of viable microorganisms; (c) the change in concentration with time; and (d) the size distribution of the collected particles. Before sampling begins, decisions should be made regarding whether the results are to be qualitative or quantitative. Comparing quantities of airborne microorganisms to those of outdoor air is also standard operating procedure. Infection preventionists, healthcare epidemiologists, industrial hygienists, and laboratory supervisors, as part of a multidisciplinary team, should discuss the potential need for microbial air sampling to determine if the capacity and expertise to conduct such sampling exist within the facility and when it is appropriate to enlist the services of an environmental microbiologist consultant.

Liquid impinger and solid impactor samplers are the most practical for sampling bacteria, particles, and fungal spores, because they can sample large volumes of air in relatively short periods of time (30). Solid impactor units are available as either "slit" or "sieve" designs. Slit impactors use a rotating disc as support for the collecting surface, which allows determinations of concentration over time. Sieve impactors commonly use stages with calibrated holes of different diameters. Some impactor-type samplers use centrifugal force to impact particles onto agar surfaces. The interior of either device must be made sterile to avoid inadvertent contamination from the sampler. Results obtained from either sampling device can be expressed as microorganisms or particles per unit volume of air (CFU/m^3).

Sampling for bacteria requires special attention, because bacteria may be present as individual microorganisms, as clumps, or mixed with or adhering to dust or covered with a protective coating of dried organic or inorganic substances. Reports of bacterial concentrations determined by air sampling therefore must indicate whether the results represent individual microorganisms or particles bearing multiple cells. Certain types of samplers (e.g., liquid impingers) will completely or partially disintegrate clumps and large particles; the sampling result will therefore reflect the total number of individual microorganisms present in the air.

The task of sizing a bioaerosol is simplified through the use of sieves or slit impactors, because these samplers will separate the particles and microorganisms into size ranges as the sample is collected. These samplers must, however, be calibrated first by sampling aerosols under similar use conditions *(37)*.

The use of settle plates (i.e., the sedimentation or depositional method) is not recommended when sampling air for fungal spores, because single spores can remain suspended in air indefinitely (30). Settle plates have been used mainly to sample for particulates and bacteria either in research studies or during epidemiologic investigations *(11,38–41)*. Results of sedimentation sampling are typically expressed as numbers of viable particles or viable bacteria per unit area per the duration of sampling time (i.e., CFU/area/time); this method cannot quantify the volume of air sampled. Because the survival of microorganisms during air sampling is inversely proportional to the velocity at which the air is taken into the sampler *(25)*, one advantage of using a settle plate is its reliance on gravity to bring microorganisms and particles into contact with its surface, thus enhancing the potential for optimal survival of collected microorganisms. This process, however, takes several hours to complete and may be impractical for some situations.

Air samplers are designed to meet differing measurement requirements. Some samplers are better suited for one form of measurement than others. No one type of sampler and assay procedure can be used to collect and enumerate 100% of airborne microorganisms. The sampler

TABLE 72-1

Air-Sampling Methods and Examples of Equipment

Method	*Principle*	*Suitable for Measuring*	*Collection Media or Surface*	*Rate of Collection (L/min)*	*Auxiliary Equipment Needed*[a]	*Points to Consider*	*Prototype Samplers*[b]
Impingement in liquids	Air drawn through a small jet and directed against a liquid surface	Viable microorganisms and concentration over time. Example use: sampling water aerosols for *Legionella* spp.	Buffered gelatin, tryptose saline, peptone, nutrient broth	12.5	Yes	Antifoaming agent may be needed. Ambient temperature and humidity will influence length of collection time.	Chemical Corps. All Glass Impinger (AGI)
Impaction on solid surfaces	Air drawn into the sampler; particles deposited on a dry surface	Viable particles; viable microorganisms (on nonnutrient surfaces, limited to microorganisms that resist drying and spores); size measurement, and concentration over time. Example use: sampling air for *Aspergillus* spp., fungal spores	Dry surface, coated surfaces, and agar	28 (sieve) 30–800 (slit)	Yes	Available as sieve impactors or slit impactors. Sieve impactors can be set up to measure particle size. Slit impactors have a rotating support stage for agar plates to allow for measurement of concentration over time	Andersen Air Sampler, Surface Air Sampler (PBI Int'l, Italy) (sieve impactor); TDL, Casella MK-2 (slit impactors)
Sedimentation	Particles and microorganisms settle onto surfaces via gravity	Viable particles. Example uses: sampling air for bacteria in the vicinity of and during a medical procedure; general measurements of microbial air quality	Nutrient media (agars) on plates or slides	—	No	Simple and inexpensive; best suited for qualitative sampling; significant airborne fungal spores are too buoyant to settle efficiently for collection using this method	Settle plates
Filtration	Air drawn through a filter unit; particles trapped; 0.2 μm pore size	Viable particles; viable microorganisms (on nonnutrient surfaces, limited to spores and microorganisms that resist drying); concentration over time. Example use: air sampling for *Aspergillus* spp., fungal spores, and dust	Paper, cellulose, glass wool, gelatin foam, and membrane filters	1–50	Yes	Filter must be agitated first in rinse fluid to remove and disperse trapped microorganisms; rinse fluid is assayed; used more for sampling dust and chemicals	Sartorius AirPort MD8 air sampler with gelatin membrane filter (Sartorius Corporation)

Centrifugation	Aerosols subjected to centrifugal force; particles impacted onto a solid surface	Viable particles; viable microorganisms (on nonnutrient surfaces, limited to spores and microorganisms that resist drying); concentration over time. Example use: air sampling for *Aspergillus* spp., and fungal spores	Coated glass or plastic slides, and agar surfaces	40–50	Yes	Calibration is difficult and is done only by the factory; relative comparison of airborne contamination is its general use	Biotest RCS Plus
Electrostatic precipitation	Air drawn over an electrostatically charged surface; particles become charged	Viable particles; viable microorganisms (on nonnutrient surfaces, limited to spores and microorganisms that resist drying); concentration over time	Solid collecting surfaces (glass, agar)	85	Yes	High-volume sampling rate, but equipment is complex and must be handled carefully; not practical for use in healthcare settings	—
Thermal precipitation	Air drawn over a thermal gradient; particles repelled from hot surfaces; settle on colder surfaces	Size measurements	Glass coverslip, and electron microscope grid	0.003–0.4	Yes	Determine particle size by direct observation; not frequently used because of complex adjustments and low sampling rates	—

[a]Most samplers require a flow meter or anemometer and a vacuum source as auxiliary equipment.
[b]Trade names listed are for identification purposes only and are not intended as endorsements by the U.S. Public Health Service.
(Data from references *27*, *28*, *35*, and *36*.)

BOX 72-2

Selecting an Air-Sampling Device

The following factors must be considered when choosing an air-sampling instrument:

- Viability and type of the microorganism to be sampled
- Compatibility with the selected method of analysis
- Sensitivity of particles to sampling
- Assumed concentrations and particle size
- Whether airborne clumps must be broken (i.e., total viable microorganism count vs. particle count)
- Volume of air to be sampled and length of time sampler is to be continuously operated
- Background contamination
- Ambient conditions
- Sampler collection efficiency
- Effort and skill required to operate sampler
- Availability and cost of sampler, plus backup samplers in case of equipment malfunction
- Availability of auxiliary equipment and utilities (e.g., vacuum pumps, electricity, and water)

(Data from Wolf HW, Skaliy P, Hall LB, et al. Sampling microbiological aerosols. Public Health Service publication No. 686. Washington, DC: Government Printing Office, 1964.)

and/or sampling method chosen should, however, have an adequate sampling rate to collect a sufficient number of particles in a reasonable time period so that a representative sample of air is obtained for biological analysis. Newer analytical techniques for assaying air samples include polymerase chain reaction (PCR) methods and enzyme-linked immunosorbent assays.

Water Sampling

A detailed discussion of the principles and practices of water sampling has been published (42). Water sampling in healthcare settings is used to detect waterborne pathogens of clinical significance or to determine the quality of finished water in a facility's distribution system. Routine testing of the water in a healthcare facility is usually not indicated, but sampling in support of outbreak investigations can help determine appropriate infection-control measures. Water-quality assessment in dialysis settings is another instance where routine microbiologic sampling of water is important and where standards have been established (see hemodialysis, Chapter 63).

Healthcare facilities that conduct water sampling should have their samples assayed in a laboratory that uses established methods and QA protocols. Water specimens are not "static specimens" at ambient temperature; potential changes in both numbers and types of microbial populations can occur during transport. Consequently, water samples should be sent to the testing laboratory cold (i.e., at ~39.2°F [4°C]) and testing should be done as soon as practical after collection (preferably within 24 hours).

Because most water sampling in healthcare facilities involves the testing of finished water from the facility's distribution system, a reducing agent (i.e., sodium thiosulfate [$Na_2S_2O_3$]) needs to be added to neutralize residual chlorine or other halogen in the collected sample. If the water contains elevated levels of heavy metals, then a chelating agent should be added to the specimen. The minimum volume of water to be collected should be sufficient to complete any and all assays indicated; 100 mL is considered a suitable minimum volume. Sterile collection equipment should always be used.

Sampling of water from the distribution sytem from a tap requires flushing of the water line before sample collection. If the tap is a mixing faucet, attachments (e.g., screens and aerators) must be removed, and hot and then cold water must be run through the tap before collecting the sample (42). If the cleanliness of the tap is questionable, disinfection with 500 to 600 parts per million (ppm) sodium hypochlorite (1:100 v/v dilution of chlorine bleach) and flushing the tap should precede sample collection. If biofilm associated organisms are sought, samples are collected from inside the faucet head, screens and aerators with a non-cotton swab prior to flushing of the tap.

Microorganisms in finished or treated water often are physically damaged ("stressed") to the point that growth is limited when assayed under standard conditions. Such situations lead to false-negative readings and misleading assessments of water quality. Appropriate neutralization of halogens and chelation of heavy metals are crucial to the recovery of these microorganisms. The choice of recovery media and incubation conditions will also affect the assay. Incubation temperatures should be closer to the ambient temperature of the water rather than at 98.6°F (37°C), optimum growth temperature of the specific microorganism sought, and recovery media should be formulated to provide appropriate concentrations of nutrients to support microorganisms exhibiting less than rigorous growth (42). High-nutrient content media (e.g., blood agar and tryptic soy agar [TSA]) may actually inhibit the growth of these damaged microorganisms. Reduced nutrient media (e.g., diluted peptone and R2A) are preferable for recovery of these microorganisms (42).

Use of aerobic, heterotrophic plate counts allows both a qualitative and quantitative measurement for water quality. If bacterial counts in water are expected to be high in number (e.g., during waterborne outbreak investigations), assaying small quantities using pour plates or spread plates is appropriate (42). Membrane filtration is used when low-count specimens are expected and larger sampling volumes are required (>100 mL). The sample is filtered through the 0.45 µm or 0.22 µm membrane, and the filter is applied directly face-up onto the surface of the agar plate and incubated.

Unlike the testing of potable water supplies for coliforms (which uses standardized test and specimen collection parameters and conditions), water sampling to support epidemiologic investigations of disease outbreaks may be subjected to modifications dictated by the circumstances present in the facility. Assay methods for waterborne pathogens may also not be standardized. Therefore, control or comparison samples should be included in the experimental design. Any departure from a standard method should be fully documented and should be considered when interpreting results and developing strategies. Assay methods specific for clinically significant waterborne pathogens (e.g., *Legionella* spp., *Aeromonas* spp., *Pseudomonas* spp., and *Acinetobacter* spp.) are more complicated and costly

compared with both methods used to detect coliforms and other standard indicators of water quality.

Microbiologic Sampling of Environmental Surfaces

Routine environmental-surface sampling (e.g., surveillance cultures) in healthcare settings is neither cost-effective nor warranted (*37*,43). When indicated, surface sampling should be conducted with multidisciplinary approval in adherence to carefully considered plans of action and policy (Box 72-3). Microbiologic sampling of nonporous and porous surfaces is used currently for research, as part of an epidemiologic investigation, or as part of a comprehensive approach for specific QA purposes. As a research tool, surface sampling has been used to determine (a) potential environmental reservoirs of pathogens *(44–47)*; (b) survival of microorganisms on surfaces *(47,48)*; and (c) the sources of the environmental contamination *(49)*. Some or all of these approaches can also be used during outbreak investigations *(47)*.

Microbiologic sampling of surfaces involves selecting a representative sample of the surface to be studied and collecting microbial contaminants from the surface with appropriate sampling devices and laboratory-approved sampling media. Choosing the appropriate sampling devices depends on the sampling phase during an investigation, the area and type of surface being sampled, and the limitations of the sampling method. The objectives for a sampling event must be defined to provide useable, defendable, applicable, and scientifically meaningful data for use in the decision-making process of an investigation. Insight and consultation with the laboratory is important to the development of a successful sampling strategy. The interpretation of results should be based on the understanding of the recovery efficiencies of the materials and the limitations of the processing method. Methods used for routine sampling of environmental surfaces include swabs, wipes/sponges, agar contact plates, surface rinse, and vacuums (2). Additionally, there are microbial properties and environmental influences that may affect the sampling, detection, or the results of the analysis (Box 72-4) (2).

BOX 72-3

Undertaking Environmental-Surface Sampling

The following factors should be considered before engaging in environmental-surface sampling:

- Background information from the literature and present activities (i.e., preliminary results from an epidemiologic investigation)
- Location of surfaces to be sampled
- Method of sample collection and the appropriate equipment for this task
- Number of replicate samples needed and which control or comparison samples are required
- Parameters of the sample assay method and whether the sampling will be qualitative, quantitative, or both
- An estimate of the maximum allowable microbial numbers or types on the surface(s) sampled (refer to the Spaulding classification for devices and surfaces)
- Some anticipation of a corrective action plan

(Data from Bond WW, Sehulster LM. Microbiological culturing of environmental and medical-device surfaces. In: Isenberg HD, Miller JM, Bell M, eds. *Clinical microbiology procedures handbook*. Washington, DC: American Society for Microbiology Press, 2004:Section 13.)

BOX 72-4

Variables Affecting Sampling, Detection, and Analysis

- Ability of the agent to survive or produce active toxins on surfaces for extended periods of time in various environmental conditions
  - Spores of *Bacillus anthracis* and *Clostridium* spp. can persist for years on surfaces such as paper or nonporous surfaces *(50)*.
  - Some vegetative bacteria (e.g., *Staphylococcus aureus*) can survive for weeks or months depending upon the presence of organic material, available moisture, or a suitable carrier.
  - If detection is dependent on culture, consider the conditions since deposition
    - If viability of the microorganism is unlikely, then sampling for detection by alternate means (i.e., polymerase chain reaction [PCR]) should be considered or used in conjunction with culture.
- Interference from particulates, other microorganisms, growth inhibitors, or assay inhibitors
  - Particulates such as dust, heavy metals, or fibers may inhibit growth, interfere with PCR, or make recognition of characteristic colony morphology difficult in culture *(51)*.
  - Large numbers of background bacteria present can compete with the target microorganism in culture, or interfere with PCR by providing an excess of nontarget deoxyribonucleic acid (DNA) *(52)*.
  - Clay and organic substances (e.g., humic acid in soil) can inhibit growth in culture and interfere with PCR assays *(51)*.
- Adherence properties of microorganisms
  - Vegetative bacteria are more likely to be affected than bacterial spores by the chemical and/or physical properties of the surface.
  - Adherence can be influenced by temperature, humidity, presence of other organics on the surface or deposition media.
- Laboratory assay used for detection
  - Materials and wetting compounds may not be compatible with assay reagents.
  - Growth media, diluents, or neutralizers may be inhibitory to the microorganism being detected.

Surface Sampling Considerations Essential components of a successful sampling strategy during any microbiological investigation include (a) properly trained personnel; (b) a sound sampling strategy; (c) a qualified laboratory; (d) laboratory-approved sample media and supplies; (e) appropriate safety policies; (f) thorough recordkeeping and documentation; and (g) QA and quality-control (QC) procedures (53). The condition and documentation of the sample received by the laboratory for analysis are of primary importance. If samples are improperly

collected and mishandled or are not representative of the area/location, the laboratory results will be meaningless. Decisions about an area in question are based on a relatively small numbers of representative samples; therefore, established sampling procedures must be applied uniformly and consistently (54).

Two basic elements must be present in any plan to sample: the use of sterile equipment and the use of the aseptic technique. In order to ensure the reliability of the results, it is critical to ensure that the media, solutions, and the sample containers are sterile and remain sterile. Use of prepackaged sterile supplies and equipment prior to their end-of-use date are the easiest way to ensure that sampling is done with sterile materials. Aseptic technique ensures that no additional contamination is introduced into the sample during the collection process and that a representative sample has been collected (54). In order to utilize the aseptic technique during sampling, the concept of the "clean person/contaminated person" is suggested for sampling in hospitals, but must be used by responsible persons when evaluating a biological agent event. In practical terms, this becomes a two-person sampling team, with one individual only handling the sampling media (the sampler) and the other individual handling all other supplies (support person) (54). The support person will employ aseptic techniques to open packages and make sampling devices and equipment available to the sampler. The sampler is the only person to touch the sample media. The sampler will collect the sample and place the device into an open sample container that is held by the support person. Once the sample is placed into the sample container and two plastic sealable bags, the sample will be decontaminated and placed into a third bag or container. All individuals for either role should be trained in aseptic techniques prior to undertaking microbiologic sampling (2). Additionally, persons involved with microbiologic sampling should use personal protective equipment appropriate to the task (e.g., gloves, lab coat, respirator) (53).

Depending on the overall objective indicating the need for microbiologic sampling, the approach to sampling may encompass three phases—the screening phase, the characterization phase, and the clearance or postremediation phase (2). It may not be necessary to include all three of these phases in the sampling plan. The screening phase provides an opportunity to get a general sense and extent of potential contamination through the use of qualitative sampling and analysis. Outbreak investigations that utilize screening phase activities most likely are attempting to evaluate contamination involving large and/or diverse areas of the healthcare facility. The characterization phase activities involve a more focused, quantitative approach to sampling. This is typically used in outbreak investigations to ascertain specific information about pathogens (i.e., potential for infection, viability of the microorganism, possible source and extent of contamination, and routes of spread) (2). Sampling for quantitative results requires attention to the surface area sampled, since results will be reported as the concentration of the agent in a given area sampled (Box 72-5). There must be uniformity of sample collection materials or devices, as well as personnel techniques. Laboratory processing for quantitative results involves more time and effort, as well as more supplies and reagents; communication with the laboratory early in the planning stages is, therefore, crucial. The clearance or postremediation phase sampling activities are typically used to determine if an area is safe for occupancy, usually following a decontamination or disinfecting treatment (2). Either qualitative or quantitative microbiologic sampling can be used depending on the type of information needed and the anticipated action plan based on the results. When undertaking environmental sampling to evaluate the effectiveness of a large space decontamination process, biological indicators (e.g., spore strips) should always be included in the sampling design (2). Environmental sampling of surfaces does not stand alone on its own merit. Rather, there must be evidence that the decontamination process was successful (i.e., inactivation of biological indicators placed throughout the treated space). Spore strips of *Geobacillus stearothermophilus* or *Bacillus atrophaeus* are suitable for this purpose. Postremediation phase sampling in healthcare facilities is currently used with contemporary room treatments such as vaporized hydrogen peroxide.

BOX 72-5

Sampling Area and Sampling Devices

- Moist swab: 100 cm^2, approximately 4 $in.^2$
- Moist wipe: 8 ft^2 for 9 in. × 9 in. wipe
  Up to several square meters with a 15 × 25 cm rayon wipe
  1 ft^2 with a 3 in. × 3 in. noncotton gauze pad
- Moist sponge: ≤1 m^2 with a 1.5 in. × 3 in. sponge
- HEPA[a] sock: No known documented guidelines
- Contact plate: Area of plate only
- Historic guidelines for sampling areas are based on knowledge from the food industry and experience from sampling in a clinical setting. These guidelines are subject to change.

[a]HEPA, high efficiency particulate air.
(Data from References 2, 24, 53, 55, and 56.)

Use of Neutralizers The presence of residual disinfectants should be considered when sampling after a germicidal treatment. This is most important when using such disinfectants such as sodium hypochlorite, quaternary ammonium compounds, hydrogen peroxide, and phenolics. In such cases, inclusion of specific neutralizers in the recovery media or sampling media is important to prevent carrying the residual disinfectant into the assay or culture media (Table 72-2). Such carry over may result in toxic effects and reduced numbers or erroneous assay results. When incorporating neutralizers into a sampling device or analytical method, the potential toxic effect of the neutralizer should be evaluated for each microorganism. The sampling team should consult with laboratory personnel when making decisions on the appropriate neutralizers to be incorporated in the sampling device. The choice of neutralizer will be based on the type of disinfectant used for decontamination and knowledge of the neutralizer's toxicity to the agent to be sampled (2,24,57).

Media and Diluents Meaningful results depend on the selection of appropriate sampling and assay techniques (24). The media, reagents, and equipment required for

TABLE 72-2

Neutralizing Agents

Disinfectant	*Neutralizer or Neutralizing Media*
Sodium hypochlorite, chlorine dioxide, iodine	Sodium thiosulfate, Dey Engley (D/E) broth or agar (Becton Dickinson, Sparks, MD)
Formaldehyde, glutaraldehyde	Glycine, D/E broth or agar
Hydrogen peroxide	Catalase
Phenolics	Tween 80®, D/E broth or agar
Quaternary ammonium compounds	Lecithin + Lubrol W, Letheen broth or agar (Becton Dickinson), or D/E broth or agar
Vaporized hydrogen peroxide	None needed—end products H_2O and O_2

(Adapted from Russell AD. Principles of antimicrobial activity and resistance. In: Block SS, ed. *Disinfection, sterilization, and preservation*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2001:31–56.)

TABLE 72-3

Examples of Eluents and Diluents for Environmental-Surface Sampling[a]

Solutions	*Concentration in Water*
Ringer	1/4 strength
Peptone water	0.1–1.0%
Buffered peptone water	0.067 M phosphate, 0.43% NaCl, 0.1% peptone
Phosphate-buffered saline phosphate, 0.9% NaCl	0.02 M
Sodium chloride (NaCl)	0.25–0.9%
Calgon Ringer[b]	1/4 strength
Thiosulfate Ringer[c]	1/4 strength
Water	—
Tryptic soy broth (TSB)	—
Brain–heart infusion broth (BHI) supplemented with 0.5% beef extract	—

[a]A surfactant (e.g., polysorbate [i.e., Tween 80®]) may be added to eluents and diluents. A concentration ranging from 0.01% to 0.1% is generally used, depending on the specific application. Foaming may occur during use.
[b]This solution is used for dissolution of calcium alginate swabs.
[c]This solution is used for neutralization of residual chlorine.
(Data from Bond WW, Sehulster LM. Microbiological culturing of environmental and medical-device surfaces. In: Isenberg HD, Miller JM, Bell M, eds. *Clinical microbiology procedures handbook*. Washington, DC: American Society for Microbiology Press, 2004:Section 13 and International Organization for Standardization (ISO). *Sterilization of medical devices—microbiological methods, Part 1*. ISO Standard 11737-1. Geneva, Switzerland: International Organization for Standardization, 1995.)

surface sampling are available from any well-equipped microbiology laboratory and laboratory supplier. For quantitative assessment of surface microorganisms, dilutions of eluents from sampling devices are cultured on nonselective, nutrient-rich agar media (e.g., TSA and brain–heart infusion broth [BHI] with or without 5% sheep or rabbit blood supplement). Further sample workup may require the use of selective media for the isolation and enumeration of specific groups of microorganisms. Examples of selective media are MacConkey agar (MAC [selects for gram-negative bacteria]), Cetrimide agar (selects for *Pseudomonas aeruginosa*), or Sabouraud dextrose and malt extract agars and broths (select for fungi). Qualitative determinations of specific microorganisms from surfaces require the use of selective or nonselective media.

Effective sampling of surfaces requires moisture, either already present on the surface to be sampled or via moistened swabs, sponges, wipes, agar surfaces, or membrane filters (24,*58–60*). Dilution fluids and rinse fluids include various buffers or general purpose broth media (Table 72-3). If disinfectant residuals are expected on surfaces being sampled, specific neutralizer chemicals should be used in both the growth media and the dilution or rinse fluids (61). Alternatively, instead of adding neutralizing chemicals to existing culture media (or if the chemical nature of the disinfectant residuals is unknown), the use of either (a) commercially available media including a variety of specific and nonspecific neutralizers or (b) double-strength broth media will facilitate optimal recovery of microorganisms. The inclusion of appropriate control specimens should be included to rule out both residual antimicrobial activity from surface disinfectants and potential toxicity caused by the presence of neutralizer chemicals carried over into the assay system (24).

Microbiologic Methods for Surface Sampling Several methods can be used for collecting environmental-surface samples (Table 72-4) (2). Sample/rinse methods are frequently chosen because of their versatility. However, these sampling methods are the most prone to errors caused by manipulation of the swab, gauze pad, or sponge (62). Additionally, no microbiocidal or microbiostatic agents should be present in any of these items when used for sampling (62). Each of the rinse methods requires effective elution of microorganisms from the item used to sample the surface. Thorough mixing of the rinse fluids after elution (e.g., via manual or mechanical mixing using a vortex mixer, shaking with or without glass beads, and ultrasonic bath) will help to remove and suspend material from the sampling device and break up clumps of microorganisms for a more accurate count (62). In some instances, the item used to sample the surface (e.g., gauze pad and sponge) may be immersed in the rinse fluids in a sterile bag and subjected to stomaching (62). This technique, however, is suitable only for soft or absorbent items that will not puncture the bag during the elution process.

If sampling is conducted as part of an epidemiologic investigation of a disease outbreak, identification of isolates to species level is mandatory, and characterization beyond the species level is preferred (24). When interpreting the results of the sampling, the expected degree of microbial contamination associated with the various categories of surfaces in the Spaulding classification must be considered. Environmental surfaces should be visibly clean; recognized pathogens in numbers sufficient to result

TABLE 72-4

Comparison of Surface Sampling Methods

Nonporous and Porous Surface Sampling

Sample Type	*Description*	*Media Examples*	*Target*	*Uses*	*Microorganisms and Toxins*
Wipe	Sterile 2 in. × 2 in. noncotton gauze sponge pad. Moisten with sterile lab-determined wetting solution and wipe area of specified size (up to several square meters).]	Versalon Gauze Sponge 2 in. × 2 in. from MFASCO Health and Safety Company. *http://www.mfasco.com/*	Area sampled is small; effective on nonporous surfaces.	Screening small nonporous surfaces; discriminate sample location; extent of contamination; decontamination effectiveness.	Bacteria, viruses, and biological toxins.
	Sterile, 1.5 in. × 3 in. cellulose sponge folded over a handle and is biocide-free, packaged in sealable transport bag (wipe area up to 1 m^2)	3M™ Sponge-Stick with Neutralizing Buffer cellulose sponge pre-moistened with 10 mL Neutralizing Buffer (3M, St. Paul, MN, cat no. SSL10NB) or equivalent			
Swab	Sterile noncotton swabs individually wrapped then moistened with sterile lab-determined wetting solution. Wipe area of specified size (100 cm^2) (1,*13*).	Puritan Medical Products Company LLC,Guilford, ME 04443-0149 cat # ***25-1605 1PSF RECT*** *www.puritanmedproducts.com 1-800-321-2313*	Area sampled is very small; effective on nonporous surfaces; corners and small crevices.	Screening very small nonporous locations, crevices and corners. Often collected with other sample media. Extent of contamination and critical item screening.	Bacteria, viruses, and biological toxins.
Agar contact plates	Sample collected by firmly pressing the contact plate onto surface to be sampled. Do not move or slide the plate.	Fischer Scientific, BD BBL Prepared sterile RODAC plates, blood agar (B4392229) and neutralizing agar (L21232), *www.fischersci.com*	Area to be sampled is small, effective on nonporous surfaces. Slightly curved surfaces may be sampled with a rolling motion.	Screening small nonporous surfaces; discriminate sample location; extent of contamination; decontamination effectiveness. Often collected with other sample media.	Bacteria

HEPA vacuum collection sock	Sample collected into HEPA filter collection sock that will fit into the inlet nozzle of a small portable HEPA vacuum hose. Note the area that was sampled.	X-Cell 200 Dust Collection Sock Assembly with inlet nozzle assembly from Midwest Filtration Company, Cincinnati, OH 45246 Phone: 513-874-6510 sales@midwestfiltration.com	For large porous areas like carpets and window treatments; works best with spore-forming bacteria, must have significant volume of dust and/or small particles; method can disturb other sample locations with circulating air. Best for agents persistent in the environment.	Screening large porous surfaces and objects. Often collected with other sample media. Extent of contamination and critical item screening.	Spore-forming bacteria, and biological toxins.
Microvacuum sampling	Sample collected with collection nozzle into a filter holder containing a sample media attached to a sample pump. Vacuum the area to be sampled (size 10 cm × 10 cm to maximum of 30 cm × 30 cm) (ASTM D7144).	SKC Model No: 225–9543 or Zefon Model number 7345 CC–37 mm Micro-Vac Cassette with 0. 45-μm MCE filter	Area to be sampled is small; effective on nonporous intricate surfaces like HVAC air intakes, and porous surfaces like stucco walls, and personal items. Best for agents persistent in the environment.	Screening small and/or delicate porous surfaces and objects. Often collected with other sample media. Extent of contamination and critical item screening.	Spore-forming bacteria and biological toxins.
Bulk sampling	Visible bulk solid material collected as standard solid sample. Samples also include pieces of HVAC filters, letters, devices, containers, or pieces of personal items, clothing, or other materials.	Sterile disposable spatula	Laboratories may not accept concentrated sample. Check with laboratory prior to sending for information on restrictions for sample volume or size.	Discriminate sampling; HVAC systems screening; evidence screening; disposal acceptance samples.	Bacteria, viruses, and biological toxins.

*The use of trade names and commercial sources is for identification purposes only and does not imply endorsement by CDC or the U.S. Public Health Service, Department of Health and Human Services.
HEPA, high efficiency particulate air; HVAC, heating, ventilation, and air conditioning; cm, centimeter; in., inches; ft^2, feet square; ×, by; in^2, inches square.
(Data from references 53, 63–65. Internet sites mentioned in this table accessed January 20, 2011.)

in secondary transfer to other animate or inanimate surfaces should be absent from the surface being sampled (24). Although the interpretation of a sample with positive microbial growth is self-evident, an environmental-surface sample (especially one obtained from a housekeeping surface) that shows no growth does not represent a "sterile" surface. Sensitivities of the sampling and assay methods (i.e., level of detection) must be taken into account when no-growth samples are encountered. Properly collected control samples will help rule out extraneous contamination of the surface sample.

The methods to collect surface samples have been organized based on whether they will be collected from porous and nonporous surfaces. Each sampling method has its recommended use and advantages (Table 72-4) (2). Porous surfaces are typically uneven and include carpets, draperies, concrete, asphalt, upholstery, ceiling tiles, and stucco. Nonporous surfaces are even surfaces that include ceramics, vinyl, stainless steel, metals, painted and coated wood surfaces, and plastics. There are different methods of sampling for either type of surface, porous or nonporous.

Nonporous Surface Sampling Nonporous sampling methods include wiping the surface to remove any biological substance present. Methods to sample nonporous surfaces include wipe samples with premoistened gauze pads or sponges, swab sampling with a noncotton swab, the collection of a surface sample with an agar contact plate or replicate organism detection and counting plate (RODAC).

Wipe Sampling This sampling technique is best for screening large nonporous surfaces (Box 72-6) (2). Wipes work

BOX 72-6

Wipe-Sampling Procedures

Wipe-Sampling Procedure

Below is one possible procedure for doing a wipe sample on a nonporous surface. Please note that this protocol is not endorsed by any agency and a validated procedure has not been established.

Equipment and Apparatus

- Sterile sample containers
- Wrapped sterile noncotton gauze pad (2 in. × 2 in.) or 3M Sponge-Stick with Neutralizing Buffer (cellulose sponge premoistened with 10 mL Neutralizing Buffer [1.5 in. × 3 in. cellulose sponge folded over a handle, biocide-free, packaged in a sealable transport bag]: 3M, St. Paul MN: catalogue no. SSL 10NB or equivalent)
- 5 ml of appropriate sterile water, or other sterile laboratory-determined wetting solution in premeasured bottles or with measured sterile dropper
- Disposable, sterile sampling template with 1 ft^2 opening (optional)
- Sterile nonpowdered sampling gloves
- Sealable plastic bags
- Sample forms and permanent marker

Procedure

1. Don a sterile pair of sampling gloves before handling the gauze pad. Sterile gloves are not needed for the Sponge-Stick.
2. Choose appropriate sampling locations and attach a sample template (if using) in the designated area or simply delineate the area with masking tape.
3. Document the surface area to be wiped.
4. Gauze pad procedures:
   a. Open a new sterile package of a gauze pad.
   b. Wet the pad with an appropriate volume of the sterile water or other sterile laboratory-specified buffer solution.
   c. Wipe the designated surface area inside the opening of the sample template.
   d. Wipe twice inside the template vertically, then horizontally using an "S" pattern to ensure complete surface coverage.
   e. Fold the gauze with the exposed side in.
   f. Place the gauze pad in an appropriate sterile sample container.
   g. Cap and seal the sample container, attach a label, and triple bag in sealable bags.
   h. Change sterile gloves prior to collecting the next sample.
5. Sponge-Stick procedures:
   a. Wearing a clean pair of gloves, open the sample bag, back the handle of the sponge out of the sample bag by pushing on the outside of the bag (to avoid reaching fingers inside of the sterile bag). Tear the bag open and grasp the handle behind the thumb-stop and remove from the sample bag using aseptic technique.
   b. Sample the surface area, being careful to cover the entire surface. For flat surfaces, apply gentle but firm pressure and use an overlapping "S" pattern to cover the entire surface with horizontal strokes, then vertical and diagonal strokes.
   c. Insert sponge into the sample bag. Hold the sponge from outside of the bag with thumb and forefinger and then bend the handle backward and forward to break the sponge handle at the score mark below the sponge edge. With the sponge head inside, fold the top of the bag over at least four times and secure by folding the wire toward the center of the bag.
   d. Label the transport bag and repeat steps a–c for collection of additional samples.

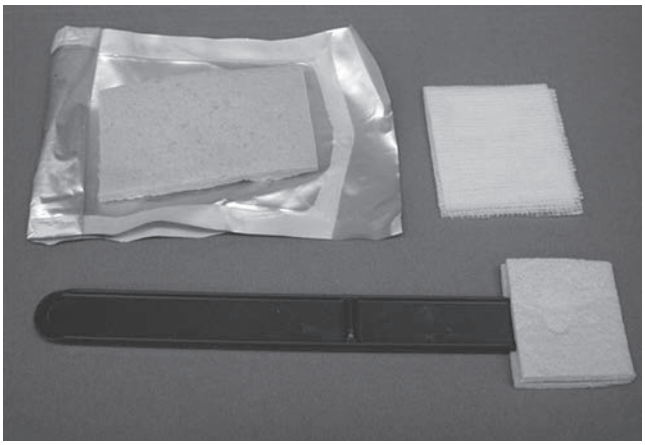

FIGURE 72-1 Sponges. Clockwise from *top left*: premoistened cellulose sponge (Solar Biologicals, Ogdensburg, NY); all-purpose gauze sponge (Kendall Healthcare, Mansfield, MA); Sponge-Stick (3M, St. Paul, MN).

best for flat, nonporous surfaces like walls, desks, and floors. Wipe sampling can be performed by using sterile gauze pads or sponges (Fig. 72-1). Wipe sampling is used to determine the extent and location of contamination, effectiveness of decontamination, and screening of specific items. Collection of wipe samples on rough, porous, or uneven surfaces may be difficult. If the surface is not flat, be sure to wipe any crevices or depressions well. The solution with which to wet the wipe is determined based on discussion with the laboratory and is dependent on the surface and the material to be sampled, and the method of analysis. The laboratory may, for QA/QC purposes, request a blank sample of the wipe and solution to be included with the samples as a negative control for each sampling event. These samples provide information about the handling, quality of the media, and other sources of contamination. If appropriate, a device used to monitor temperature during shipping may also be required by the laboratory.

Swab Sampling Swab samples work best for small nonporous areas of <100 cm^2, like crevices, corners, and hard-to-reach places (Box 72-7) (2). Several absorptive media are available, but noncotton (rayon, polyester, macrofoam) swabs are preferred. The swab to be used will be determined by the data quality objectives, input from the laboratory, and availability (Fig. 72-2).

Agar Contact Plate Sampling The agar contact method is used to sample cleaned and sanitized flat, nonabsorbent surfaces and is not suitable for visibly dirty and irregular surfaces (Box 72-8) (2). Contact plates (RODAC plates) are used to determine and count microorganisms present on surfaces and personnel (1). The method provides quantitative measurement of low numbers of microorganisms and cannot be used for heavily contaminated surfaces, because overgrowth will occur. Contact plates are constructed so that the agar medium is overfilled, producing a meniscus or dome-shaped surface that can be pressed onto a surface for sampling. A solid selective medium can be used, dependent on the microbial contaminant sought. Neutralizers can be incorporated in the medium if surface disinfectant residuals are present. After touching the surface to be sampled with the agar plate, the dish is covered and sent to a laboratory where it will be incubated at an appropriate temperature. In the laboratory, the presence and number of the microbial contaminants are determined by counting the colonies on the surface of the agar medium. One of the issues with agar contact plates is that they have a short shelf life.

BOX 72-7

Swab Sampling Procedure

Below is one possible procedure for collecting a swab sample on a nonporous surface. Please note that this protocol is not endorsed by any agency and a validated procedure has not been established.

Equipment and Apparatus

- Sterile sample containers with sealing lid, like a plastic centrifuge tube
- Sterile wrapped noncotton swab
- Wetting solution (if applicable) either appropriate sterile water, or other sterile laboratory-specific wetting solution in premeasured bottles or with measured sterile dropper
- Disposable, sterile sampling template with 100-cm^2 opening (optional)
- Sterile nonpowdered sampling gloves
- Sterile scissors
- Sealable plastic bags
- Sample forms and permanent marker

Procedures

1. Don a sterile pair of sampling gloves.
2. Choose appropriate sampling locations and attach a sample template (if using) in the designated area and photo document the template.
3. Document the surface area to be wiped.
4. Open a new sterile package of noncotton swab.
5. Wet the swab by dipping in a vial or tube of wetting solution and pressing against the side of the tube to remove the excess.
6. Wipe in an "S" pattern (vertically and horizontally) over the designated surface with the swab using firm strokes while rolling the swab to allow all surfaces of the swab to be used.
7. Place swab in appropriate sterile sample container, like a sterile centrifuge tube. It may be necessary to break, bend or cut the handle of the swab with the sterile scissors to ensure it fits into the sample container.
8. Cap the sample container, attach a label, and triple bag.
9. Change sterile gloves prior to collecting the next sample.

Porous Surface Sampling At this time, there are no validated sampling practices for suspected microorganisms from porous surfaces. The methods presented in this section are for porous sampling, which include high efficiency particulate air (HEPA) vacuum collection sock, microvacuuming, and bulk collection.

HEPA Vacuum Collection Samples of persistent biological materials deposited onto porous surfaces like carpets, fabrics, and draperies can be sampled with a portable

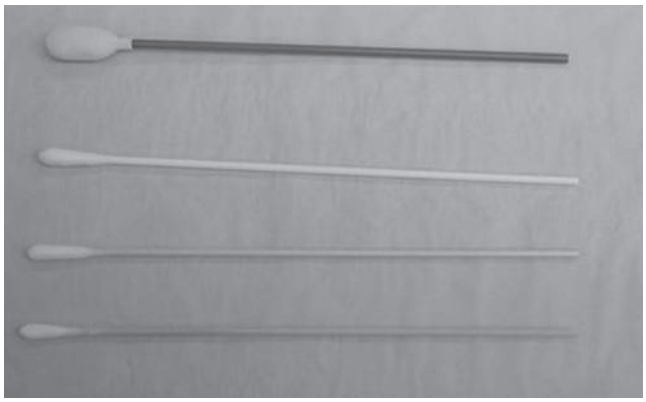

FIGURE 72-2 Swabs. From *top to bottom*: macrofoam applicator (Critical) swab (VWR International, West Chester, PA); cotton-tipped applicator swab (Baxter Healthcare Corp., McGaw Park, IL); polyester fiber-tipped applicator swab (Becton Dickinson and Company, Sparks, MD); rayon-tipped applicator swab (Hardwood Products Company, LLC, Guilford, ME).

HEPA vacuum with a collection sock filter designed to fit into the inlet nozzle of the vacuum cleaner (Fig. 72-3). The collection sock can be used to trap dust and bulk material, which is then sent for analysis. This method allows for the sampling of dust and other powdery substances from porous and nonporous surfaces (Box 72-9) (2). This method for bulk sampling can be used in postdecontamination and transitional sampling and to determine the extent and location of large areas of contamination (54). The major disadvantage of this method is the compromise of the collection efficiency by the initial loss of small biological particles through the sock filter and contamination of the HEPA filter. Collection efficiency increases when the sock filter is loaded with continued collection of dust.

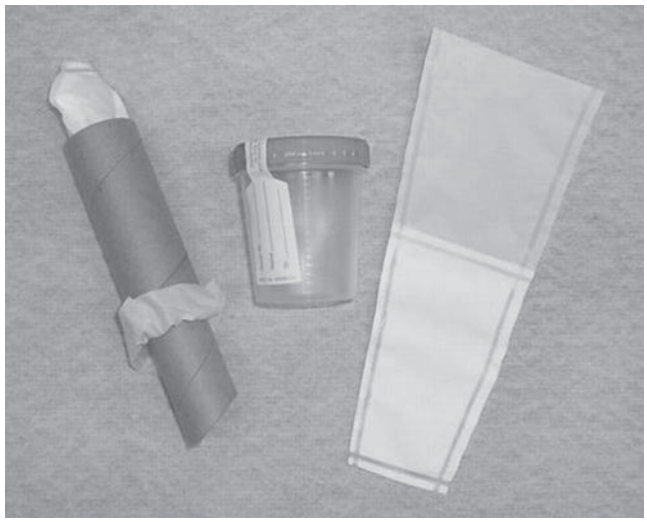

FIGURE 72-3 An X-Cell 200 HEPA vacuum sample kit with (left to right) disposable nozzle assembly, sterile sample container, and filter sock (Midwest Filtration Co., Cincinnati, OH).

Microvacuum Sampling The primary use of the microvacuum technique has been to determine the concentration of metals on a surface (63). However, the microvacuum sampling technique can be used as a surface sampling method to collect microorganisms that have been deposited on soft, rough, or porous surfaces (Box 72-10) (2). The microvacuum technique has not been validated for sampling microorganisms at this time and may not be the most efficient measure of microbial contamination on a surface (54). Microvacuum sampling can be used in postdecontamination and transitional sampling and to determine the extent and location of areas of contamination (54). The primary interference for bulk samples is large quantities of materials that may mask any microorganism that might be present in the sample. The use of dedicated sterile sampling equipment or decontamination of sampling equipment will minimize cross-contamination. Microvacuuming is carried out by using a collection nozzle attached to an air-sampling cassette or filter holder, and connected to a sampling pump. The sample can be collected within a sample template by moving the nozzle over the surface in an "S" pattern. Once the sample is collected, the cassette is then sealed and sent to the laboratory for analysis.

Bulk Sampling Bulk samples for microorganisms can be collected using a variety of methods and equipment (Box 72-11) (2). The sampling objective is to determine qualitatively if a bulk material, such as pieces of HVAC filters, devices, containers, personal items, clothing, is contaminated with microorganisms. This type of sampling can also be used as a tool for screening. Large quantities of dust and background bacteria may mask the target biological

BOX 72-8

Agar Contact Plate (RODAC) Sampling Procedure

Agar Contact Plate Sampling Procedure

Below is one possible procedure for collecting an agar plate sampling on a nonporous surface. Please note that this protocol is not endorsed by any agency and a validated procedure has not been established.

Equipment and Apparatus

- Sterile nonpowdered sampling gloves
- Sterile wrapped contact plate with appropriate agar medium.
- Parafilm® with a minimum width of 4 in.
- Sealable plastic bags
- Sample labels, forms, and permanent marker

Procedure

1. Don a sterile pair of sampling gloves.
2. Choose appropriate sampling location to be sampled with the contact plate and photo document.
3. Open the contact plate package taking precautions to maintain the sterility of the inner bag and its contents. Using aseptic techniques, remove the cover without touching the agar. Hold the lid during sampling so that it does not touch anything.
4. Firmly touch the agar to the surface to be sampled, using the same pressure for each sample. Do not move or slide the agar over the surface to be sampled, as this will spread the contamination and disturb the resolution of individual colony identification.
5. Replace the cover on the contact plate.
6. Label the contact plate with a sample label and wrap the plate with wax wrap Parafilm®.
7. Place the contact plate into a sealable bag, attach a label, and triple bag.
8. Store and transport the contact plate in a cooler but not directly on the ice, kept cold and delivered to the laboratory as soon as possible.
9. Change sterile gloves prior to collecting the next sample.

BOX 72-9

HEPA Vacuum Sampling Procedure

Below is one possible procedure for collecting a HEPA vacuum sample on a porous surface. Please note that this protocol is not endorsed by any agency and a validated procedure has not been established.

Equipment and Apparatus

The following equipment should be available in order to collect bulk samples:

- Sterile sampling gloves
- HEPA vacuum with a 1⅛;-in.-diameter hose attachment
- HEPA sample sock with cardboard inlet nozzle assembly
- Power source
- Sterile sample container of proper size
- Sealable plastic bags
- Sample forms and permanent marker

Sampling Procedure

1. For each sample collected, ensure that a new pair of sterile gloves is worn.
2. Place the cardboard inlet assembly into the inlet nozzle of the vacuum prior to inserting the HEPA sample sock into the nozzle. Fold the HEPA collection sock over the inlet nozzle.
3. Grasp the inlet nozzle and the assembly, securing the sample sock.
4. Turn on the vacuum and hold the nozzle close to the area being sampled without damaging the edge of the sample sock. Once the sample has been collected, turn off the vacuum and remove the filter sock from the nozzle touching only the blue portion of the filter sock.
5. Collect the sample in an area up to several square meters. Document the area that was sampled.
6. Do not let go of the filter sock while the vacuum is turned on. The filter sock will be sucked into the vacuum and the sample will be unusable.
7. Holding the blue portion, remove the filter sock from the assembly tube, roll or fold the top closed, and then place into a sterile sample container.
8. Label the sample container.
9. Double bag the sample container and label the outer bag.
10. Decontaminate the outer sample bag.
11. Photograph the sample at the sample location.
12. Change sterile gloves prior to collecting the next sample.

agent that might be present in the sample. The use of dedicated sterile sampling equipment for each sample collected will minimize cross-contamination. A validated method for nonporous surfaces (54) is available; however, it is not validated for porous surfaces. A solid bulk sample can be collected by placing the material into a sterile container. Prior to collecting a bulk sample, it is critical to discuss the material to be sent to the laboratory to ensure that the laboratory is able to accept and handle the sample. If the material to be sampled cannot be broken or cut into smaller pieces, discuss additional sample collection options with the laboratory. The laboratory will also provide information regarding the amount of sample that they require for analysis and the required QA/QC samples.

BOX 72-10

Microvacuuming Sampling Procedure

Below is one possible procedure for collecting a microvacuum sample from a porous surface. Please note that this protocol is not endorsed by any agency for sampling biological agents and a validated procedure has not been established.

Equipment and Apparatus

- Calibrated sampling pump
- Rotometer (air flow meter) or dry cell calibrator
- Sterile closed-faced 37-mm cassette with microvacuum nozzle preloaded with 0.45 µm sample filter made of mixed cellulose esterase (MCE) or Teflon
- Disposable, sterile sampling template with 100-cm^2 opening (to a maximum of 30 cm × 30 cm opening (63)).
- Flexible Tygon™ tubing
- Sterile tweezers
- Sterile sampling gloves
- Sealable plastic bags
- Sample forms and permanent marker

Procedure

1. Set up the sampling train by attaching one end of the Tygon™ tubing to the outlet of a filter cassette used for calibration and the other end to the manifold of the pump inlet.
2. Calibrate the pump with the rotometer or dry cell calibrator to the flow rate specified by the laboratory: >2.5 lpm (63) for MCE or Teflon filters.
3. Don sterile sampling gloves.
4. Use one preloaded cassette with either a Teflon or an MCE filter (65) and nozzle per sample. Remove the outlet and inlet end caps on the sample filter cassette. Attach the sample nozzle to the inlet side of the cassette.
5. Place the template in the selected sampling location.
6. Hold the collection nozzle at a 45 degree angle to the surface to be sampled. Vacuum the area inside the template, in a horizontal “S” pattern, followed by vacuuming in a vertical “S” pattern to ensure complete coverage of sample area. Record the rate at which nozzle is moved (~10 cm/s), approximately 1 minute for entire sample.
7. Once the sample has been collected, record pump flow rate.
8. Detach the sample filter cassette from the sample stand and remove the Tygon™ tubing. Place the cap on the outlet of the sample filter cassette. Remove the nozzle carefully and cap the inlet.
9. To prevent cross-contamination, use a dedicated collection nozzle for each sample.
10. Triple bag the sample filter cassette in sealable plastic bags.
11. Label properly.
12. Prepare the sample cassette for transport.
13. Change sterile gloves prior to collecting the next sample.

BOX 72-11

Bulk Sampling Procedure

Below is one possible procedure for collecting a bulk sample. Please note that this protocol is not endorsed by any agency. Please refer to ASTM Method # E2458-06 *(26)* for collection of powders from nonporous surfaces.

Equipment and Apparatus

The following equipment should be available in order to collect bulk samples:

- Sterile sampling gloves
- Disposable or decontaminated spade, spatula, scoop, or trowel
- Sterile forceps, scissors, scalpel, or sharp knife
- Sterile sample container of proper size
- Sealable plastic bags
- Sample forms and permanent marker

Sampling Procedures

1. For each sample collected, ensure that a new pair of sterile gloves is worn
2. Prior to initiating collection, document the area from which the bulk sample will be collected or from the object which will become the bulk sample.
3. All sample equipment must be sterile prior to use.
4. For solids, powders, or granular material, collect the laboratory-specified quantity of the bulk sample with a dedicated sterile spoon, trowel, or spatula and place material into a sterile sample container.
5. For large pieces of material that require analysis, the laboratory-specified quantity of material is collected with dedicated sterile scissors, scalpel, or knife by breaking, cutting, chipping, or shaving small pieces of the material into a sterile sample container.
6. Label the sample container.
7. Double bag the sample container and label the outer bag.
8. Decontaminate the outer bag.
9. Photograph the sample at the sample location.
10. Change sterile gloves prior to collecting the next sample.

Microbiologic Sampling of the Environment: Current Analytic Challenges Although significant research is being conducted, validated sampling collection methods do not exist for porous and nonporous surfaces. Overall detection limits for surface sampling methods are generally unknown and are dependent on many factors, which include variable collection efficiency of sampling devices, recovery efficiency from sampling devices due to variable extraction liquid and extraction method. Indeed, research investigators have determined that the sampling devices and processing methods have varying recovery efficiencies. It is critical to understand the collection efficiency of each sampling device from various types of surfaces to develop criteria for surface contamination. Results from the analyses of the surface samples should be interpreted based on the validity of the collection method, extraction method, and detection or identification assay. Interpretations during the various sampling phases should be based on (a) consistency in sample collection; (b) the number of samples collected; (c) the maximum sample area for which the method is validated; (d) sampling materials used; (e) sample stability; (f) the extraction efficiency for the sampling method; and (g) sensitivity of the detection or identification assay.

BOX 72-12

Validation Criteria Definition

Accuracy

The closeness of the results obtained to those predicted from a known concentration of microorganisms.

Precision

The agreement among individual results when applied repeatedly to multiple samplings across the range of the test. It is usually expressed as a standard deviation or coefficient of variation. It can be a measure of either reproducibility or repeatability.

Specificity

The ability to detect a range of the agent, which demonstrates whether the method is fit for the intended purpose. It should also be demonstrated to be compatible with the expected range of sample types.

Limit of detection

The lowest number of the agent that can be detected, but not necessarily quantified.

Limit of quantification

For assays where quantification of low levels of microorganisms is critical, it is the lowest number of microorganisms that can be determined with acceptable precision and accuracy.

Linearity

The ability to determine results that are proportional to the concentration of the agent within a given range.

Ruggedness

The degree of reproducibility of results from analysis of the samples under a variety of normal conditions (different analysts, instruments, lots of reagents, etc.). It can be expressed as a lack of influence of operational and environmental variables on the method.

Robustness

It is a measure of the methods capacity to remain unaffected by small but deliberate variations in the method parameters. It provides a measure of reliability during normal use.

Range

The interval between upper and lower levels that have been determined with acceptable precision, accuracy, and linearity.

(Data from Microbiology Guideline: AOAC International qualitative and quantitative microbiology guidelines for methods validation. *J AOAC Int* 1999;82:404–416; General Information <1225>. Validation of compendial methods. United States Pharmacopeia 26, National Formulary 27. Rockville, MD: The United States Pharmacopeial Convention, Inc., 2003:2439–2442.)

The following validation parameters to consider during a quantitative method validation are accuracy, precision, ruggedness, robustness, specificity, limit of detection, limit of quantification, linearity and range. Parameters to assess

during validation of qualitative methods are specificity, limit of detection, and ruggedness (Box 72-12) (2). Before approval of a validated method, it may be necessary to consider results from interlaboratory and intralaboratory validations to allow various analytical groups (experienced and nonexperienced) an opportunity to interpret and execute the method, impart deliberate documented minor changes, and utilize their own analytical materials and equipment. The qualitative method is generally validated to detect the presence of a low concentration of the agent in question (e.g., growth of the agent in selective cultures and PCR methods). The quantitative method is generally validated to enumerate the concentration of the agent from a specific sample area collected.

CONCLUSION

Though microbiologic sampling of the environment appears at first glance to be a simple task, each of the sampling strategies and methods discussed in this chapter is complex, and the success of the sampling endeavor depends on meticulous attention to details in sampling design and aseptic technique. Environmental sampling may never be extremely precise because of all the variables that come into play when utilizing culture methods. A good sampling strategy for the various investigation phases, a consistent approach, understanding the limitations of the different sampling methods, and knowledge of the target microorganism are the most important factors in obtaining the best possible information from a microbiologic environmental sampling event.

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SECTION X

Epidemiology and Prevention of Healthcare-Associated Infections in Healthcare Workers

CHAPTER 73

Prevention of Occupationally Acquired Viral Hepatitis in Healthcare Workers

David K. Henderson and Susan E. Beekmann

Viral hepatitis was first recognized as an occupational hazard for healthcare workers nearly half a century ago when a blood bank worker acquired viral hepatitis after sustaining multiple needlesticks *(1)*. Since then, we have witnessed an explosion of knowledge in the fields of both basic virology and healthcare epidemiology. Five primarily hepatotropic viruses (hepatitis A–E, see Hepatitis Viruses, Chapter 46) have been identified and characterized, their modes of occupational transmission have been determined, and strategies for prevention have been developed. This chapter addresses the healthcare-associated epidemiologies of these five agents and does not specifically address the several additional agents that currently contribute to the viral hepatitis alphabet, including the agent called hepatitis French (origin) virus (HFV) (hepatitis F) *(2)*; the bloodborne "GB" agents (GB virus A [GBV-A], GB virus B [GBV-B] and GB virus C, [GBV-C] *(3,4)* which rarely cause hepatitis; and hepatitis G virus (HGV), a common, easily transmitted bloodborne agent that is closely related to GBV-C, which causes clinically mild, if any, hepatitis (5,*6–8*), and may not, in fact, be hepatotropic *(9)*. Until these "non-A–E hepatitis" viruses, and other putative hepatitis agents *(10–12)* are formally recognized as hepatitis viruses and have their respective epidemiologies delineated, general infection control practices for protecting healthcare workers from enterically transmitted or parenterally transmitted agents, as appropriate, are indicated. This chapter focuses on the etiology of occupationally acquired viral hepatitis, the epidemiology of these viruses in the healthcare setting, and the specific prevention and control strategies for each of the five hepatotropic agents identified above.

ETIOLOGY AND EPIDEMIOLOGY

The risk of occupational transmission of each of the hepatitis viruses differs according to the infective body substance, the modes of transmission, the occupations and work responsibilities of individual healthcare workers, the varying prevalences of infection in the patient population, healthcare workers' immune statuses, and the individual worker's compliance with infection control procedures. An overview of the five major hepatitis viruses, risks for occupational transmission in the healthcare setting, modes of occupational transmission, relevant prevention strategies and currently imprecise or unanswered questions is presented in Table 73-1. Factors affecting the risks for occupational transmission for each virus are discussed separately, below, in more detail.

Hepatitis A Virus

Although healthcare workers are generally not considered to be at substantially increased risk for acquiring hepatitis A virus (HAV) infection *(13–17)*, occupational transmission of this virus has been well documented and occurs, albeit rarely, under unusual circumstances. Most HAV transmission in healthcare settings occurs from index patients who are asymptomatic, from those in whom the infection is otherwise unsuspected and/or undiagnosed, from patients who are in the prodromal phase of the infection when viral shedding in the stool is maximal, in instances in which when infection control procedures are less than optimal, and/or in settings in which patients are incontinent of feces *(18–33)*. Occupational HAV transmission occurs primarily

TABLE 73-1

Major Hepatitis Viruses and Occupational Transmission to Healthcare Workers

Feature	*Hepatitis A (HAV)*	*Hepatitis B (HBV)*	*Hepatitis C (HCV)*	*Hepatitis D (HDV)*	*Hepatitis E (HEV)*
Occupational transmission problem	Rare	Common	Infrequent	Uncommon	Rare
Major mode of occupational transmission	Fecal/oral	Blood	Blood	Blood	Fecal/oral
Isolation precautions for patient	Standard Precautions	Standard Precautions	Standard Precautions	Standard Precautions	Standard Precautions
Prophylaxis for occupational exposure	IG	Hepatitis B vaccine and HBIG	None	Hepatitis B vaccine and HBIG for persons without HBV infection; none available for HBV carriers	Vaccine in development
Controversy/ alternative approaches/ unresolved issues	Adjunctive HAV immunization for individuals at-risk	Additional booster dose of HBV vaccine for healthcare workers who fail to maintain protective antibody levels	No postexposure prophylaxis, but some advocate either "preemptive therapy" or "watchful waiting" (see text)	None	None

IG, immune globulin; HBIG, hepatitis B immune globulin.

via the fecal–oral route, following direct or indirect contact with the index patient's fecal material and is generally only recognized when a cluster of cases occurs. Although healthcare workers can acquire HAV from contaminated food or drink *(34–36)*, occupational infection usually occurs following direct contact with infectious patients. Neonatal intensive care units may provide a unique setting for healthcare-associated/occupational transmission, because several reported outbreaks, some with widespread secondary transmission, have occurred in this setting *(20,22,23,28,31,37,38)*. Outbreaks in neonatal intensive care units have most frequently followed the rare occurrence of transfusion-acquired infection of a neonate. Unless staff members practice strict hand washing and environmental cleaning, neonatal and pediatric intensive care settings may provide optimal opportunities for fecal contamination of healthcare workers' hands and environmental surfaces. HAV can survive on workers' hands and this aspect of HAV epidemiology may contribute to the indirect spread of the virus to other patients and staff members *(39)*.

Although occupational HAV infection occurs rarely in US healthcare workers, seroepidemiological studies in other countries suggest that selected healthcare workers may be at increased risk for occupational infection. One study proposed that HAV is an occupational hazard in Germany, ranking third, with respect to morbidity statistics, among infectious occupational diseases, based on frequency of compensation *(40)*. Compared to the general population, medical occupational groups with the highest anti-HAV seroprevalences, in decreasing order, included medical charwomen, foodhandlers, pediatric nurses, other nurses, and physicians. Another study in Belgium found that healthcare workers in a pediatric hospital had a higher seroprevalence of anti-HAV than workers in general hospitals *(41)*, and a study in France reported a higher seroprevalence among nursing staff when compared to nonmedical employees *(42)*. A study of healthcare personnel in Korea found no evidence of occupational infection, an overall prevalence of prior infection in 28.3%, and a substantial increase in seroprevalence associated with increasing age *(43)*. Of interest, lower seroprevalences were identified among physicians between the ages of 25 and 39 *(43)*.

Various studies have investigated risk factors for occupational infection with HAV. Factors that facilitate fecal–oral spread enhance transmission. Fecal material from most normal HAV-infected patients is usually easily contained and presents a limited risk to staff members who practice good hand washing and rigorously follow infection control procedures. Conversely, patients who are incontinent of feces and those who have diarrhea present a much

higher risk. Factors associated with occupational infection include an index case with diarrhea or incontinent of feces *(19,21,22,24–27,29,30,32)*; an index case hospitalized during the prodromal period of maximal virus fecal excretion *(18,19,21,24–30,44)*; adult patients who have poor hygiene *(44)*; and less-than-optimal adherence to recommended infection control procedures, including lack of adherence to Standard and/or Contact Precautions *(29,33,38,44)*. One study identified four additional activities that may have enhanced fecal–oral spread in the occupational setting: sharing food with patients or their families, drinking coffee, sharing cigarettes, and eating in the nurses' office on an intensive care unit *(30)*. Another study *(31)* identified risk factors for transmission to staff during an outbreak in a neonatal intensive care unit, including caring for an infant with HAV infection, drinking beverages in the unit, and not wearing gloves when taping an intravenous line. This study also documented prolonged viral excretion in infected neonates; some infected infants excreted virus for 4 to 5 months after infection. This prolonged period of viral excretion in neonates and infants may also contribute to the risk for healthcare-associated transmission. Other studies in neonatal intensive care units found that risk of occupational infection was greater among staff members who did not routinely wash their hands after treating an infected infant *(38)* and among staff members who cared for the index (i.e., infected) case for longer periods of time *(28)*. Another outbreak investigation in a burn treatment center implicated eating on the hospital ward as the single most important risk factor for HAV infection among staff members *(45)*. Vomitus, bile-stained emesis, or bile-contaminated nasogastric suction material may also serve as a reservoir for HAV transmission *(21,25,29,46)*, since there is evidence that HAV is excreted in bile *(47)*. One study that involved an index patient who had neither diarrhea nor fecal incontinence identified intensive handling of infectious bile, rather than contact with feces, as the most likely mode of transmission *(46)*. Other likely factors contributing to this outbreak included inadequate terminal cleaning of equipment, food consumption in the unit, and inadequate hand-washing practices *(46)*. Recent studies have documented decreasing risks for HAV infection, in great measure due to improving sanitary conditions and aggressive vaccination of populations at risk (*43,48,*49).

Because most patients are hospitalized for hepatitis A only after they become jaundiced, (and at a time when viral excretion is often substantially reduced from peak excretion during the prodromal stage of infection), these patients are generally considered less infectious. Although fecal excretion of HAV may persist longer in children than in adults, quantitative determinations may be important to determine the risk of exposure to infected pediatric patients *(50)*.

Reported attack rates for occupationally acquired HAV have varied, ranging from a low of 2% of exposed susceptible staff members *(29)*, to 10% *(21)*, 12% *(24)*, 4% to 16% *(23)*, 3% to 30% *(28)*, and 21% to 50% *(25)*. Reasons for the wide variability in attack rates may include differing definitions of occupational exposure to the index case, differing levels of infectivity of source patients, differing intensity of exposures, and the effectiveness and timing of prophylactic immunoglobulin administration.

Hepatitis B Virus

Historically, the highest risk for occupationally acquired hepatitis among healthcare workers has been associated with exposure to hepatitis B virus (HBV); in fact, before the advent of the hepatitis B vaccine, HBV infection was *the* major occupational risk to healthcare workers *(51)*. In the 1980s, the annual incidence of HBV infection among healthcare workers in the United States was staggering. The Centers for Disease Control and Prevention (CDC) estimated that in the mid-1980s approximately 12,000 HBV infections occurred annually in healthcare workers who had frequent occupational exposure to blood or other potentially infectious materials, with an annual rate of infection between 4.89 and 6.63 per 1,000 exposed susceptible workers *(52)*. Of these 12,000 occupationally infected workers each year, CDC scientists estimated that 3,000 developed symptomatic clinical illnesses, more than 600 were hospitalized, and more than 250 of these healthcare workers died. CDC estimated that between 600 and 1,200 of these healthcare workers became chronic hepatitis B carriers. Since the HBV vaccine was developed and aggressive hepatitis B vaccination of healthcare workers in the United States has been promoted, HBV infections among healthcare providers has decreased dramatically to an estimated 400 annually by 1995 (53).

Numerous studies have documented that healthcare workers exposed to blood are at high risk for acquiring HBV infection. In one of the earliest studies, Williams et al. *(54)* investigated a large epidemic of hepatitis B infections among hospital personnel and found that clinical hepatitis attack rates and HBV antibody prevalence rates correlated with occupational exposure to blood from patients being treated with hemodialysis. Transmission was thought to occur by both accidental parenteral and so-called inapparent parenteral routes of inoculation of contaminated blood. Pattison et al. *(55)* studied workers in a large community hospital between 1972 and 1974 and found a significant association between frequency of blood contact and prevalence of HBV, but no association between frequency of patient contact and HBV prevalence. The first nationwide, cross-sectional seroepidemiological survey of occupationally acquired HBV infection among physicians was conducted by Denes et al. *(56)* in 1975 to 1976. These investigators found that infection rates were higher among those practicing in urban settings, that the risk for infection increased with the number of years in practice, and that infection rates were highest among pathologists and surgeons. Dienstag and Ryan *(57)* studied workers at a large urban hospital and found that the prevalence of HBV serologic markers increased as a function of contact with blood, years in a healthcare occupation, and age, but not as a function of contact with patients, years of education, previous needlestick, transfusion, or globulin injection. The highest seroprevalences were found among emergency room nurses, pathology staff members, blood bank staff members, laboratory technicians, intravenous teams, and surgical house officers. Similar high-risk occupations (emergency room, medical and surgical intensive care units, and dentistry–oral surgery) were identified by Jovanovich et al. *(58)* in a study conducted in an urban hospital.

Snydman et al. *(59)* conducted a multi-institutional seroepidemiological survey of hospital employees in 1980

and 1981 and found that the duration of employment for laboratory workers, surgical staff members, and medical staff members was associated with increased risk for having HBV markers. In this study, the highest gradient of risk in these occupations occurred during the first 5 years of employment. Another large multi-institutional study of nearly 5,700 hospital employees conducted by Hadler et al. *(60)* controlled for nonoccupational risk factors and confirmed the earlier findings of Dienstag and Ryan that occupational blood exposure, but not patient contact, was associated with risk for prior HBV infection. Hadler and coworkers also found that the frequency of needle accidents during daily work was directly related to HBV seroprevalence. The occupational group with the highest HBV infection rate was clinical laboratory and blood bank technicians, who routinely handled large numbers of blood specimens. In general, these and similar studies in the pre–HBV-vaccine era may be summarized by noting that healthcare workers who have occupational exposure to blood had a prevalence of HBV markers several times both that of workers who did not have blood exposure and that of the general population. This prevalence of HBV infection increased with increasing years of occupational exposure. HBV infection was related to the degree and frequency of blood exposure and not to the degree of patient contact. West reviewed studies evaluating the risk for HBV infection in healthcare providers and found the risk to be approximately four times elevated when compared to the risk for infection in the at-large adult population *(61)*. In West's review, physicians and dentists were found to be five to 10 times more likely to experience hepatitis B infection and surgeons, dialysis personnel, personnel providing care for developmentally disabled individuals, and clinical laboratorians to be at 10-fold or higher risks for HBV infection *(61)*.

The risk of occupational exposure to HBV depends on several other factors besides occupation and frequency of occupational exposures. The prevalence of HBV infection in the patient population also influences the risk for occupational exposure. Because HBV prevalence is generally higher in urban settings, workers in urban hospitals have been found to be at higher risk for HBV infection *(56)* than are workers in rural hospitals *(62)*. Renal dialysis patients (see also Chapter 63) who require frequent blood transfusions and have suppressed immune responses have long been known to be at high risk, both for acquiring HBV infection and for developing chronic HBV infections. For this reason, staff caring for dialysis patients are at increased risk for occupational HBV infection *(61,63,64)*. Workers in hospitals serving large numbers of other patient population groups at risk for HBV infection, such as intravenous drug users, homosexual men, prison inmates, the developmentally disabled, or immigrants from highly endemic areas, are also at higher risk for occupational exposure and infection with HBV *(65)*. Patients who are asymptomatic HBV carriers are the primary reservoir for HBV infection in the healthcare setting. Broad-scale testing to identify infected patients is neither practical nor cost-effective. In one study, testing patients who reported a history of hepatitis would have detected fewer than 20% of HBV-infected patients *(66)*.

The infectivity of the source material also influences the risk of acquiring HBV infection. Although hepatitis B surface antigen (HBsAg) has been detected in nearly all body fluids, blood is considered the most infectious and is probably responsible for most occupationally acquired infections. The infectivity of blood is generally correlated with the presence of increased circulating viral burdens, HBV DNA polymerase activity, or hepatitis B e antigen (HBeAg) in the blood. The risk for HBV infection after a percutaneous ("needlestick") exposure to blood from an HBV-infected individual has been estimated to range from 19% to 37% if the donor blood is HBeAg positive *(67,68)*. In the dental setting, saliva, particularly bloody saliva, is also considered to represent a substantial infectious risk.

The type of exposure to blood or other potentially infectious materials also influences the risk of acquiring infection. Percutaneous exposures, such as needlesticks or injuries with contaminated sharp instruments, are associated with the highest risks for occupational infection. Very small inocula of HBsAg-positive blood may produce infection, since the blood of acute or chronic HBV carriers may contain as many as 10^{13} virus particles of HBV per milliliter of blood *(51)*. Infectivity studies in chimpanzees have demonstrated that serum positive for HBeAg is infectious in dilutions up to 10^{-8} *(69)*. Despite the fact that percutaneous exposures are the most efficient route of infection, CDC estimates that fewer than 20% of HBV-infected healthcare workers recall an injury/exposure of this type *(70)*. Thus, other, so-called inapparent parenteral exposures account for a substantial fraction of occupational HBV infections. Preexisting cuts, dermatitis, other skin lesions, or mucous membranes may provide portals of entry for HBV infection. Blood-contaminated inanimate objects or environmental surfaces also have been implicated in occupational transmission in certain settings. In one study, sustaining paper cuts while handling laboratory computer cards in a hospital clinical laboratory was associated with an outbreak of HBV infection *(71)*. Before strict infection prevention measures were implemented in hemodialysis centers, environmental contamination with blood that subsequently resulted in contaminated workers' hands was hypothesized to facilitate HBV transmission *(72,73)*. Contamination of mucous membranes of the eye or mouth, which may occur with accidental splashes or pipetting accidents, also may result in HBV transmission *(74)*.

In the past 25 years, seroprevalence studies in healthcare workers have documented the importance of hepatitis B vaccine in preventing infections. Thomas et al. *(75)* studied 943 healthcare personnel in an inner city hospital. Their multivariate analysis identified only one risk factor—absence of HBV vaccination—to be independently associated with HBV infection in this population of healthcare workers. Similarly, Panlilio et al. *(76)* studied 770 surgeons for markers of HBV infection and found two risk factors—not receiving hepatitis B vaccine and practicing surgery for at least 10 years—for HBV infection. Another study in 114 operating room personnel in Pakistan also documented that nonvaccinated workers were more likely to be infected with HBV *(76)*. Supplementing these seroprevalence studies, Lanphear et al. *(77)* investigated the incidence of clinical HBV infection in hospital workers and found a dramatic decrease associated with increased immunity due to vaccination.

Hepatitis C Virus

Our current understanding of the role of hepatitis C virus (HCV) in occupationally acquired infections is less clear than for HAV and HBV and is complicated by the evolving understanding of the pathogenesis and immunopathogenesis of exposure and infection with this flavivirus (see also Chapter 46). Since the parenteral mode of transmission of HCV has been clearly established as a primary route of infection for transfusion recipients and intravenous substance users, by analogy to HBV, occupational transmission of HCV in the healthcare setting—including transmission from patients to staff, from patient to patient, and from infected providers to their patients—is likely to be linked to apparent and inapparent parenteral exposure to blood. To date, exposure to blood remains the primary vehicle for occupationally acquired HCV infection as is evidenced by the overwhelming majority of the cases of occupational infection that have been described in the literature *(78–94)*. HCV also has been transmitted by a punch *(95)*. HCV RNA has been detected in saliva *(96–98)*, and two cases suggest that transmission of HCV occurred following human bites *(99,100)*. Abe et al. *(101)* also provided experimental documentation of HCV transmission by saliva. When present in saliva, HCV titers are lower than in blood. The potential infectivity of saliva may have important implications for patient to provider transmission, primarily in the dental healthcare setting. HCV RNA also has been detected in a variety of other body fluids from infected patients, including menstrual fluid *(102)*, semen *(98,103,104)*, urine *(98)*, spinal fluid *(105)*, and ascites *(98)*. The relevance of these latter body substances to the transmission of HCV is unclear. One recent study demonstrated transmission of HCV as a result of a nurse providing care for a patient with severe epistaxis and concluded that the transmission occurred as a result of the exposure of the nurse's nonintact skin to the patient's blood *(106)*. In summary, blood is the body substance that presents the most risk for HCV transmission in the healthcare setting. Despite the fact that transmission of HCV resulting from exposures to body fluids other than blood has not yet been documented; presumably because viral titers in these fluids are substantially lower than in blood, other body substances may present measurable risks for occupational infection, particularly if the healthcare worker is exposed by the parenteral route and/or receives a large inoculum.

Parenteral exposures represent the primary mode of occupationally acquired infection, as is evidenced by the overwhelming majority of the cases of occupational infection that have been described in the literature *(82–94)*. However, two cases of HCV infection have been documented following mucosal exposures to blood *(107,108)* and one case has been associated with exposure of "nonintact skin" to blood *(106)*. Extensive HCV environmental contamination of instruments and surfaces in hemodialysis *(109–113)* and dental surgery settings *(114)* can occur, and such HCV environmental contamination has been suggested to play a role in transmission of HCV (115). However, to our knowledge, transmission of a specific HCV strain through environmental contamination has not yet been documented. Transmission resulting from environmental contamination should be an extremely unlikely consequence if proper sterilization and disinfection procedures are practiced and if current standards of infection control, particularly hand hygiene, are followed.

Numerous cases of healthcare-associated transmission from patient to patient (often as a result of cross-contamination from an index case, for example, in hemodialysis, from multidose vials for sequential patients, reuse of spring-loaded finger-stick devices, and contamination of endoscopes and other devices for invasive procedures) have been reported in the literature. The past 5 years have seen a disturbing increase in the detection of such cases *(116–126)*. A detailed discussion of this topic is beyond the scope of this chapter (see also Chapter 46).

Recognizing the epidemiological similarities between HCV and HBV, several investigators attempted to assess the risk of occupational infection by testing healthcare workers for the serological prevalence of HCV antibodies, when serologic tests for HCV became available. Interpretation of these studies must take into account both the limitations of the serological assays *(127)* and the inadequacy of assessing only the humoral immune response as a measure of exposure and HCV infection *(128)*. Many of the published studies employed the first-generation anti-HCV test that detects an antibody directed against a nonstructural HCV protein, anti-c100-3, and that has low sensitivity and specificity for diagnosing HCV infection when compared with second- and third-generation tests. Even later-generation anti-HCV antibody tests still may not detect 100% of infected persons, and tests designed to detect circulating HCV RNA may be necessary to identify some infected individuals. In addition, the anti-HCV tests have a high rate of false positivity in populations with a low prevalence of infection, and supplemental tests for specificity are necessary. The recombinant immunoblot assay (RIBA) or another supplemental HCV neutralization assay should be used to verify repeatedly reactive enzyme immunoassays. Even HCV RNA detection assays are problematic. These tests are subject to false-positive and false-negative results following improper collection, handling, or storage of test samples, and their interpretation is not conclusive: a single negative test may not indicate lack of infection but may be due to fluctuating RNA levels *(129)* and a single positive test should be repeated to exclude the high likelihood of contamination and a false-positive assay. In summary, the evolving diagnostic technology has complicated comparisons of HCV seroprevalence and incidence among the various published studies. Keeping these limitations in mind, Table 73-2 summarizes published studies of anti-HCV seroprevalence among many diverse types of healthcare workers (*75,76,130–155,*156,*157–176*).

In addition to the substantial variation in study design, the differences in healthcare worker populations studied, and the differences in the technologies used for detection, other considerations further complicate comparing and interpreting these studies. HCV seroprevalence varies geographically, so similar occupational groups from different locations cannot be compared directly, and local comparison groups are needed for determining if particular healthcare worker groups are at increased risk. Because blood donor seroprevalence data are readily available, blood donors were often used for comparison in these prevalence studies. However, blood donors are not a good comparison group, because they are preselected to avoid a history of

TABLE 73-2

Seroprevalence Studies of Anti-HCV Among Healthcare Workers

Study Location and Population (Reference)	*HCV Assay*[a]	*Number Tested*	*% of Anti-HCV Seroprevalence*	*Comparison Group, Number Tested (% of Seroprevalence)*
Italy, hospital workers *(130)*	Not specified	945	4.8	Blood donors, 3,575 (1.1) Factory workers, 576 (10.0)
India, healthcare workers *(131)*	Not specified	90	0	
England, hospital workers *(132)*	EIA-1	100	0	
Austria, hospital workers *(133)*	EIA-1	294	2.0	Voluntary blood donors, number not specified (0.7)
Germany, healthcare workers *(134)*	EIA-1	217	2.8	Blood donors, 500 (0.4)
Germany, hospital workers *(135)*	EIA-1	738	1.1	
Italy, healthcare workers *(136)*	EIA-1	1,008	4.1	Blood donors, 3,572 (0.95)
Pakistan, operating room personnel *(137)*	EIA-1	114	4.4	Blood donors, number not specified (0.7)
United States, dental personnel *(138)*	EIA-1, RIBA-1	960	1.0	
New York, hemodialysis workers *(139)*	EIA-1, RIBA	51	2.0	
California, hospital workers *(140)*	EIA-1, SN	1,677	1.4	
New York, surgeons *(76)*	EIA-1, SN	770	0.9	
United States and Canada, orthopedic surgeons *(141)*	EIA-1, SN	3,262	0.8	
New York, healthcare workers *(142)*	EIA-1, RIBA	158	1.3	
New York, dentists *(143)*	EIA-1, RIBA	456	1.8	Nonhealthcare worker controls matched by graduate education level, 723 (0.1)
Connecticut, healthcare workers *(144)*	EIA-1, RIBA-2	243	1.6	
Japan, hospital workers *(145)*	EIA-1, RIBA	1,097	2.5	Blood donors, 526 (1.1)
Japan, acupuncturists *(145)*	EIA-1, RIBA	183	5.5	Blood donors, 710 (3.2)
United States, hemodialysis workers *(146)*	EIA-1, SN	142	1.4	
Italy, hospital workers *(147)*	EIA-1, RIBA	1,347	0.7	Volunteer blood donors, number not specified (0.9)
Maryland, hospital workers *(75)*	EIA-1 or EIA-2, RIBA	943	0.7	Blood donors, 104, 239 (0.4)
Wales, dental surgeons *(148)*	EIA-2	94	0	Blood donors, number not specified (0.3)
Italy, hospital workers *(149)*	EIA-2, SN	635	0.6	
Japan, hemodialysis workers *(150)*	EIA-2	152	8.6	Blood donors, 919 (1.5)
Italy, healthcare workers *(151)*	EIA-2, SN	407	1.2	General population, 253 (0.8)
Germany, hospital workers *(152)*	EIA-2, RIBA-2	1,033	0.6	Volunteer blood donors, 2,113 (0.24)
Taiwan, dentists *(153)*	EIA-2, PCR	461	0.7	Volunteer blood donors, number not specified (0.95 by EIA-1)
South Africa, nurses *(154)*	EIA-2, SN	212	0	Volunteer blood donors, 35,685 (0.3)
Ohio, clinical and laboratory-based healthcare workers *(248)*	EIA-2, RIBA-2	861	2.0	Volunteer blood donors, 20,304 (0.5)
California, healthcare workers (156)	EIA-1, EIA-2, RIBA-2	851	1.4	
London, healthcare workers *(157)*	EIA-2, RIBA-2	1,053	0.3	Blood donors, number not specified (0.3)
Belgium, hemodialysis nurses *(158)*	EIA-2, RIBA-2	120	4.1	Blood donors, number not specified (0.6)
Italy, healthcare workers *(159)*	EIA-2, RIBA	937	0.9	Voluntary blood donors, 1,136 (0.5), pregnant women, 657 (0.8)
Sweden, healthcare workers *(160)*	EIA-2, SN	880	0.7	Blood donors, number not specified (0.6)
France, hospital employees *(161)*	EIA-2, RIBA-2	430	0.9	Office workers, 180 (1.7)
Italy, healthcare workers *(162)*	EIA-2, RIBA-2	3,073	2.2	Blood donors, 11,000 (0–1.7)
Italy, psychiatric hospital workers *(163)*	EIA-2, RIBA-2	145	1.4	
England, hospital workers *(164)*	EIA-2, EIA-3	1,949	0.2	Blood donors, 1,350 (0.1)
Belgium, hospital workers *(165)*	EIA-3, RIBA-3	2,031	1.5	

(*Continued*)

TABLE 73-2

Seroprevalence Studies of Anti-HCV Among Healthcare Workers (*Continued*)

Study Location and Population (Reference)	*HCV Assay*[a]	*Number Tested*	*% of Anti-HCV Seroprevalence*	*Comparison Group, Number Tested (% of Seroprevalence)*
Italy, hospital workers *(166)*	RIBA-2	472	2.5	
Japan, hospital workers *(167)*	EIA-2	1,638	2.8	
UK, dental workers (168)	EIA-3, EIA-3, PCR	167	1.2	
Hungary, hospital workers *(169)*	EIA-2, EIA-3, RIBA-2	409	2.4	
Lebanon, hospital workers *(170)*	EIA-3, EIA-3, PCR	502	0.4	Blood donors, 600 (0.4)
Mexico, medical residents *(171)*	EIA-3, RIBA-2	89	1.1	
India, hospital workers *(172)*	EIA-3, RIBA-3	200	0	
Switzerland, dental workers *(173)*	EIA-3, EIA-3 RIBA-3, PCR	1,056	0.09	
Syria, healthcare workers *(174)*	EIA-3	189	3.0	
Italy, hospital workers *(175)*	EIA-3	4,517	1.97	
Libya, hospital workers *(176)*	EIA-3	459	2.0	

[a]EIA, enzyme immunoassay; RIBA, recombinant immunoblot assay; SN, supplemental neutralization; PCR, polymerase chain reaction.

hepatitis as well as a history of risk factors for bloodborne infections *(177)*. Most of these studies were not designed to investigate risk factors for HCV seroprevalence, or had too few HCV-seropositive subjects to do so. Those studies that did identify risk factors for HCV infection found associations with increasing age *(141,162)*, years in healthcare occupations *(143,158,162)*, a history of blood transfusions *(140,162)*, and a history of prior needlestick injuries *(140,151)*. In aggregate, given the limitations of the study designs, testing methodology, and selection bias, these studies suggest that healthcare workers' risk of HCV infection is only minimally higher than that of volunteer blood donors and appears to be approximately 10-fold lower than the occupational/healthcare-associated risks posed by HBV in the healthcare setting.

Table 73-3 summarizes the results of HCV incidence studies conducted in various populations of healthcare workers who had sustained occupational exposures to HCV *(86,90,147,149,155,157,162,178–195)*. Although most of studies employed anti-HCV antibody testing as the primary detection system for HCV infection, nine of the studies used polymerase chain reaction (PCR) technology to attempt to detect HCV RNA as a marker for infection among individuals who had sustained parenteral exposures to blood from patients known to harbor HCV infection *(90,147,180,187,189–191,193,195)*.

Several factors contribute to the wide variance in the transmission rates (0–22.2%) observed in these studies, among them: different study designs and testing methods, widely differing sample sizes, variable populations of workers followed, different types of exposures, different infectivity of source patients, and potential geographical variability. Recognizing these limitations and acknowledging that the studies are not directly comparable, the pooled infection rate following percutaneous exposures was 1.9%. The risk for infection following other types of exposures has been less intensively studied, but, to date, no infections have been identified in the longitudinal studies following either mucous membrane or other less commonly occurring exposures. Monitoring for infection by measuring HCV RNA may be a more reliable marker for HCV viremia and infectivity *(181,196–198)*, but even when PCR monitoring is combined with antibody testing, the risk for infection may still be underestimated because neither of these technologies will identify individuals who mount only a brisk cellular response and quickly clear the infection *(128)*. Noting all of these limitations, if one pools the data from the nine studies that used RNA PCR testing, the calculated transmission rate for percutaneous injuries is somewhat higher (3.6%) than is found in the studies assessing incidence by anti-HCV antibody tests alone.

At least four cohort studies of hospital workers initially negative for anti-HCV have attempted to measure the incidence of HCV infection. In the first study, samples collected from 960 dental staff during 1979 to 1981 were retrospectively tested for anti-HCV and two were found to seroconvert, for an incidence of 0.15 per 100 person years of follow-up *(138)*. In the second, in a cohort of hospital staff in Cincinnati followed from 1980 to 1989, 6 cases of occupationally acquired non-A, non-B hepatitis occurred, for an incidence of 21 cases per 100,000 healthcare workers per year *(155)*. Four of the six cases were confirmed to be HCV infection. This incidence was approximately three times higher than that of nonhealthcare workers. The third study followed 765 hospital workers in Italy who were screened for HCV in 1986 and retested in 1992 *(159)*. One worker became infected, for an annual incidence of HCV infection of 0.02%. The fourth cohort study, conducted in San Francisco, observed a single seroconversion between 1984 and 1992, and found an incidence density rate of 0.08 per 100 person years (156). For perspective, this study also measured an incidence density rate of 3.05 per 100 person years for HBV among nonvaccinated susceptible workers and 0.055 for human immunodeficiency virus (HIV). A population-based surveillance system for acute viral hepatitis in Italy found that in 1991 healthcare workers were 2.95 times as likely to acquire acute hepatitis C compared to the general population, and in 1994 they were 1.72 times as likely *(199)*.

TABLE 73-3

Longitudinal Studies Assessing Occupational Risk for HCV Infection Following Parenteral Occupational Exposures to Blood from Patients Infected with Hepatitis C

Reference	*Year*	*Location*	*Parenteral HCV Exposures*	*HCV Infections*	*% of HCV Infected*	*Testing Methodology*[a]	*Comments*
Kiyosawa[b] *(178)*	1991	Japan	110	3[b]	2.7[b]	EIA-1, RIBA-1	
Francavilla *(149)*	1992	Italy	30	0	0	EIA-2	
Hernandez *(179)*	1992	Spain	81	0	0	EIA-2, RIBA	
Marranconi *(86)*	1992	Italy	117	3	2.6	EIA, RIBA	
Mitsui *(180)*	1992	Japan	68	7	10.0	EIA-2, PCR	
Stellini *(147)*	1993	Italy	30	0	0	EIA-1, RIBA-1, PCR	
Sodeyama *(181)*	1993	Japan	62	3	4.8	EIA-2	
Lanphear *(155)*	1994	US	50	3	4.2	EIA-2, SN	
Perez-Trallero *(182)*	1994	Spain	53	1	2.0	EIA-2, EIA-3	
Petrosillo (*183*)	1994	Italy	61	0	0	EIA-2, RIBA-2	Dialysis settings
Ippolito[c] *(184)*	1994	Italy	123[c]	2[c]	1.6	EIA-2, RIBA-2	HIV Coinfected Sources
Zuckerman *(157)*	1994	UK	24	0	0	EIA-2, RIBA-2	
Puro[c] *(162)*	1995	Italy	97	1[c]	1.0	EIA-2, RIBA-2	
Puro[c] *(185)*	1995	Italy	436	4[c]	0.6	EIA-2, RIBA-2	
Puro[c] *(186)*	1995	Italy	61	0	0	EIA-2, RIBA-2	HIV uninfected sources
Arai *(187)*	1996	Japan	56	3	5.4	RIA-1, PHA-2, PCR	
Mizuno *(90)*	1997	Japan	37	2	5.4	EIA-2, PCR, Sequencing	
Serra *(188)*	1998	Spain	443	3	0.7	EIA-2, EIA-3	
Takagi *(189)*	1998	Japan	251	4	1.6	EIA-1, EIA-2, PCR	
Veeder *(190)*	1998	US	9	2	22.2	EIA, PCR	
Hamid *(191)*	1999	Pakistan	53	2	3.8	EIA-2, PCR	
Hasan *(192)*	1999	Kuwait	24	0	0	EIA-2, RIBA	
Baldo *(193)*	2002	Italy	68	0	0	EIA-3, RIBA-2, PCR	
Regez *(194)*	2002	Netherlands	23	0	0	EIA-3, RIBA-2	
Wang *(195)*	2002	Taiwan, ROC	14	1	7.1	EIA-3, RIBA-2, PCR	
Total (see text)	—		2381	44	1.8		

[a]Some patients may overlap with reference *(181)*.
[b]Some patients may be counted more than once from these studies reported by the same set of investigators.
[c]EIA-1, first-generation enzyme immunoassay; EIA-2, second-generation immunoassay; EIA-3, third-generation immunoassay; RIBA-1, first-generation recombinant immunoblot assay; RIBA-2, second-generation recombinant immunoblot assay; PCR, polymerase chain assay; RIA, radioimmunoassay; PHA, passive hemagglutination; SN, supplemental neutralization.
(Adapted from Henderson DK. Managing occupational risks for hepatitis C transmission in the health care setting. *Clin Microbiol Rev* 2003;16(3):546–568.)

The findings of a low seroprevalence of HCV infection among healthcare workers and the moderate risk of documented transmission by needlestick injury suggest that the occupational risk of HCV infection exists and is intermediate between the 0.3% per percutaneous exposure risk for occupational HIV exposure *(200)* and the 19% to 37% risk for parenteral exposure to an "e" antigen-positive, HBV-infected source *(67,68)*. The most probable reason for the lower risk is that titers of HCV circulating in blood are relatively low (probably 2–3 logs lower than HBV titers, as noted above) *(69,199)*, so that transmission by small inocula such as needlesticks or other injuries in the occupational setting is less efficient than is the case for HBV. However, because most HCV infections are persistent, the prevalence of HCV infection in some patient populations actually may be higher than for hepatitis B (201), providing a larger pool of potential sources for occupational infection. Because of the wide variability in HCV prevalence by geographic region and patient populations, occupational risk will necessarily vary by these conditions.

As noted above, recent studies of the immunopathogenesis of HCV infection suggest that none of the techniques that have been applied in the longitudinal studies of risk for occupational HCV infection may provide a true denominator of healthcare workers sustaining occupational HCV infections. Anecdotal case reports document HCV antigen circulation in individuals who never made anti-HCV antibody, despite the development of productive HCV infection *(202)*. Additionally, some investigators have suggested that both antibody tests and tests for circulating HCV nucleic acid underestimate the true denominator of exposures, further suggesting that the most sensitive measure of past exposure may well be assessment of specific cellular immunity directed against HCV *(128)*. As noted above, none of the longitudinal studies of healthcare workers measured cellular immune responses.

Further cohort incidence studies and exposure follow-up studies, with larger numbers of workers, employing both HCV RNA testing and sensitive measures of cellular immune

responses directed against HCV will be needed to define more precisely the occupational risk of HCV infection.

Hepatitis D Virus

Hepatitis D virus (HDV), formerly called the delta agent, is a defective virus that needs HBV as a helper virus (see also Chapter 46). Thus, HDV may infect healthcare workers either as a coinfection with HBV (i.e., a simultaneous exposure) or as a superinfection when healthcare workers already have HBV infection. The extent of HDV infection in healthcare workers has not been determined, because HDV antibody testing is not routinely performed *(203)*. Even if HDV antibody screening were routine, the prevalence would be difficult to determine, because infection may elicit only a transient and low-titered response *(204)*. Nevertheless, there is anecdotal evidence for occupational HDV transmission in a hemodialysis nurse *(205)*, and documented evidence for transmission to a surgeon following a deep needlestick injury *(206)*.

Because of its dependence on HBV, the epidemiology and mode of transmission of HDV are similar to those of hepatitis B. Worldwide, approximately 5% of HBsAg carriers are infected with HDV *(207)*. However, not all HBV-infected individuals have the same risk for HDV infection, because geographic and risk group distribution vary substantially. Patient populations that include HBV-infected persons from HDV-endemic areas, such as southern Italy, the Amazon basin, the Middle East, and certain Pacific islands, are more likely to be coinfected with HDV and, therefore, present a greater risk to healthcare workers. Among risk groups for HBV infection, HBV-infected hemophiliacs, intravenous drug abusers, and hemodialysis patients are more likely to be coinfected with HDV than are homosexual men. A major benefit of the efficacy of the HBV vaccine has been a significance decrease in HDV infections in high prevalence areas (49).

Hepatitis E Virus

The etiologic agent of the syndrome of enterically transmitted non-A, non-B hepatitis prevalent in India, Pakistan, Nepal, southwestern China, central Asia, the former Soviet Union, and parts of Africa and Mexico is now recognized to be the hepatitis E virus (HEV). HEV is not prevalent in the United States, although the disease has been imported from endemic areas by immigrants or travelers *(208–212)*. However, although still very rare, the first cases acquired within the United States have been reported *(213)*, and a new strain, called HEV US-1, has been identified as the cause in one instance *(214,215)*. Caution is required when interpreting results from seroprevalence studies; results of assays for antibody to HEV vary widely and are highly discrepant among populations in non–HEV-endemic areas *(216–218)*.

HEV, as is the case for HAV, is transmitted by the fecal–oral route. In the epidemic setting, fecal contamination of water is the most common vehicle for transmission *(219)*. Although person-to-person transmission can occur, infection in household contacts is uncommon *(220)*, suggesting that this mode of transmission is relatively inefficient. Some studies have suggested that animals may be a reservoir for HEV infection *(221)*. Medical staff members in refugee camps have become infected *(222)*. However, the exact mode of transmission in this report is unknown, and the fact that sanitation conditions in refugee camps differ significantly from those in most healthcare settings must be recognized. As with HAV, a period of viremia occurs during the prodromal phase of illness, before virus is shed in the feces, so bloodborne transmission is also possible *(223)*. Presumptive transmission of HEV to a doctor and two nurses has been reported following exposure to amniotic fluid, blood, and stool from a patient with acute hepatitis E acquired following travel to India *(224)*. Until more information becomes available, the risk for occupational acquisition of HEV by healthcare workers in most settings should be considered real, but rare, occurring only under distinctly unusual circumstances in the United States.

Some evidence suggests that hepatitis E may have a zoonotic reservoir, with pigs and possibly rats serving as reservoirs for human infection *(221,225)*. In fact, pigs have been identified as a potential reservoir, even in industrialized countries *(226,227)*. In support of this latter concept, one paper suggests a risk to surgical trainees who work with swine *(228)*. Critical information about hepatitis E and its etiology, epidemiology and prevention has been developed over the past 30 years, and serologic tests have been developed and used extensively to characterize HEV epidemiology. When the prior edition of this text was published in 2003, a candidate vaccine was already being evaluated in phase III clinical trials; nonetheless, no vaccine has yet been marketed. One study conducted in a high-risk population in an endemic area demonstrated that a recombinant HEV vaccine was highly effective in the prevention of hepatitis E (229).

PATHOGENESIS

Other than the clear association of needles, scalpels, and other medical "sharps" with the bloodborne hepatitis syndromes, the pathogenesis of these syndromes in the healthcare setting is not substantially different from the pathogenesis in the community. Chapter 46 thoroughly discusses the pathogenesis of these syndromes.

CLINICAL MANIFESTATIONS

Similarly, the clinical manifestations of the viral hepatitis infections arising as a result of occupational exposures in healthcare workers are not distinct from those in other adults (see also Chapter 46). An exception may exist for occupationally acquired HCV. One follow-up study suggested that, when hepatitis C develops following occupational exposure, the disease tends to be mild and transient *(180)* in contrast to posttransfusion-acquired hepatitis C, which tends to become persistent and chronic. Another study of community-acquired HCV infection, however, found that the frequency of development of chronic hepatitis is similar regardless of how the HCV infection is initially contracted but that severe chronic disease in the form of chronic active hepatitis is more common following transfusion-acquired infection (perhaps because of an inoculum effect) (230). Further studies are needed to confirm these preliminary observations.

DIAGNOSIS

The diagnosis of hepatitis infections in healthcare workers who have sustained occupational exposures is no different from diagnosis in a patient presenting with a hepatitis syndrome (see also Chapter 46). One diagnosis-related issue that is worthy of some emphasis (especially when the source patient is known) is that of determining the hepatitis infection status of the source patient. When the source patient is identifiable and the hepatitis infection status is not known, documenting the source patient's infection status will facilitate both risk assessment and the healthcare worker's postexposure management and follow-up and, in the event that the source patient is found to be infected with the same virus, will likely solidify the healthcare worker's compensation claim. As is done with postexposure testing of source patients for HIV infection, we feel strongly that such testing should be done with the informed consent of the source patient. State laws vary regarding the need for informed consent for testing. In occupational exposure settings, some states permit testing of available serum without consent. Hospitals and infection control committees should construct (and follow) policies that are consonant with their state and local laws. A major controversy currently exists concerning the use of periodic monitoring by RNA PCR of healthcare workers who have sustained occupational exposures to a source patient's blood for the so-called preemptive therapy or watchful waiting strategies (231) (discussed in more detail below).

PREVENTION AND CONTROL

As the hepatitis viruses differ in their modes of transmission and mechanisms of immunity, so will their methods of prevention and control. Components of a multidimensional prevention program include (a) education and training of staff members, (b) administrative controls (identification and isolation of infectious patients), (c) engineering controls (e.g., adequate hand-washing facilities, proper selection, and use of sharp disposal containers *(232)* and safety equipment such as protective needle-safety devices), (d) safe work practices and appropriate use of protective barrier equipment to minimize occupational exposures (practicing Standard [Universal] Precautions with all patients), and (e) employee immunization and postexposure management through occupational health services. Prevention of HAV and HEV infection focuses primarily on interrupting fecal–oral transmission, whereas HBV, HCV, and HDV are bloodborne pathogens requiring different precautions and strategies. Education and training of staff members regarding the methods of infection control and specific prevention strategies is the most important and fundamental component of prevention. When accidental exposures occur, appropriate postexposure prophylaxis, if available, should be administered. Postexposure prophylaxis strategies vary for each virus; currently, HAV and HBV are the only hepatitis viruses for which there are vaccines for preexposure prevention and immune globulins for postexposure prevention; however, as noted above, a hepatitis E vaccine has been shown to be safe and efficacious.

Hepatitis A Virus

To prevent occupational transmission of HAV, healthcare workers should practice good basic infection control techniques, particularly strict hand washing, with *all* patients. Because virus is shed in the feces in the highest concentrations during the incubation period and early in the prodromal period (when hepatitis A infection may not be suspected), identifying and isolating infectious patients may not be possible. In the neonatal or pediatric hospital setting in particular, HAV infections are usually asymptomatic and unsuspected. Hospitalized patients known to have had a recent exposure to known or suspected hepatitis A should undergo serologic studies, should receive appropriate immunoprophylaxis, and should be isolated appropriately. When a patient is known or suspected to have hepatitis A or has unspecified hepatitis consistent with a viral etiology, the CDC traditionally recommended enteric precautions through the first week after onset of jaundice *(233)*. The CDC's current guidelines recommend Standard Precautions for most patients with hepatitis A, but Contact Precautions for patients who are diapered or incontinent *(234)*. Contact Precautions should be maintained for the duration of the hospitalization for infants and children <3 years old, for 2 weeks after onset of symptoms in children 3 to 14 years old, and until 1 week after onset of symptoms for others. Standard Precautions dictate that gloves should be worn when handling all feces or feces-contaminated articles from all patients. Gloves should be worn routinely for contact with patients who have diarrhea or are incontinent of feces. To minimize inapparent contact with fecal material, healthcare workers should wash their hands after even minimal patient contact, and environmental contamination must be minimized by cleaning and disinfection procedures.

In the event of occupational exposure to HAV, postexposure prophylaxis with immune globulin (IG) is recommended *(65,235,236)*. Immunization with the hepatitis A vaccine is another reasonable postexposure immunoprophylaxis strategy, with or without the passive administration of immunoglobulin. As a practical matter, however, IG is seldom used during the primary outbreak, because the index case is often not diagnosed until after the first cluster of infections has occurred. In the healthcare setting, IG is more commonly employed to prevent secondary transmission. When administered before exposure or during the incubation period, IG protects against clinical illness (i.e., IG may not prevent infection but minimizes the clinical signs and symptoms of infection). Protective effects are greatest when administered early in the incubation period, and IG should be given no later than 2 weeks after exposure. Serologic screening of exposed workers for anti-HAV is not recommended, because screening is more costly than administering IG and would unnecessarily delay IG administration, compromising its efficacy. For postexposure prophylaxis, a single intramuscular dose of 0.02 mL/kg of standard lot immunoglobulin is recommended. Because the risk of occupational transmission in healthcare workers is so low, IG is not recommended for preexposure prophylaxis.

Inactivated hepatitis A vaccines have been marketed for more than 15 years *(237)* and the CDC's Advisory Committee on Immunization Practices (ACIP) has issued

recommendations concerning their use *(235,236,238)*. Because healthcare workers in general are not at high risk for HAV infection, preexposure use of the vaccine in healthcare workers has not been recommended by the ACIP. However, selected workers, such as those in laboratories or primate animal facilities who work with HAV, should be vaccinated. For outbreaks occurring in hospitals or institutions for developmentally challenged patients, the CDC still recommends aggressive use of IG, as there are no data concerning the role of hepatitis A vaccine in these settings, though some investigators (particularly those from outside the United States in settings in which the risk for transmission may be higher) have recommended it *(33)*. Because the vaccine should be administered at least 2 weeks prior to exposure to HAV, IG is still recommended for postexposure prophylaxis. In one of the authors' institution, however, the Occupational Medical Service occasionally makes exceptions to the CDC's general recommendations. If the exposed healthcare worker is likely to have additional future exposures to HAV and both immediate and long-term protection is desired, both the vaccine and IG may be administered. Vaccine should be administered with a different syringe at a different site from the IG; the ultimate antibody titer obtained is likely to be lower than when the vaccine is given alone. Both hepatitis A vaccines currently available in the United States require two doses, the second administered 6 months after the first (VAQTA) or 6 to 12 months after the first (HAVRIX). Vaccine protection has been shown to persist for at least 9 years *(239)*, is likely to last for at least 15 years, and possibly for as long as 50 years *(240,241)*.

One study has examined the cost-effectiveness of vaccinating medical students for hepatitis A and concluded that, although the cost per year of life saved was similar to that of many other medical interventions, in order to be cost saving, the incidence of hepatitis A infection would have to be at least 10 times higher than the present rate *(242)*. One selected set of healthcare workers who should be considered for hepatitis A vaccination includes individuals identified as having chronic liver disease (of any etiology, including HBV- and HCV-induced). One study documented the substantial risk of fulminant hepatitis and death among persons with chronic hepatitis C with chronic liver disease who acquired HAV infection *(243)*, and universal vaccination of all patients who have chronic liver disease of any etiology has been proposed *(238,244)*.

Fortunately, unlike HBV, HCV, and HDV infections, HAV does not result in a chronic infection state requiring difficult management decisions and long-term work restriction. Healthcare workers with hepatitis A infection should be restricted from patient contact and food handling until 7 days after onset of jaundice *(245)*.

Hepatitis B Virus

Of all the hepatitis syndromes, prevention efforts in the healthcare setting have focused most aggressively on occupational HBV infection. Results of these efforts are encouraging, but there are still opportunities for improvement. The CDC estimates that the incidence of HBV in healthcare workers declined from 17,000 per year in 1983 to approximately 400 annual infections in 1995 (53). This decline is generally attributed to the introduction of the hepatitis B vaccine in 1982, the institution of universal blood and body fluid Precautions (Universal Precautions) in 1987, and the issuance of OSHA's bloodborne pathogens standard in 1991 (53,*77,246–248*). The use of postexposure prophylaxis, and, to a much lesser extent, patient screening to identify those infected with HBV for special precautions, also may have contributed to decreased infections.

Because the source patients for most occupationally acquired HBV infections are never identified, all patients should be assumed to be infectious. This concept is the cornerstone of Universal/Standard Precautions and was originally developed in 1987 to address concerns about the transmission of HIV (see Prevention of Occupationally Acquired Human Immunodeficiency Virus Infection in Healthcare Workers, Chapter 74). All healthcare workers who have potential occupational exposure to blood or other potentially infectious materials must receive training in the various aspects of Universal/Standard Precautions: administrative and engineering controls, appropriate work practices, and use of protective barrier equipment to minimize occupational exposures. Such training is required both by the OSHA final rule on bloodborne pathogens *(70)* and by federal law. Engineering controls include the provision of hand-washing facilities and equipment designed to minimize percutaneous injuries, (e.g., impervious needle disposal units and self-blunting, shielded, or needleless devices). Work practices include appropriate hand washing, safe handling of needles and other sharp devices, and avoiding risky behaviors such as oral pipetting, recapping needles, and improper handling or disposal of needles and other sharp instruments. Employees must also know how and when to use appropriate protective barrier equipment, such as gloves, gowns, masks, and eye protection, to prevent occupational exposure to blood or other infectious substances. Employee training should also include safe disposal of infectious wastes, housekeeping practices to prevent environmental contamination, and first aid procedures and injury-reporting procedures to follow in the event of an occupational exposure. A summary of specific methods to reduce exposure to blood and other body fluids in the higher-risk operating room setting has also been published *(249)*.

HEPATITIS B VACCINE

Healthcare institutions are also required by the OSHA final rule to provide hepatitis B vaccine free of charge to all at-risk employees; workers who refuse the vaccine are required to sign a declination. Despite the fact that the vaccine provides the best available means of protection from hepatitis B, it has, unfortunately, been underutilized. The original hepatitis B vaccine licensed for use in the United States in 1981 was derived from human plasma and, the vaccine's proven safety and efficacy notwithstanding, vaccination programs were plagued with unfounded safety concerns about possible contamination with other bloodborne pathogens. Currently, the two US-licensed vaccines are marketed, and both are genetically engineered by inserting the gene for HBsAg into the yeast *Saccharomyces cerevisiae* and harvesting the HBsAg particles produced in culture. The recommended dose and schedule

for immunizing healthcare workers is 1.0 mL, injected into the deltoid muscle, at 0, 1, and 4 to 6 months. An adequate antibody response is generally considered to be at least 10 milli-International Units (mIU)/mL, which is approximately equivalent to 10 sample ratio units (SRU) by RIA or a positive test result by enzyme immunoassay (EIA) *(65)*.

Several factors affect the immunogenicity of the vaccine. Care must be taken to prevent freezing the vaccine during shipping and storage, or vaccine potency will be reduced. The vaccine manufacturer's recommended schedule should be followed. Satisfactory protection is obtained if the vaccine doses are administered at longer intervals, but optimal protection does not occur until the third dose. The response may be suboptimal if the vaccine is administered by gluteal injection, rather than being injected into the deltoid muscle. However, age of the recipient is probably the most important determinant of vaccine response. Vaccine response ranges from 90% to 95% among young adults to only 50% to 70% in vaccinees over 60 years of age *(250,251)*. Persons with immunosuppressive illnesses, such as renal failure and HIV infection, and persons with chronic diseases such as diabetes and chronic liver disease, also have diminished vaccine responses. Smokers have been found to have decreased immune responses compared to nonsmokers *(250,252–254)*, and obesity is also associated with diminished response *(250,254,255)*. Unlicensed, reduced vaccine dosages and intradermal routes of injection have been studied extensively, but the OSHA final rule stipulates that vaccine must be provided to healthcare workers according to current recommendations of the U.S. Public Health Service *(245)*.

Prevaccination antibody testing of potential vaccine recipients for evidence of existing immunity is not necessary, but may be sensible if the prevalence of prior infection in the population to be immunized is >10%. The decision to implement a screening program should be based on an institution-specific cost-benefit analysis considering the HBV seroprevalence rate among employees, the cost of serologic screening to the institution, and the costs of vaccination *(65)*. The issue of postvaccination anti-HBs testing has been more controversial. The decline in the occupational HBV transmission rate has been proposed as one argument against routine testing *(256)*. Although postvaccination assessment of antibody response was not recommended routinely in the past, testing was advisable for persons 50 years of age or older, those who were vaccinated with unlicensed dosages or routes of administration, those with immunosuppressive conditions or chronic diseases, and those whose subsequent management depended on knowing their immune status (such as dialysis staff members) *(65,250)*. In one of the authors' institutions, postvaccination testing is offered to anyone who desires it. The CDC's ACIP and the Healthcare Infection Control Practices Advisory Committee (HICPAC) now recommend that postvaccination testing be performed 1 to 2 months after the third dose for healthcare workers who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks *(245)*. Other researchers have proffered what they believe to be a more cost-effective strategy of not performing postvaccination antibody testing, but instead providing postexposure testing and prophylaxis (257). Unfortunately, in our view, this approach has significant limitations. Workers who have inapparent or unreported occupational exposures would not benefit from this alternate strategy, nor would nonresponders be identified and counseled accordingly.

Workers who do not respond adequately to the primary series (nonresponders) may respond to additional vaccine doses. Nonresponders should be revaccinated with a second, three-dose series or be evaluated to determine if they are positive for HBsAg *(245)*. Revaccinated workers should be retested after completion of the second vaccine series. Nonresponders who are HBsAg-negative should also be counseled that they are susceptible to HBV infection, they should practice scrupulous Standard (formerly Universal) Precautions, and they need HBIG for postexposure prophylaxis (see below). CDC further recommends that workers in chronic dialysis centers who do not respond to the vaccine should be tested for HBsAg and anti-HBs semiannually *(258)*. Alternate vaccine formulations appear promising and may be effective in immunizing some nonresponders to current vaccines *(259)*.

The U.S. Public Health Service does not currently recommend either booster doses for workers who initially respond to the vaccine but whose antibody levels decline over time or periodic serologic testing to monitor anti-HBs levels *(245)*. Studies of duration of vaccine-induced immunity in healthy young adults have shown that between 28% and 50% of those who responded to vaccination lost adequate levels of antibody by 5 years, and 30% to 60% had no or low antibody levels by 8 years *(250)*. However, data suggest that, in the rare instances in which HBV infection occurs in adult vaccine responders, the infection is transient and does not result in clinical illness. Other studies have shown that there is excellent persistence of immunologic memory for up to 10 to 11 years following vaccination (53,*260,261*). Some institutions do offer booster doses of vaccine to healthcare workers who have previously responded to hepatitis B vaccination, who remain in at-risk professions, and whose anti-HBs antibody titers have dropped in the negative range (see Table 73-4).

Another important consideration is emphasizing the importance of vaccination of healthcare workers during orientation, training and/or before occupational exposures can occur. This approach has two advantages: it may increase vaccine acceptance and it will prevent infection in trainees who are unskilled and at increased risk of accidental injuries while learning techniques. Studies to determine vaccine coverage among healthcare workers have reported variable results. One study of randomly selected hospitals conducted in 1992 found that only 51% of eligible (and therefore presumably at-risk) employees were vaccinated with three doses of vaccine *(247)*. A large study of American and Canadian orthopedic surgeons found that the prevalence of vaccination decreased steadily with age, from 90% of 20- to 29-year-old surgeons to only 35% of those 60 or more years old *(141)*. Only 55% of hospital-based surgeons in a multicenter survey reported receiving all three doses of vaccine *(76)*. Another national study determined that only 66.5% of eligible employees had received three doses of the vaccine, although coverage was somewhat higher (75%) in workers with frequent exposure to potentially infectious body fluids (53). Hospitals with increased

TABLE 73-4

Guidelines for Management of Hepatitis Exposures to Blood and Other Potentially Infectious Materials at the NIH Clinical Center

Laboratory Results Obtained on Source (Donor) Patient[a]	*Exposed HCW's HB Vaccine Status*	*Exposed HCW's Laboratory Studies Ordered*[b]	*Exposed HCW's Laboratory Results*	*HCW Treatment*[c] *and Follow-Up*
$HBsAg^+$ or unknown, possibly $HBsAg^+$	Unvaccinated	HBsAg, anti-HBs, ALT/AST	$Anti\text{-}HBs^+$ $Anti\text{-}HBs^-$	None HBIG, begin HB vaccine series.[d] Obtain HBsAg, anti-HBs, anti-HBc, ALT/AST in 3 and 6 mo.
	Vaccinated, known nonresponder (anti-HBs–)	HBsAg, anti-HBs, ALT/AST	$HBsAg^+$ and $anti\text{-}HBs^-$ $HBsAg^+$ and $anti\text{-}HBs^-$	None HBIG and either: initiate revaccination as soon as possible or second HBIG dose in 1 mo. Obtain HBsAg, anti-HBs, anti-HBc, ALT/AST in 3 and 6 mo.
	Vaccinated, undocumented anti-HBs response	HBsAg, anti-HBs, ALT/AST	$Anti\text{-}HBs^+$ $Anti\text{-}HBs^-$	None HBIG and initiate revaccination as soon as possible. Obtain HBsAg, anti-HBs, anti-HBc, ALT/ AST in 3 and 6 mo
	Vaccinated, known responder (anti-HBs+)	Anti-HBs	$Anti\text{-}HBs^+$ $Anti\text{-}HBs^-$	None HB vaccine booster dose[e]
HCV PCR^+, $Anti\text{-}HCV^+$ or unknown, possible $anti\text{-}HCV^+$		Anti-HCV, ALT/AST; PCR for HCV RNA	$Anti\text{-}HCV^+$ $Anti\text{-}HCV^-$	None. If unvaccinated, begin HB vaccine series. Refer for follow-up If unvaccinated, begin HB vaccine series. Obtain anti-HCV, ALT/AST at 3 and 6 mo. Repeat HCV PCR at q2 week intervals for 6 mo. If positive, follow closely for resolution of infection (see text); After 4 mo of positivity, refer for consideration of IFN-alpha treatment.[e] Obtain anti-HAV. If anti-HAV neg., begin HA vaccine series.
AST/ALT abnormal, $anti\text{-}HCV^-$, NANBNC suspected, or unknown, possible NANBNC		Anti-HCV, ALT/AST	ALT/AST abnormal, NANBNC suspected ALT/AST abnormal or normal, NANBNC not suspected	None. If unvaccinated, begin HB vaccine series. None. If unvaccinated, begin HB vaccine series. Obtain anti-HCV, ALT/AST at 3 and 6 mo

[a] If the source of the exposure is known, obtain written, informed consent and order HBsAg, anti-HCV, and AST/ALT.
[b] If resources permit, obtain informed consent and freeze an aliquot of serum for future reference.
[c] Unless HCW is known to be positive for HBsAg or has adequate levels of anti-HBs, postexposure treatment should always include counseling and initiation of HB vaccine series (if unvaccinated or if HB vaccine series is incomplete), or administration of booster doses if indicated.
[d] Alternatively, if the employee refuses vaccine, administer HBIG as soon as possible and repeat in 1 month.
[e] Not a current USPHS recommendation.
HCW, healthcare worker; HBsAg, hepatitis B surface antigen; anti-HBs, antibody to hepatitis B surface antigen; anti-HBc, antibody to hepatitis B core antigen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; anti-HCV, antibody to hepatitis C virus; HBIG, hepatitis B immune serum globulin, 0.06 mL/kg IM, as soon as possible (value beyond 7 days unknown); HB vaccine, hepatitis B vaccine; anti-HBs+, ≥10 SRU by RIA or positive by EIA; anti-HAV, antibody to hepatitis A virus; HA vaccine, hepatitis A vaccine; NANBNC, non-A, non-B, non-C hepatitis.
(Courtesy of Dr. James M. Schmitt, Occupational Medical Service, National Institutes of Health [modified].)

vaccination coverage often provided incentives, used employee performance measures (e.g., supervisors were notified if an employee refused vaccination, sanctions were imposed for refusing vaccination, or vaccination was required as a condition of employment), sent reminder notices when vaccine doses were due, and used a computerized tracking system. Clearly, we are making progress, but efforts are still needed to improve vaccine acceptance among healthcare workers. Although there is no precedent for federal law requiring workers to receive a vaccine, mandatory immunization of susceptible healthcare workers has been proposed as the best strategy to further prevent occupational and healthcare-associated hepatitis B infection. Many healthcare institutions and medical schools have adopted this strategy.

MANAGEMENT OF EMPLOYEES SUSTAINING OCCUPATIONAL EXPOSURES

The CDC recommends *(245,262)*, and the OSHA final bloodborne standard requires, that postexposure prophylaxis be provided to employees experiencing adverse exposures to hepatitis B. Healthcare institutions should have established protocols for providing immediate appropriate first aid for injuries and exposures, mechanisms for reporting employee injuries/exposures, and protocols to manage these exposures (263) (see also Chapter 74). Table 73-4 summarizes the management of employees following exposures to blood or other potentially infectious materials as practiced at the Clinical Center, National Institutes of Health (NIH) *(264)*. Although the complete protocol also includes other bloodborne pathogens, such as HIV and human T-cell lymphotropic virus, only the hepatitides are discussed here (see also Chapter 74). Management of exposures includes assessing the type, source, and circumstances of the exposure incident; evaluating the source (donor) patient for clinical, epidemiological, and laboratory evidence of hepatitis; and evaluating the hepatitis B vaccination history and hepatitis infection/immunity status of the exposed healthcare worker. Prophylactic treatment must be provided to susceptible healthcare workers as soon as possible following accidental occupational percutaneous or mucosal exposures to HBsAg-positive blood. A regimen combining hepatitis B immune globulin (HBIG) and hepatitis B vaccine will provide both short- and long-term protection and is the treatment of choice. At the Clinical Center, we often already know not only the vaccination status and HBV immunity status of the exposed healthcare worker but also the hepatitis status of many of the patients participating in research protocols. In many hospitals, this information will not be readily available and employee treatment may have to be initiated pending laboratory test results. The most current CDC recommendations *(262)* for prophylaxis should be followed. As soon as possible following the exposure, the vaccination status and immunity status of the exposed worker should be reviewed. If the exposed worker has not been vaccinated or has not completed vaccination, the vaccine series should be started and a single dose of HBIG (0.06 mL/kg) should be given as soon as possible, preferably within 24 hours of exposure. The vaccine should be administered in the deltoid at a separate site and can be given simultaneously with HBIG or within 7 days of exposure. If the exposed worker has already been vaccinated for hepatitis B and is known to have detectable antibody (anti-HBs ≥10 mIU/mL), no treatment is indicated. If the exposed worker has already been vaccinated and is known to be a nonresponder (anti-HBs <10 mIU/mL), either administration of a single dose of HBIG and initiation of revaccination is indicated, or a dose of HBIG should be given as soon as possible followed by a second dose 1 month later. If the exposed worker has been vaccinated but the employee's anti-HBs response status is unknown, the worker should be tested for antibody; if adequate no treatment is indicated; if <10 mIU/mL, a single dose of HBIG and a vaccine booster dose should be given. CDC recommendations *(245,262)* should be consulted for prophylaxis of healthcare workers when the source is HBsAg negative, not tested for HBsAg, or the status is unknown.

The Occupational Medical Service (Employee Health Service) plays an especially important role in the management of employees who have sustained occupational exposures to bloodborne pathogens. Counseling exposed employees is a crucial component of postexposure management. Counseling these employees is complex, labor-intensive, and often time-consuming and emotionally draining *(265)*. The counselor should collect the epidemiological details relevant to the exposure (i.e., how and why the exposure took place). In addition, the counselor should (a) provide the exposed healthcare worker with estimates (based on the literature) of the risk of infection associated with exposures of the type sustained by the worker, (b) discuss, in detail, the therapeutic postexposure management options (e.g., HBIG, vaccine), and the short-term and long-term side effects associated with these options, (c) discuss the plan for follow-up (and the importance of compliance with that plan), (d) discuss precautions that may be useful to avoid transmission to others should the injury result in infection, (e) provide emotional support for the exposed worker, (f) respond to any and all questions related to the exposure, and (g) encourage the exposed employee to call or return with additional questions *(265)*.

MANAGEMENT OF EMPLOYEES WHO ARE CHRONIC CARRIERS OF HEPATITIS B

The risk of HBV being transmitted from an infected healthcare provider to a patient is virtually nonexistent in the setting of routine patient care contact. A small but, nonetheless, real risk for provider-to-patient HBV transmission does exist for "invasive" patient contact (i.e., situations accompanied by some risk for the patient to be exposed to the blood of the healthcare provider). Personnel who have high circulating viral burdens, such as those who are HBeAg-positive HBV carriers, present higher risk to their patients. Through 1994, investigators at the CDC identified 42 instances of provider-to-patient HBV transmission (infecting over 375 patients) *(266)*. Almost immediately following the publication of this review, two additional clusters

of provider-to-patient transmission of HBV infection were reported that involved surgeons who were hepatitis B "e" antigen (HBeAg) positive *(267,268)*. These clusters of HBV infection from HBeAg-positive surgeons occurred, despite increased attention to infection control measures. In one of these clusters, four patients acquired clinical hepatitis B infection from an orthopedic surgeon *(268)*, and in the other, 19 patients of a thoracic surgery resident became infected *(267)*. No specific events or breaks in technique were identified in either cluster that could have led to the transmissions, although the surgical resident did not wear double gloves. In further investigations, the CDC had the resident perform laboratory simulations of tying surgical knots for an hour, which resulted in paper-cut–like skin lesions on the index fingers, and HBsAg and HBV DNA were detected in rinsings from his gloves. These lesions, combined with serous exudates and glove failure, could theoretically have caused HBV contamination of the patients' surgical wounds.

Since 1996, 10 additional reports of hepatitis B transmission from providers to patients have been published. These cases are generally associated with HBV infected surgeons; one case was associated with an infected dentist (*269,270*; I. Williams, CDC Personal Communication). A publication from the United Kingdom underscored the potential for transmission from providers who have high viral burdens, but are "e" antigen negative. Such providers are often infected with so-called precore mutants of hepatitis B *(269)*. This report underscores the importance of assessing the provider's circulating viral burden. One provider to patient case cluster was reported from Canada in 2000. In this cluster, 75 patients were infected during placement of subdermal EEG electrodes by an HBeAg-positive EEG technician *(271)*. No clear mechanism of transmission was identified in this epidemic. More recently, an orthopedic surgeon was found to have transmitted HBV to two patients; the surgeon was found to have a circulating viral burden of more than 1.7×10^7 virions/mL *(271a)*. Whereas such clusters continue to occur, (acknowledging that the United States does not have systemic surveillance measures to detect such cases) they appear to be occurring less frequently than in the past.

Historically, HB "e" antigen has been the most reliable marker for risk (i.e., high circulating viral burdens). In fact, historically, nearly all providers who have transmitted HBV to patients were "e" antigen positive. In 1997, UK public health authorities reported on four surgeons who had transmitted HBV to patients; all four were infected with HBV viruses that were precore mutants (i.e., these strains are genetically unable to express HBeAg but are still capable of assembling infectious virions) *(272)*. With the exception of providers who have been shown to transmit infection to patients, historically, no restrictions were placed on healthcare workers who were chronically infected with HBV *(273–275)*. Although contrary to previously issued guidelines and recommendations, new guidelines were issued by the CDC in July 1991 recommending that healthcare workers who perform "exposure-prone invasive procedures" be aware of their HBV infection statuses; those who are found to be HBeAg positive should not perform such procedures unless they have sought the counsel of an expert review panel and been advised under what circumstances (if any) they would be allowed to perform these procedures *(275)*. Further, these guidelines note that HBeAg-positive healthcare workers should inform prospective patients about their (i.e., the provider's) infection status *(275)*. Congress subsequently passed Public Law 102–141 mandating that states must implement either the CDC guidelines or create state guidelines and certify them as equivalent to the CDC Guidelines, as a condition for continued federal public health funding.

Consequently, local or state public health officials should be contacted to determine the regulations or the recommendations applicable in a given area.

The United Kingdom has implemented reasonably restrictive guidelines for providers infected with bloodborne pathogens. In the United Kingdom, providers who are infected with HBV and are "e"-antigen positive may not conduct exposure-prone invasive procedures; HBV-infected providers who are "e"-antigen negative, but have HBV DNA levels of $>10^3$ genome equivalents/mL may not conduct exposure-prone invasive procedures; and HBV-infected providers who are "e"-antigen negative, and have HBV DNA levels of $<10^3$ genome equivalents/mL may conduct exposure-prone invasive procedures, but must be retested at least every 12 months to assure that the level of viremia remains below 10^3 copies/mL (276). UK authorities have also recommended that HBV-infected healthcare providers who are HBeAg negative and who have pretreatment HBV DNA levels between 10^3 and 10^5 genome-equivalents/mL could be allowed to perform exposure prone procedures if they are successfully treated with suppressive oral antiviral therapy, such that their circulating viral burdens are suppressed below 10^3 genome equivalents/mL *(277)*. UK authorities are still wrestling with the development of an effective monitoring strategy to make certain that the circulating viral burden remains $<10^3$ genome equivalents/mL *(277)*. The differential sensitivity of available testing systems further complicates this issue.

A thorough discussion of the problems raised by excluding practitioners infected with bloodborne pathogens is beyond the scope of this chapter. These complex management issues have been addressed in detail elsewhere (278,*279–283*). The Society for Healthcare Epidemiology of America (SHEA) has recently issued updated recommendations regarding the management of healthcare workers infected with bloodborne pathogens (Table 73-5) (284). SHEA recommends that HBV-infected healthcare providers who are either "e" antigen positive or "e" antigen negative, but have circulating HBV burdens of greater than or equal to $<10^4$ genome equivalents/mL routinely double-glove for all invasive procedures, for all contact with mucous membranes or nonintact skin, and for all instances in patient care for which gloving is recommended, and that they not perform those Category III activities identified as associated with a risk for provider-to-patient HBV transmission despite the use of appropriate infection control procedures (284). SHEA recommends that healthcare providers who have circulating HBV burdens of genome equivalents per mL be allowed to perform those Category III activities identified as associated with a risk

for provider-to-patient transmission of bloodborne pathogens, so long as the infected provider: (a) is not detected as having transmitted infection to patients; (b) obtains advice from an Expert Review Panel about continued practice; (c) is followed routinely by Occupational Medicine, who tests the provider twice annually to demonstrate the maintenance of a viral burden of $<10^4$ genome equivalents/mL; (d) is also followed by a personal physician who has expertise in the management of HBV infection and who is allowed by the provider to communicate with the Expert Review Panel about the provider's clinical status; (e) consults with an expert about optimal infection control procedures (and strictly adheres to the recommended procedures, including the routine use of double-gloves and frequent glove changes during procedures, particularly if performing technical tasks known to compromise glove integrity [e.g., placing sternal wires]) and (f) agrees to the information in, and signs, a contract or letter from the Expert Review Panel that characterizes her/his responsibilities (284).

The management of practitioners who are chronically infected with bloodborne pathogens is complex for a variety of reasons. Because of the extremely limited data available, no single approach to this complex issue addresses all the relevant issues. Further, individuals who hold quite disparate positions with respect to the patients' right to know and the providers' right to privacy and medical confidentiality likely will have polar views of any individual approach to managing infected providers. Historically, science has provided the foundation for sentient public health policy. In many respects, the hepatitis B–infected practitioner has been "additional baggage" on the bandwagon of public sentiment being driven by societal anxiety about iatrogenic HIV transmission (278). Nonetheless, as additional data accumulate, the argument for considering the management of providers infected with each of the bloodborne viral infections on the evidence that relates specifically to that infection becomes increasingly more compelling. Hopefully, the guideline recently issued by SHEA (284) will provide some additional clarity for this complex problem.

Hepatitis C Virus

Unfortunately, unlike hepatitis B, there are no passive or active immunization products to prevent HCV infection. Prevention relies primarily on healthcare workers practicing Standard Precautions (which includes Universal Precautions) (see discussion in Hepatitis B Virus, above, and Chapter 74). Importantly, use of Universal Precautions has also been shown to decrease transmission to patients in a high-risk setting *(285)*.

MANAGEMENT OF EMPLOYEES SUSTAINING OCCUPATIONAL EXPOSURES TO HCV

The issue of postexposure prevention of HCV infection remains controversial. Testing for antibodies to HCV in source patients and in the exposed healthcare worker is subject to the limitations of serological testing discussed previously. The HCV antibodies identified in the currently available antibody assays are not neutralizing for HCV and are not protective, due to substantial HCV strain variability that permits multiple infections *(138,286,287)*. Therefore, anti-HCV identified in the "baseline" serum of an exposed employee does not indicate immunity. Conversely, HCV antibodies present in the source patient are not necessarily markers for infectivity of the source patient (although the source should be assumed to be infectious); such antibodies do not distinguish between acute, chronic, or resolved infection. Even third-generation anti-HCV testing will still not detect 5% to 10% of persons with HCV infection *(129)*. Direct detection of circulating HCV RNA by the PCR or other molecular method is probably the best approach to identify source patients who are HCV-infected and infectious. As noted above, even the PCR methodology is fraught with complexity.

CURRENT USPHS GUIDELINES

The CDC, in collaboration with HICPAC, has issued recommendations for follow-up of healthcare workers following occupational exposure to HCV *(288,289)*. These recommendations emphasize that institutions should have policies and procedures for follow-up of personnel who sustain percutaneous or permucosal exposure to anti-HCV-positive blood. Such policies should include, at a minimum: (a) for the source, baseline testing for anti-HCV; (b) for the exposed worker, baseline and follow-up (e.g., 6 months) testing for anti-HCV and alanine aminotransferase activity; (c) confirmation by supplemental anti-HCV testing of all anti-HCV results reported as repeatedly reactive by EIA; (d) recommending against immediate postexposure prophylaxis with IG or antiviral agents (e.g., interferon); and (e) education of workers about the risk for and prevention of bloodborne infections, including hepatitis C, in occupational settings, with the information routinely updated to ensure accuracy.

Several other potential interventions have been proposed for managing occupational exposures to HCV, including immunoprophylaxis with immunoglobulin, preemptive therapy of acute infection with immunomodulators, so-called watchful waiting with immunomodulators (231), and postexposure chemoprophylaxis (or chemoprophylaxis plus immunoprophylaxis with immunomodulators). Each of these approaches is worthy of additional consideration.

IMMUNOPROPHYLAXIS WITH IMMUNOGLOBULIN

The issue of postexposure immunoprophylaxis with IG also has been controversial, because no data demonstrate the efficacy of IG in this setting. Data from earlier trials of IG to prevent posttransfusion non-A, non-B hepatitis demonstrated mixed results (231,*290–292*). Although the CDC recommendations *(65)* once stated that "it may be reasonable to administer IG (0.06 mL/kg) as soon as possible after exposure," more recent data have led the U.S. Public Health Service's HICPAC no longer to endorse this practice *(288,293)*. In fact, neither of the authors' institutions offers postexposure treatment with immunoglobulin for occupational exposures to HCV. Although plasma pools for fractionation

to derive IG in the United States once included antibodies for HCV *(294)*, currently the United States and other countries screen plasma donors and exclude HCV-positive donors; thus, IG products no longer contain antibodies to HCV and therefore offer even less theoretical benefit *(289,295)*. Postexposure studies in experimentally infected chimpanzees have demonstrated that neither anti-HCV-negative intravenous immune globulin nor specially prepared hepatitis C immune globulin (containing significant titers of ant-HCV antibody) prevents HCV infection *(296)*.

POSTEXPOSURE IMMUNOPROPHYLAXIS WITH IMMUNOMODULATORS

Immediate postexposure, short duration interferon treatment has been attempted, but was not successful in preventing infection *(89)*. For several theoretical reasons (delineated in detail in reference (231)), and in spite of inferences in the literature suggesting its efficacy, no current rationale supports the use of immunomodulating substances in the immediate postexposure setting. One paper has examined this issue and found no evidence to support this approach *(297)*. As noted above, one could actually mount reasonable arguments as to why immunomodulators should not be administered in the very early phase of infection.

POSTEXPOSURE ANTIVIRAL CHEMOPROPHYLAXIS

Agent(s) with clearly defined antiviral activity against HCV (as compared with immunomodulatory activities) have yet to be made available in the healthcare market. Some agents that are designed to have specific anti-HCV activity are in the drug-development process. In the absence of data demonstrating both the relative safety (i.e., since the transmission risk is, at most, 2% to –3%, 97% to 98% of those given the agent would not need the treatment) as well as efficacy of anti-HCV agents, no recommendation can be made about their potential for use in the postexposure setting. Should some of these compounds be demonstrated to have specific antiviral activity against HCV (and to be reasonably safe), they could become candidates for postexposure chemoprophylaxis for occupational exposure to HCV (231).

PREEMPTIVE TREATMENT OF ACUTE HCV INFECTION VERSUS "WATCHFUL WAITING" AND TREATMENT OF ESTABLISHED HCV INFECTION

Another proposed postexposure management strategy, first suggested by Schiff in 1990, involves weekly monitoring of exposed persons for HCV RNA and initiating interferon treatment when infection is either first detected (i.e., "preemptive treatment") *(138)* or when it appears that the infection may become chronic *(298)*. The practicality of such an approach notwithstanding, definitive data are not yet available to document the efficacy of this approach, though many institutions in the United States are adopting this approach or some modification of it (299).

Perhaps one of the most compelling arguments for the use of one of the PCR monitoring strategies is the remarkable experience published over the past few years describing the treatment of patients who have the acute hepatitis C syndrome *(300–306)*. These studies have shown cure/resolution rates among patients who received treatment for their acute infections that are much higher than one would expect, based on the experience treating patients who have chronic HCV infection (*307,308,*309). In one of the studies of the therapy of "acute hepatitis C," HCV-RNA was undetectable and alanine aminotransferase levels were entirely normal in 43 of the 44 patients who were studied *(305)*. This 98% cure rate literally dwarfs any previously published study of the treatment of HCV infection.

Comparing the treatment of patients with the "acute hepatitis C" syndrome with those who are chronically infected may not be entirely appropriate. Immunological responses to HCV infection are complex; in fact, individuals who develop symptomatic acute hepatitis at the time of infection may represent a population of individuals who are capable of mounting more aggressive immunological responses to the infection. Other studies of therapy of "acute hepatitis C" have produced similar, but not quite so striking successes *(302,310,311)*.

Despite the fact that all of the studies describing the treatment of early or acute HCV infection have substantial limitations (discussed in detail in references (231,*298*)), the outcomes associated with the therapy of the "acute hepatitis C" syndrome almost uniformly suggest that treatment of acute HCV infection is advantageous. The NIH Consensus Conference on Hepatitis C concluded that patients identified with acute hepatitis C should receive immunomodulators *(306)*.

Following this approach, an institution's Occupational Medicine staff monitors healthcare workers who have sustained occupational exposures (at periodic intervals [e.g., 1–2 months] following an occupational exposure to HCV) using HCV RNA-PCR. In some institutions, if infection is definitively identified (as demonstrated by repeatedly positive HCV RNA detection from the serum of the exposed worker), interferon therapy is initiated. Regimens selected have varied. Jaeckel et al. *(305)* used a regimen of five million units of interferon alfa-2b subcutaneously daily for 4 weeks and then the same dose administered three times per week for an additional 20 weeks.

Others have suggested "watchful waiting," also using PCR monitoring. Following this strategy, the institution's Occupational Medicine staff would also monitor the exposed healthcare worker at 1 to 2 monthly intervals by HCV-PCR, and then closely follow individuals who become HCV PCR positive to see if chronic infection develops. One approach has been to recommend interferon treatment only for those who remain HCV-RNA-PCR positive and have elevated alanine aminotransferase levels 2 to 4 months into the course of their infections (231,*298,306*). This approach will allow a substantial fraction of individuals to resolve their infections spontaneously and would not put individuals who spontaneously recover at risk for the substantial toxicity associated with therapy with interferon *(298)*. Both these approaches have merit and

both have at least anecdotal support in the literature. The "preemptive therapy" approach has been used successfully in several instances *(91,187,189,195,312)* and unsuccessfully in others *(89)*. The case report describing failure of a postexposure interferon intervention provides indirect support for the "watchful waiting" strategy. In this case, the exposed individual received "postexposure prophylaxis" with interferon-alpha, five million units per day intramuscularly for 4 days, beginning on the day of exposure *(89)*. One month later, he developed elevated aminotransferase levels and was positive for HCV RNA by PCR, 11 weeks later, his anti-HCV antibody test was positive, and 6 months after the exposure his liver biopsy demonstrated chronic persistent hepatitis. The patient subsequently was treated with a 6-month course of interferon-alpha and was apparently cured *(89)*.

The CDC has not made formal recommendations concerning the use of either of these latter two strategies; however, as noted above, a substantial number of hospitals in the United States have adopted these strategies for managing occupational HCV exposures (299). Both the "preemptive therapy" and "watchful waiting" models represent entirely reasonable approaches to the management of occupational HCV exposure based on the currently available information, though, for the reasons cited above, we prefer the "watchful waiting" approach. Monitoring for HCV by PCR, monitoring alanine aminotransferase levels, and making management decisions based on these data and the individual's clinical status represent perhaps the most reasonable approach to postexposure management, in our view and seems, in our opinion, to represent a substantially improved strategy over the current USPHS recommendation to monitor anti-HCV antibody at 3 and 6 months following exposure *(262,313)*.

MANAGEMENT OF EMPLOYEES WHO ARE CHRONICALLY INFECTED WITH HEPATITIS C

The transmission of HCV from healthcare provider to patient has been reported uncommonly, albeit with some increased frequency in the past decade. As is the case for HBV carriers, individuals chronically infected with HCV are unlikely to transmit infection during routine patient contact. The risk for provider-to-patient HCV transmission during "invasive" patient contact (in which the patient may be exposed to the blood of the healthcare provider) is very small and, because of the lower titers of virus present in the circulation, is likely to be even lower than the risk for HBV transmission.

In the past 15 years, several instances of provider-to-patient transmission of hepatitis C have been reported (*314–327*,328,*329–334*). The first instance of provider-to-patient HCV transmission was reported from the United Kingdom in 1995 *(314)*. A postoperative cardiac surgery patient who had no risk factors for HCV infection developed acute hepatitis C infection, and one of the patient's surgeons was identified as HCV-infected. Only one of the surgeon's 278 patients who could be tested was infected with an HCV strain similar to the surgeon's *(325)*. The second case of provider-to-patient HCV transmission of HCV was reported from Spain *(315)*. Two postoperative cases of HCV infection were detected in cardiac surgery patients, prompting a retrospective evaluation of the patients of the chronically HCV-infected surgeon who had performed these cases. The look-back study identified 6 patients (of the 222 who could be tested) with HCV infection; 5 of these cases were caused by isolates closely related to the surgeon's isolate *(315)*. All of these five patients had undergone valve replacement surgery *(315)*. The third cluster (also from the United Kingdom) involved an HCV-infected gynecologist who was detected as transmitting HCV to a patient, resulting in an extensive look-back study that involved the testing of more than 4,500 patients, including 3,628 who had undergone "high-risk, exposure-prone procedures." Seven additional patients were found to have HCV infection caused by strains of HCV closely related to the surgeon's *(318,320)*.

Ross et al. *(330)* evaluated the 207 of 229 patients of a German orthopedic surgeon. Whereas 3 of the 207 were found to be HCV infected, only one was infected with an HCV strain similar to the orthopedist's *(330)*. This same team also evaluated patients of an HCV-infected obstetrician/gynecologist. One instance of transmission was detected among the 2,286 patients evaluated *(324)*. Three additional provider-to-patient HCV look-back studies are ongoing in the United Kingdom *(293,323)*. In the first of these studies, 3 of 1,900 patients were identified as having infection with a strain of HCV similar to that of the infected provider. In the second, 1 of 749 patients was found to be infected with a strain of HCV similar to the patient's provider, (328) and for the third, results have not yet been published *(323)*.

Several additional reports of provider-to-patient transmission of HCV implicate HCV-infected anesthesiologists. In one such case in the United Kingdom *(326)*, an HCV-infected anesthesiologist infected a patient during a procedure in which the anesthesiologist endotracheally intubated the patient, inserted a peripheral venous catheter, and provided general anesthesia. The anesthesiologist vehemently denied injection drug use *(326)*; however, in several similar cases described below, drug diversion was implicated as the cause of bloodborne pathogen transmission. Ross et al. *(329)* reported a cluster of five cases of HCV infection from an anesthesia assistant who was thought to have acquired acute HCV infection as a result of an occupational exposure to an HCV-infected patient in the operating room. In the course of 3 weeks, the assistant infected five patients. He vehemently denied intravenous substance abuse; however, the similarity of this case to the case described by Sehulster et al. *(331)* (discussed below) is striking. One important point about this cluster is the fact that the anesthesia assistant did not follow recommended infection control procedures in caring for his patients (i.e., Universal/Standard Precautions). He did not wear gloves, even when he had an open lesion on his hand.

The experience in the United States is strikingly at variance with the United Kingdom and European experience. Drug diversion by the infected provider played a pivotal role in four of the five reported instances of provider-to-patient HCV transmission in the United States. Williams et al. *(334)* reviewed the US experience *(334)*. The first instance of provider-to-patient HCV transmission in the United States involved an HCV-infected surgical technician who infected

approximately 40 of 346 patients over a 3-month period *(331,334)*. The surgical technician admitted diverting and self-injecting anesthesia medications from his patients and then used the same syringe to administer saline to patients. The second instance involved an anesthesiologist who was also suspected of using narcotics and diverting drugs from patients. He acquired HCV infection from one patient and subsequently transmitted the same strain to a patient during his acute phase of HCV infection *(322,334)*. The third case of HCV transmission is similar to the UK cases and involved an HCV-infected cardiac surgeon. The surgeon was found to have infected 14 of the 937 patients who could be evaluated from over a decade of surgical practice *(334)*. In the fourth case (again, an individual suspected of diverting patient narcotics), a nurse anesthetist transmitted HCV to 15 of 164 patients over a 4-month period coinciding with the acute phase of his own HCV infection *(334)*. The fifth instance of provider-to-patient transmission of HCV in the United States involved a surgical technician who diverted drugs and infected as many as 23 of her patients; she was convicted and sentenced to 35 years in jail (Joseph Perz, CDC, personal communication).

Thus, four of five detected instances of provider-to-patient HCV transmission in the US have been linked to diversion of patients' drugs to healthcare providers who were abusing injectable narcotics. Two additional cases, one from Spain, the other from Israel, emphasize the importance of narcotics abuse in provider-to-patient transmission of HCV. In the Spanish case, an opiate-addicted anesthesiologist infected more than 200 patients *(316,319)*. In the report from Israel, an opiate-using anesthetist infected 33 patients with HCV *(332)*.

The United Kingdom has recommended broad practice restrictions for HCV-infected providers who conduct exposure prone procedures, recommending that any provider who has circulating HCV RNA should be precluded from the conduct of such procedures *(335)*. Further, the United Kingdom recommended that trainees who are found to have circulating HCV RNA should be restricted from starting training in disciplines involving exposure-prone invasive procedures *(336)*. A European consortium could not reach consensus about HCV-infected providers and concluded, "on balance it is not recommended that exposure-prone procedures be forbidden for HCV-infected HCWs" (337). The SHEA guidelines published early in 2010 recommend that HCV-infected providers who have circulating HCV viral burdens of greater than or equal to 10^4 genome equivalents/mL routinely double-glove for all invasive procedures, for all contact with mucous membranes or nonintact skin, and for all instances in patient care for which gloving is routinely recommended, and that they not perform those Category III procedures identified as associated with a risk for provider-to-patient transmission of bloodborne pathogen infection despite the use of appropriate infection control procedures (Table 73-5) (284). SHEA also recommends that HCV-infected providers who have viral burdens of $<10^4$ genome equivalents/mL not be excluded from any aspect of patient care, including the conduct of Category III procedures, so long as the infected provider: (a) is not detected as having transmitted infection to patients; (b) obtains advice from an Expert Review Panel about continued practice; (c) is followed routinely by Occupational Medicine, who tests the provider twice annually to demonstrate the maintenance of a viral burden of $<10^4$ as well as by a personal physician who has expertise in the management of HCV infection and who is allowed by the provider to communicate with the Expert Review Panel about the provider's clinical status; (d) consults with an infection control expert about optimal infection control procedures (and strictly adheres to the recommended procedures, including the routine use of double-gloves and frequent glove changes during procedures, particularly if performing technical tasks known to compromise glove integrity [e.g., placing sternal wires]) and (e) agrees to the information in, and signs, a contract or letter from the Expert Review Panel that characterizes her/his responsibilities (284).

Hepatitis D Virus

Prevention of HDV in healthcare workers is best accomplished by preventing primary HBV infection. Although preliminary immunization studies in animals show some promise in limiting HDV infection *(338)*, no agents are currently available for active or passive immunization of healthcare workers who are already infected with HBV against HDV. This situation is worrisome, because workers who are already infected with HBV are at risk of developing severe acute illness and chronic liver disease should they acquire HDV superinfection *(204)*. This possibility provides an additional compelling reason for healthcare workers to become vaccinated against HBV. Preliminary experimental studies of treatment of chronic HDV infection with interferon alpha indicate that HDV replication may be inhibited, but this response may be transient. In one study, treatment for a year with high doses of interferon alfa-2a resulted in improvement in about half of treated patients, but relapse was still common *(339)*. Further long-term studies are needed to clarify the role of interferon alpha in the therapy of HDV infection *(340)*. Currently, the only preventive measure available for those infected with HBV is scrupulous adherence to Standard Precautions (Universal Precautions) to minimize occupational exposures to blood.

Hepatitis E Virus

HEV transmission to healthcare workers in most developed countries is extremely rare, although one study documented transmission to a trainee in urology who was operating on swine *(228)*. The diagnosis of HEV infection should be considered in travelers who have diarrhea and hepatitis and are returning from endemic areas. Precautions similar to those for preventing healthcare-associated acquisition of HAV should be adequate to prevent fecal–oral transmission. Workers in settings in which HEV may be present, such as refugee camps, should be especially careful to practice meticulous hand washing after patient contact and before eating and smoking *(222)*. Unlike HAV, no agents are currently available for immunization or passive immunoprophylaxis following exposure to HEV. An experimental vaccine has been successful in monkeys *(341)*, and a recombinant vaccine is currently in Phase III clinical trials *(221,225)*. IG manufactured in nonendemic areas is likely not to be protective because of a lack of antibody to HEV *(342)*, and the efficacy of IG from endemic areas is unknown. There is conflicting evidence that IgG anti-HEV protects against hepatitis E and HEV infection in monkeys and

TABLE 73-5

SHEA Guideline for Management of Healthcare Workers Infected with Bloodborne Pathogens[a]

Virus	*Circulating Viral Burden[b]*	*Clinical Activities[c]*	*Recommendation*	*Recommended Testing*
HBV	$<10^4$	Categories 1, 2, and 3	No restrictions[d]	Twice annually
	$\geq 10^4$	Categories 1, 2	No restrictions[d]	N/A
	$\geq 10^4$	Category 3	Restricted[e]	N/A
HCV	$<10^4$	Categories 1, 2, and 3	No restrictions[d]	Twice annually
	$\geq 10^4$	Categories 1, 2	No restrictions[d]	N/A
	$\geq 10^4$	Category 3	Restricted[e]	N/A

[a]These recommendations provide a framework within which to consider such cases; however, each such case is sufficiently complex that each should be independently considered in context by the expert review panel.
[b]Viral burdens are measured in genome equivalents per mL; currently available tests are not standardized. Individual institutions will need to make the best approximation of genome-equivalents per mL from available tests.
[c]See reference (284) for characterization of clinical activities.
[d]No restrictions recommended, so long as provider: is not detected as having transmitted infection to patients; obtains advice from an Expert Review Panel about continued practice; is followed routinely by Occupational Medicine, who tests the provider twice annually to demonstrate the maintenance of a viral burden of less than the recommended threshold, as well as by a personal physician who has expertise in the management of her/his infection who is allowed by the provider to communicate with the Expert Review Panel about the provider's clinical status; consults with an expert about optimal infection control procedures (and strictly adheres to the recommended procedures, including the routine use of double-gloves and frequent glove changes during procedures, particularly if performing technical tasks known to compromise glove integrity [e.g., placing sternal wires]); and agrees to the information in, and signs, a contract or letter from the Expert Review Panel that characterizes her/his responsibilities.
[e]These procedures permissible only when viral burden is $<10^4$ for both infections.
(Adapted from Henderson DK, Dembry L, Fishman NO, Grady C, Lundstrom T, Palmore TN, et al. SHEA guideline for management of healthcare workers who are infected with hepatitis B virus, hepatitis C virus, and/or human immunodeficiency virus. *Infect Control Hosp Epidemiol* 2010;31(3):203–232.)

humans. Earlier studies suggested that protective antibodies exist *(341,343)*, but a later study demonstrated that passive immunization with HEV antibodies was not protective *(344)*. No HEV-specific IG is currently available for protection from HEV.

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CHAPTER 74

Prevention of Occupationally Acquired Human Immunodeficiency Virus Infection in Healthcare Workers

Susan E. Beekmann and David K. Henderson

In October of 2008, scientists from the Centers for Disease Control and Prevention (CDC) estimated that more than 1.1 million people were living with human immunodeficiency virus type 1 (HIV-1) infection in the United States, a prevalence of nearly 450 per 100,000 population *(1)*. Since the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic in 1981 more than 1 million cases of AIDS had occurred in the United States, resulting in more than 560,000 deaths *(2)*. Established risk factors for infection include both homosexual and heterosexual contact, perinatal exposure and parenteral exposure. Parenteral exposure includes such specific risks as sharing needles during intravenous drug use and receiving blood, blood products, or tissues that are contaminated by HIV. Healthcare workers, in addition to these traditional risk behaviors, are at occupational risk for acquiring HIV infection following a parenteral or mucous membrane exposure to blood or blood-containing body fluids from HIV-infected patients.

Exposure to contaminated body fluids from HIV-infected patients and the potential for acquiring occupational HIV infection are issues that usually result in substantial healthcare worker anxiety. Even though the risk for occupational infection with hepatitis B virus (HBV) (see Chapter 73) in the healthcare environment has been documented since 1949 (3) and is associated with significantly more morbidity and mortality in the healthcare setting than is HIV, a clear focus on defining and minimizing healthcare workplace risks was not developed until the HIV epidemic was well underway *(4,5)*. Since the early 1980s, the subject of occupationally acquired HIV infection has received extensive media coverage, both in the lay press and in scientific forums. In this chapter, we attempt to frame these occupational risks in the context of available scientific knowledge in an attempt to provide a somewhat broader perspective regarding the risks for HIV transmission in society.

ETIOLOGY

HIV-1 is the only retrovirus that has been associated with serious occupational morbidity and mortality. Several cases of simian immunodeficiency virus (SIV) seroconversion have been reported *(6,7)*, but this virus has not yet been shown to cause disease in humans, and the SIV-seropositive laboratory workers remain well. Because several other human retroviruses have routes of transmission similar to those of HIV-1 (e.g., HIV-2, human T-cell lymphotrophic virus [HTLV] I *(8)*, and HTLV-II), occupational transmission of these viruses may someday be detected, although no reports of occupational infection with these other agents have been published. Nonetheless, risks of transmission associated with other retroviruses are likely to be extremely low, and current guidelines for prevention of transmission of HIV-1 are thought to be adequate to prevent transmission of all bloodborne viruses, including other retroviruses.

PATHOGENESIS

HIV derives a major survival advantage from its ability to target the immune system by infecting CD4+ T cells and by inducing a specific cytokine milieu. The wide range of immunologic abnormalities in HIV-infected patients results primarily from the impairment of T cell–mediated immunity. The virus produces billions of virions and T-cell turnover is estimated at a billion cells/day, accounting for the very rapid emergence of viral variants and the progressive nature of T-cell depletion. Even during clinical latency, this battle between countless virions and a continuous but slow repopulation with newly produced T-cells results in a highly activated immune system that attempts to control virus replication and renew itself. Several pathologic mechanisms have been suggested as resulting in T-cell loss, including indirect viral killing and activation-induced apoptosis. Highly active antiretroviral regimens can produce sustained reductions of plasma viral RNA to below detectable limits. Even in those with no detectable plasma RNA, viral DNA could be detected in lymph nodes and peripheral blood mononuclear cells (PBMCs) and virus could be grown from peripheral lymphocytes after removal of CD8+ cells and activation *(9)*. These observations that substantial viral replication occurs in lymphatic tissue during the period of clinical latency *(10)* while viral levels

in peripheral lymphocytes are undetectable or detectable at low levels *(11)* reinforce the insidious nature of the immunopathogenic effects of this virus. Disease progression is determined by the complicated interplay between viral and host factors, including different genetic polymorphisms of receptors, ligands, and key immune proteins that result in specific modulations of the host response to HIV infection (12). Inoculum size and certain inherent properties of the virus (e.g., syncytium-inducing viral phenotype) appear to confer greater overall HIV pathogenicity and may shorten the time to development of symptomatic HIV infection. In the 24 years since the introduction of zidovudine for the treatment of HIV, 25 drugs in six different classes used in varying combinations have resulted in predicted survival of nearly 40 years after combination antiretroviral therapy is initiated *(13)*. Combination antiretroviral therapy has been clearly linked with reductions in morbidity and mortality, with the most dramatic reductions coinciding with increases in the use of protease inhibitors *(14)*. Despite these therapeutic advances, reservoirs of HIV-1 have been identified that represent major impediments to eradication, including latent CD4+ T cells, hematopoietic stem cells of the monocyte/macrophage lineage, and dendritic cells *(15,16)*. Current antiretroviral therapy effectively suppresses but does not eradicate HIV infection *(17)*. The low rate of occupational infection following parenteral exposures to blood from patients known to be infected (i.e., ~3/1,000) may relate to the very low inoculum and/or to spontaneous clearance by cellular immune mechanisms. In one study, T-cells from six of eight HIV-exposed, but uninfected healthcare workers produced interleukin-2 when exposed to HIV peptide antigens *(18)*, and in a second study, cytotoxic T-lymphocytic responses to HIV envelope peptides were detected in 7/20 (35%) of healthcare workers who had sustained occupational exposures to HIV-positive blood compare with only 1 of 20 controls *(19)*.

Evidence has accumulated that infection of Langerhans cells, which are the dendritic cells of the epidermis, plays a pivotal role in early transmucosal and transepidermal transmission *(20)*. HIV infection of these Langerhans cells is regulated by surface expression of CD4 and HIV coreceptors, specifically CCR5. Langerhans cells, which represent only 2% to 3% of all epidermal cells, become infected very early (within 24 hours of exposure), and within an additional 24 to 48 hours this cell population has migrated from epithelial tissue to lymphoid tissue *(21,22)*. Within 5 days, HIV is detectable in peripheral blood in the SIV model. In addition, a molecule called DC-SIGN functions as an attachment factor and mediates capture of HIV by dendritic cells without infection of these cells *(20)*. HIV captured by dendritic cells maintains infectivity for 25 days *in vitro* in the absence of replication within dendritic cells, whereas free virus rapidly loses its infectious potential. Langerhans cells are the major epidermal cell type that is involved in transmission of HIV to lymphoid tissue *(23)*. Thus, the ability to block infection of dendritic cells or to block the handoff from dendritic cells bearing HIV on their membranes to susceptible T cells by HIV may importantly impact occupational transmission of HIV *(24)*. Recently, sequencing viruses in heterosexual transmission pairs and in acute HIV infection provided evidence that a single virus (or infected cell) initiated productive infection in close to 80% of the individuals tested, and two to five viruses in the other 20% (*25*,26). The greatest opportunities for prevention are strategies that target these initially small and genetically homogeneous foci of infection in the first week of infection (27). Additionally, since systemic HIV infection is not thought to occur immediately following exposure, a brief window of opportunity may allow modification of viral replication in the initial target cells or lymph nodes with postexposure antiretroviral treatment.

Once occupational transmission of HIV has occurred, the pathogenesis of infection is not thought to be different from that following other modes of transmission. As occurs with other HIV transmission modalities, some healthcare workers who have acquired occupational HIV infection have progressed quite rapidly to AIDS, while others remain asymptomatic after many years of infection.

DIAGNOSIS AND CLINICAL MANIFESTATIONS

The clinical and laboratory manifestations of HIV infection are generally no different for healthcare workers who acquire occupational infections than they are for persons infected through other routes. Findings that may be useful in establishing the diagnosis of HIV infection of healthcare workers are discussed in detail in the following paragraphs.

HIV-specific antibodies usually appear from 6 weeks to 4 months following exposure. An analysis of 51 seroconversions in healthcare workers determined that the estimated median interval from exposure to seroconversion was 46 days, with a mean interval of 65 days *(28)*. Serodiagnosis consists of screening enzyme-linked immunosorbent assays (ELISAs) followed by a diagnostic Western blot when the ELISA is positive. On evaluation using the Western blot technique, antibodies to the group-specific antigen/core (GAG) proteins (i.e., p18, p24, and/or p55) may be the first to appear, but antibodies to the envelope (ENV) (e.g., gp120, gp160, and gp41) and polymerase (POL) gene products (e.g., p31) develop thereafter, confirming the serodiagnosis of HIV infection. Rapid HIV antibody testing with high sensitivity and specificity (99.6% and 100%, respectively) and 20-minute turnaround time are now widely available with six rapid HIV tests approved by the U.S. Food and Drug Administration (FDA). Rapid testing may facilitate source patient testing and decrease the length of time healthcare workers take postexposure prophylaxis (PEP) pending the source patient HIV test result. Delayed seroconversion has been suggested following sexual exposures *(29,30)*, and the relatively low-inoculum exposures sustained by healthcare workers could result in latent HIV infection and delayed seroconversion. PEP does not appear to prolong time to development of HIV antibodies *(31)*. In 95% of healthcare workers who became infected after occupational exposures, seroconversion occurred within 6 months of the exposures *(31)* when routine testing has been performed. According to CDC, two cases of delayed seroconversion occurring in healthcare workers have been reported *(31)*. These healthcare workers had both tested seronegative for HIV at least 6 months following exposure, but were seropositive within 12 months after the exposure. One of these delayed seroconversions was associated with

concomitant exposure to hepatitis C virus (HCV), and this individual developed co-infection with hepatitis C that was rapidly fatal *(32)*. CDC models indicate that the upper 95th percentile of the distribution of time between exposure and seroconversion is 190 days, and that 5% of healthcare workers are estimated to seroconvert in <6 months following exposure *(33)*. Acute retroviral syndrome *(34–36)* associated with primary HIV infection has been a relatively common finding among healthcare workers in whom documented occupational HIV infection has occurred. This syndrome usually occurs 4 to 6 weeks after the occupational exposure. The CDC reported that 81% of healthcare workers experienced a syndrome compatible with primary HIV infection in a median of 25 days after exposure *(28)*. This clinical syndrome has been described as resembling acute infectious mononucleosis: fever, rash, malaise, myalgias/arthralgias, headaches, night sweats, pharyngitis, and lymphadenopathy have been documented *(34–36)*. Laboratory abnormalities have also been described, including reduced total lymphocyte count, elevated sedimentation rate, and elevated transaminases and alkaline phosphatase levels.

Core (i.e., p24) antigenemia may be detected coincident with the onset of symptoms and usually resolves within several weeks to months, as antibodies to p24 are produced and become detectable in the peripheral circulation *(37)*. One can also detect the presence of virus, either by culture or by polymerase chain reaction (PCR) in cerebrospinal fluid, PBMCs, and plasma before the development of an antibody response in persons who have sustained nonoccupational exposures *(35,38–40)*. Plasma HIV RNA levels are highest immediately after acquisition and then rapidly decrease *(41)*. These direct virus assays (including HIV p24 antigen EIA, PCR for HIV RNA, and the branched-chain DNA assay) consistently detect infections 1 to 2 weeks earlier than the most sensitive antibodies, but they still do not become positive until weeks or months postexposure and they may revert to negative following antibody seroconversion *(33)*. Interestingly, no association between plasma HIV RNA levels at the time of seroconversion and subsequent rate of CD4+ cell loss or AIDS progression has been detected *(41)*. The use of PCR to detect circulating viral RNA will likely supplant the use of the p24 antigen test, although the p24 assay turnaround time is much shorter than for the PCR assay in some centers.

Although direct virus assays have been used as ancillary tests in the diagnosis of occupational HIV infection, these tests should not routinely be used to detect infection in exposed healthcare workers *(33)*. These tests may be helpful in defined adjunctive circumstances, such as when the ELISA is positive but the Western blot is indeterminate, or when symptoms are consistent with the acute retroviral syndrome but serologic testing remains negative for more than several weeks. A negative direct virus assay should never be the basis for excluding infection. Although ultrasensitive direct virus assays are available (quantitation of HIV-1 RNA down to 50 copies/mL), the risk for false positive results increases accordingly.

Symptoms consistent with the acute retroviral syndrome signal that HIV antibodies will appear, usually within 1 to 10 weeks *(35)* if infection has indeed occurred. Healthcare workers who sustain occupational exposures should be educated about the symptoms of the seroconversion illness and should be instructed to seek urgent attention in the employee health clinic if these symptoms appear. In most occupational seroconversions, HIV seropositivity has not been documented as part of the routine serologic follow-up but has been detected after the healthcare worker seeks medical attention for an illness consistent with seroconversion. Nonetheless, the CDC recommends HIV antibody testing at 6 weeks, 3 months, and 6 months following the occupational exposure (*42*,43). The National Institute of Health (NIH) Clinical Center Occupational Medical Service also elects to check HIV antibody status at 12 months following exposure, although this is not routinely recommended by the CDC because of the rarity of delayed seroconversion events (*42*,43). Because of the anecdotal experience with delayed HIV seroconversion occurring following concomitant exposures to HIV and HCV, most authorities would recommend extending follow-up to 12 months following simultaneous exposures to hepatitis C and HIV.

EPIDEMIOLOGY

Occupational injuries and exposures to blood and body fluids continue to be commonplace in virtually every healthcare setting. Healthcare workers who sustain these injuries often react immediately with anxiety, fear, and concern over their risk for acquiring HIV. Framing the issue of HIV transmission risk is quite complex. Nonetheless, more than a decade of dealing with HIV infection in the healthcare workplace has led to a fairly extensive database characterizing these occupational risks.

Healthcare workers' perceptions of risk were initially affected by the news media and publicity regarding cases of occupational infection. The sensationalism that traditionally accompanied HIV-related issues in the media artificially inflated perceptions of occupational risk. We frequently find that both the lay public and, particularly, healthcare workers believe that large numbers of occupational HIV infections have been documented. Depending on the definition of "occupational infection" chosen for the analysis, one can arrive at quite disparate assessments of the number of occupational HIV infections documented in the United States (44). The number of cases of occupational HIV infections in healthcare workers has clearly decreased dramatically over the past decade.

Reports of Occupational Infections

A wide variety of sources have provided information about HIV infection in healthcare workers (44). Several general types of case reports have appeared in the literature, ranging from healthcare workers in whom HIV seroconversions have been documented following an occupational exposure to healthcare workers who are found to be seropositive but in whom the seropositivity cannot be linked to a discrete injury or exposure.

Documented seroconversions are generally defined as cases in which a healthcare worker sustains an injury with a device contaminated with blood from an HIV-seropositive or indeterminate source; the healthcare worker is documented to be HIV-seronegative at the time of the exposure, and then the healthcare worker develops

serologic evidence of HIV infection within the ensuing 6 months. Documented seroconversions are the source of the most detailed and reliable epidemiologic information about occupational infections and are, in fact, the standard against which other types of information about occupational HIV infection can be measured. Through June 30, 2009, 57 cases of occupational seroconversions had been documented either in the medical literature or in individual case reports to the CDC that meet the criteria established for this category of occupational infection (45,46). Of the 57 infected healthcare workers, 48 had percutaneous injuries, 5 had mucocutaneous exposures, 2 had both percutaneous and mucous membrane exposures, and 2 had unknown routes of exposure.

In addition to these documented seroconversions, a number of additional cases of HIV infection have been categorized by the CDC as "possible" occupational infections. This "possible occupational infection" category exhibits different demographics from the set of individuals who have documented occupational infections, and likely include individuals who have confounding community-based risk for infection (44). Since the overwhelming majority of these cases have been reported as anecdotes, these data provide only limited insight into the magnitude of risk for occupational infection (i.e., based on these data, one can state only that healthcare workers are at risk for occupational HIV infection). Some conclusions can be drawn, however, from the cases of documented seroconversions regarding the epidemiology of occupational infection. For example, by examining cases of documented seroconversion for circumstances of occupational exposure, one can gain substantial insight into the types of exposures likely to result in transmission of HIV. Even these relatively small databases provide evidence that the risk associated with mucocutaneous exposures appears to be lower than the risk associated with percutaneous injuries.

Data Describing the Magnitude of Risk of HIV Transmission in the Healthcare Setting

Longitudinal cohort studies of healthcare workers involved in the day-to-day care of HIV-infected patients and in the handling and processing of specimens from such patients provide the best available data regarding the magnitude of risk for transmission in the healthcare setting. A number of prospective studies have followed healthcare workers who have sustained documented exposure to blood or blood-containing body fluids from HIV-infected patients. In all of these studies, healthcare workers undergo baseline and follow up HIV serologic testing (at a minimum) any time a healthcare worker sustains a percutaneous exposure to blood from an HIV-infected patient. The average risk of HIV infection following percutaneous exposure to HIV-infected blood has remained at approximately 0.3% (95% confidence interval [CI] = 0.2–0.5%) for a number of years.

Similarly, other prospective studies have examined the risk associated with mucous membrane exposures to blood or body fluids from HIV-infected patients. Although mucous membrane exposures that resulted in HIV transmission have been reported anecdotally *(47,48)* no seroconversions have occurred following the mucous membrane exposures that were prospectively collected from enrollees in these longitudinal studies.

Factors that Might Influence the Risk of Transmission

Although these data are reasonably specific, and CIs around the calculated risks of transmission are narrow, we still lack sufficient information to predict which injuries will result in transmission of infection. Many of the percutaneous injuries that have been associated with documented seroconversions have been quite deep or extensive or have involved injection of a volume of blood into the healthcare worker, whereas other percutaneous injuries associated with transmission have been relatively minor. Mucous membrane or nonintact skin exposures that resulted in transmission have almost uniformly been quite extensive (e.g., the contact with blood has been for a prolonged period [>15 minutes] or has involved large areas of skin surface). Occasionally, injuries that one might intuitively think would have a higher than average risk for infection have not resulted in infection. For example, a healthcare worker at the Clinical Center, NIH, sustained a severe injury with a bone marrow aspiration needle that had been used on a patient with end-stage HIV disease; the needle actually penetrated through the palm and was visible from the dorsum of the worker's hand. This exposure did not transmit HIV infection.

The epidemiologic factors contributing to the risk for occupational infection have been explored using the case-control method (49). Thirty-three cases of occupational HIV seroconversion following percutaneous exposures to HIV-infected blood and 665 controls who did not seroconvert were studied by Cardo et al. (49) at the CDC. Multivariate logistic regression identified several risk factors associated with HIV transmission after percutaneous exposure: deep injury (odds ratio [OR] 15, 95% CI 6.0–41), visible blood on device (OR 6.2, 95% CI 2.2–21), procedure involving needle in artery or vein (OR 4.3, 95% CI 1.7–12), terminal illness in source patient (OR 5.6, 95% CI 2.0–16), and postexposure use of zidovudine (OR 0.19, 95% CI 0.06–0.52). Increased risk was associated with factors that are indirect measures of the inoculum size (i.e., the quantity of blood transferred in the exposure) or higher viral burden (i.e., source patient in the terminal stage of AIDS). Thus, although the average risk of HIV transmission following a percutaneous exposure is 0.3%, the risk of transmission following exposures involving large quantities of blood or high viral titers may be substantially higher than the average risk. Corroborating evidence for the factors identified by the case-control study was supplied by a laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles *(50)*. Mast and Gerberding *(51)* also determined that glove use reduced the transferred blood volume by nearly 50% in their laboratory model.

Despite our inability to predict with precision which exposures will result in transmission of HIV infection, the documented seroconversions have provided us with specific information about which body fluids have resulted in transmission. Of the 57 documented seroconversions, 49 exposures were to HIV-infected blood, 1 to visibly bloody pleural fluid, 4 to an unspecified fluid, and 3 to a concentrated viral preparation in a laboratory *(42)*. Thus, blood appears to be the major clinical risk associated with transmission. One case report documented transmission of HIV to a laboratory technician from Germany who sustained an

accidental splash of serum from an infected patient to his eye *(52)*. Transmission in this case was likely facilitated by failure to wash the eye and by concomitant conjunctivitis related to a contact lens present in his eye at the time of exposure. Blood, visibly bloody body fluid, and now serum clearly remain the primary risk for occupational transmission of HIV in the healthcare setting *(47)*.

The type and, likely, size of the needle or sharp object involved in the injury also appears to affect the risk of transmission. To date, to our knowledge, no cases of occupational infection have been definitively linked to an exposure resulting from a solid (i.e., suture) needle. Transmission has been associated with several types of hollow-bore needles (including injection needles and intravenous catheters) and other sharp objects (including contaminated broken glass, scalpels and an orthopedic pin *(47)*).

Finally, certain source patient variables, and, perhaps, even several factors relating to the recipient healthcare worker's status, likely affect transmission. Source patients with terminal HIV disease were found to be associated with higher risks of HIV transmission in the case-control study discussed previously (49). Although data regarding specific measurement of HIV viral burden were not available to the CDC researchers, the increased risk of HIV transmission from source patients who are in the late-stage of HIV infection likely is a surrogate marker for the source patient's circulating viral burden. Some also have postulated that the recipient healthcare worker's histocompatibility with the source patient (i.e., human leukocyte antigen [HLA] type, etc.) or any concurrent viral illnesses, such as Epstein Barr virus, cytomegalovirus infection, or infection with human herpesvirus-6 that results in increased CD4 expression, or the presence of chronic inflammation at or around the skin entry site, might also influence the risk of transmission. Despite this educated speculation, the numbers of cases of documented seroconversions with these data available are too few to permit adequate characterization of these risks.

Comparison of the Risk of HIV Transmission to the risk of Transmission of other Bloodborne Pathogens

When assessing the risk of acquiring occupational HIV infection, healthcare workers must be able to place that risk into the broader context of risks associated with other bloodborne pathogens such as hepatitis B and hepatitis C (see Chapter 73). Hepatitis B has long been recognized as a significant cause of healthcare worker morbidity and mortality; healthcare worker risks associated with hepatitis C have been documented and partially characterized in the past decade *(53–55)*.

The CDC estimated in 1987 that 12,000 cases of hepatitis B infection per year occurred among healthcare workers in the United States and that 500 healthcare workers were hospitalized each year because of the complications of occupationally acquired hepatitis B *(56)*. Additionally, prior to the full-scale implementation of hepatitis B immunization, approximately 200 workers died each year from occupational hepatitis B or its complications *(57)*. Subsequently, Mahoney et al. *(58)* found that the calculated number of HBV infections among healthcare workers declined from 17,000 in 1983 to 400 in 1995. This dramatic decline was associated with implementation of Universal Precautions policies, with licensure of recombinant-DNA hepatitis B vaccines, and with the implementation of the Occupational Safety and Health Administration (OSHA) Bloodborne Pathogens Standard *(59)*.

The risk associated with hepatitis C appears to be lower than the risk associated with hepatitis B: healthcare workers with frequent blood contact account for 1% to 2% of reported cases of hepatitis C infection *(60)*, and seroprevalence studies indicate that healthcare workers' risk of hepatitis C infection is only slightly higher than that of volunteer blood donors. Several small prospective studies have measured the risk of transmission after percutaneous exposure to average 1.9% (see Chapter 73) *(61)* with a range from approximately 0% (in six studies, summarized in reference *(54)*) to 22% *(62)*, depending on the size of the population studied and the assays used to test source patients and employees, among other important variables. Lower rates of transmission have been associated with the use of the (much less sensitive) first generation hepatitis C serologic test and with an interesting geographic distribution (see Chapter 73).

PREVENTION AND CONTROL

Despite the fact that several indirect pieces of evidence suggest that the administration of antiretrovirals as PEP may reduce the risk of HIV transmission (46,49,*63*), because of the toxicity and inconvenience of the agents administered as PEP, the attention of the healthcare community should be focused first on preventing occupational exposures as a means of preventing transmission of HIV. The U.S. Federal government has issued regulations that have just this intent. In 1991, the OSHA issued regulations *(59)* that were designed to ensure employer compliance with full implementation of Universal Precautions *(64)*. This "Bloodborne Pathogen Standard" also mandates that employers offer hepatitis B immunization to healthcare workers at risk for occupational exposure at no cost to the employee.

Primary Prevention of Exposures in the Healthcare Workplace

In the time that has elapsed since the initial cluster of cases of *Pneumocystis jiroveci* pneumonia was identified in Los Angeles in the summer of 1981 *(65)*, the CDC issued a series of guidelines with the goal of preventing transmission of HIV infection to healthcare providers (*4,42*,43,*56,64, 66–75*). The concept of "universal precautions," or use of blood and body-fluid precautions for the care of all patients was first proposed by the CDC in 1985 *(4)* and again in 1986 *(69)*. The August 1987 guidelines (frequently referred to as the Universal Precautions guidelines) consolidated and updated all previous CDC recommendations concerning the prevention of occupational infection with HIV *(64)*.

The 1987 Universal Precautions guidelines (summarized in Table 74-1) strongly emphasized the need for every healthcare worker to consider all patients as potentially infected with HIV or other bloodborne pathogens and to adhere to infection-control precautions for minimizing the risk of exposure to blood and body fluids from all patients. These guidelines have been updated by the Hospital Infection Control Practices Advisory Committee *(76)*. Universal Precautions

TABLE 74-1

Use of the Measures in Standard Precautions to Prevent the Transmission of HIV in Healthcare Settings[a]

- Standard Precautions should be consistently used for all patients since only serologic testing reliably identifies all patients infected with HIV or other bloodborne pathogens.
- Standard Precautions apply to blood and bloody body fluids, semen and vaginal secretions, tissues, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid
- Appropriate barrier precautions should routinely be followed to prevent skin and mucous membrane exposure when contact with blood or other body fluids of any patient is anticipated
- Gloves are required for touching blood and body fluids, mucous membranes, or nonintact skin of all patients; for handling items soiled with blood or body fluids; and for performing vascular access procedures
- Masks and protective eyewear or face shields are required when droplets of blood or other body fluids might be generated that could contact mucous membranes (eyes, nose, mouth)
- Gowns are required when splashes of fluids might be generated
- Hand washing is required after contamination with blood or other body fluids and immediately after gloves are removed
- Precautions should be taken to prevent sharps injuries during procedures, during cleaning of instruments, and during disposal of used needles
- Needles should never be recapped, purposely bent or broken, or removed from disposable syringes
- Disposable syringes and needles, scalpels, and other sharps should be placed in puncture-resistant containers for disposal; these containers should be placed as close as practical to the area where sharps are being used
- Mouthpieces, resuscitation bags, or other ventilation devices should be available where their use can be readily anticipated
- Healthcare[b] workers who have exudative lesions or weeping dermatitis should refrain from all direct patient care
- Pregnant[b] healthcare workers should be especially familiar with and should strictly adhere to the concepts of Universal Precautions

[a]Standard Precautions are now used in place of Universal Precaution for prevention of the transmission of HIV and other bloodborne infections in healthcare settings (Siegel JD, Rhinehart E, Jackson M, et al. *Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings*, 2007).
[b]Recommendations not included in Standard Precautions.

and body substance isolation *(77)* are now amalgamated into a single set of guidelines called Standard Precautions *(76)*.

Although the use of Universal or Standard Precautions (see Chapter 90) has been advocated as a means to prevent occupational exposures to blood and other body fluids, neither the efficacy nor the cost-effectiveness of these admittedly labor-intensive and costly *(78)* precautions has been demonstrated definitively. Furthermore, Standard Precautions, with its emphasis on barrier precautions, may not prevent percutaneous injuries, which are the major risk associated with occupational infections, although appropriate handling and disposal of needles and other sharp objects is an integral component of these guidelines.

Studies of the efficacy of Standard Precautions have produced inconsistent results. At least one study has concluded that Universal Precautions training was associated with increased incidence of injuries *(79)*, whereas others have reported stable exposure rates *(80)*. Some studies have shown decreases in recapping or needle-disposal device-related injuries, but stable (or slightly increased) overall injury rates *(81–85)*. The studies indicating that implementation of Universal Precautions did not decrease overall injury rates almost uniformly suggest poor healthcare worker adherence to the components of Universal/Standard Precautions or failure to assess adherence to the precautions. Several other groups have reported trends toward fewer needlestick injuries in association with Universal Precautions *(78,86)*. Investigators at the Clinical Center, NIH, reported that implementation of Universal Precautions was associated with a significant decrease in both cutaneous *(87)* and reported parenteral exposures to blood (88). A review of published percutaneous injury rates per 100 employees found that injury rates following implementation of the Bloodborne Pathogens Standard in 1992 (see paragraph below) were lower than those based on pre-1992 data *(89)*. To the extent that these precautions are actually followed, they will very likely reduce occupational exposures to bloodborne pathogens. Ensuring adherence to the recommended precautions, however, is a challenging matter. Despite these controversies, Universal/Standard Precautions have been widely implemented and are now mandated by the OSHA *(59)*.

This mandate was published by the Department of Labor *(59)* as the "Occupational Exposure to Bloodborne Pathogens; Final Rule" in the Federal Register in December 1991 (the details of this Final Rule are summarized in Table 74-2). Employers, including hospitals and virtually any setting in which exposure to blood might occur, are now required to have in place an Exposure Control Plan that mandated implementation of Universal Precautions. In addition, a series of other requirements have been imposed, including extensive documentation and record-keeping regarding compliance with these regulations. Other requirements relate to engineering and work practice controls, use of appropriate personal protective equipment, detailed housekeeping standards, and requirements for "biohazard" labeling. Free hepatitis B immunization is now required for all employees with any potential for exposure; healthcare workers who decline vaccination must sign an "informed refusal," the content of which is specified in the Final Rule. Finally, the OSHA has established an obligatory federal standard of practice

TABLE 74-2

Requirements of the OSHA's Bloodborne Pathogens Standard

Hospitals and other healthcare employers are required to:

- Develop an exposure control plan that identifies employees with occupational risk of exposure to blood or body fluid
- Train all employees annually on occupational risks and methods to reduce risk of exposure
- Maintain records of employee training for 3 y and of medical evaluations for the duration of employment plus 30 y
- Use warning labels and signs to identify biohazards; red bags or containers are allowed to substitute for the label in many cases
- Implement engineering and work practice controls for worker protection, including specific requirements for:
  - Hand washing
  - Safe handling and disposal of sharps
  - Employee conduct in areas of potential exposure
  - Management, storage, and shipping of specimens
- Provide personal protective clothing and equipment
  - Employees must be trained how and when to use equipment
  - Cleaning, laundering, repair, and replacement is the employer's responsibility
- Maintain detailed housekeeping standards, including requirements for special handling and bagging of "contaminated" laundry
- Provide voluntary hepatitis B vaccine at no cost to employees
  - Prevaccination screening cannot be required
  - Employees declining vaccination must sign an "Informed Refusal," the content of which is specified
- Provide medical evaluation after exposure incidents
  - Ensure testing of the source patient when consent is obtained
  - Provide postexposure prophylaxis as recommended by the U.S. Public Health Service
- Institute additional precautions for HIV and HBV research and production facilities, where applicable

(Adapted from: 29 CFR 1910.1030. Available at *http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10051)*

for employers when an employee is involved in an exposure incident; current recommendations of the U.S. Public Health Service must be implemented following an exposure incident.

Certain portions of the Final Rule were impatiently awaited by occupational medicine and healthcare epidemiology personnel, in particular the requirement to document compliance with the hepatitis B vaccination. Although the rates of occupational hepatitis B have decreased dramatically with the OSHA Final Rule and use of Universal Precautions *(58)*, absolute protection can only be assured with evidence of serologic immunity. Prior to publication of the OSHA Final Rule, the CDC estimated that only 30% to 40% of healthcare workers had been vaccinated *(90,91)*. In 1995, Agerton et al. *(92)* concluded that the OSHA Final Rule resulted in a greater awareness in healthcare workers of their risk for hepatitis B and an increase in the number of workers receiving the vaccine; nonetheless, only 51% of eligible workers had completed a vaccination series. Other portions of the Final Rule, such as the "exposure determination" requirement, in which employers must list all job classifications in which some employees have occupational exposure to blood, and then list every task and procedure performed by the employees in those job classifications, are remarkably onerous and have undoubtedly greatly increased the workload of healthcare epidemiology personnel with, in our opinion, little likely benefit to the employee.

Management of Occupational Exposures

Healthcare institutions have ethical and now legal responsibilities to develop and implement protocols for managing healthcare workers who are occupationally exposed to bloodborne pathogens. However, given the major gaps in the available scientific data regarding these issues, the optimal management of employees sustaining exposures remains elusive. Thus, this issue, which is particularly difficult for the healthcare workers who sustain the exposures, is likely to remain as problematic for hospital administrators, hospital legal staff members, healthcare epidemiologists, Infection Preventionists, hospital infection control committees, and employee health staff members, who often are responsible for development and implementation of policies and procedures designed to manage exposed employees.

In addition to the routine difficulties inherent in any occupational exposure, HIV-related exposures present the additional concern of secondary transmission of HIV to significant others. Healthcare workers who sustain occupational HIV exposures often react with profound anxiety and experience severe emotional and psychological stress. Managing these exposures is complex, labor-intensive, and often emotionally draining for the physician/counselor in the occupational health service *(93)*.

Postexposure management of occupational exposures should be routinely taught in professional schools and reinforced during healthcare epidemiology and occupational health interactions with healthcare workers (e.g., during orientation of new employees and during initial and recurring Standard Precautions training). Institutions should not defer disseminating this information until after an exposure; all healthcare workers should be aware of the appropriate procedures to follow irrespective of whether an exposure has occurred. The process of immediate

postexposure management should consist of three basic steps: administration of immediate first aid at the work site, informing one's supervisor of the event if the supervisor is immediately available, and immediately reporting to the Occupational Medical Service (or through another institutionally established reporting mechanism). We encourage our employees to report all exposures for two reasons: first, proper treatment (e.g., first aid and—when appropriate or desirable—postexposure chemoprophylaxis) can be administered, and second, reporting allows documentation of work-related exposures and facilitates workers' compensation claims when such claims are appropriate.

Although no data address the efficacy of immediate application of first aid in preventing transmission of occupational bloodborne infections, most authorities recommend administration of first aid immediately following an exposure as a logical action (*42*,43,*94*). Given a lack of data with which to make a scientific recommendation regarding first aid, selection of agents for decontamination (e.g., soap and water, chlorhexidine, iodophors, peroxide) should depend, in part, on which agents are most readily available. Although following an established institutional regimen seems an entirely reasonable approach, occupational medicine staff should explain that no data document the efficacy of these first-aid interventions in preventing occupational infection with bloodborne pathogens. In fact, an anecdotal report documents occupational infection with HIV despite the immediate application of first aid, including thoroughly rinsing the injury site (a cut from glass contaminated with blood from an AIDS patient) with undiluted bleach *(95)*. At the Clinical Center, NIH, our routinely recommended procedure is immediately to scrub the site of the injury or cutaneous exposure with a povidone-iodine solution and to attempt to "milk" the site of a transcutaneous exposure to express blood. Clinical Center guidelines also recommend that mucous membrane exposures affecting the mouth or nose be rinsed thoroughly with water or saline; exposures affecting the eyes should be rinsed thoroughly with water, saline, or sterile irrigants *(93,96)*.

Once the site has been decontaminated, the healthcare worker should inform his or her supervisor about the exposure (if the supervisor is in the immediate vicinity or can be reached within a minute or two) so that the supervisor can provide coverage while the employee is away from the area. The healthcare worker should then report immediately to the institution's employee health service. Reporting of exposures is essential both to ensure adequate care for the injured employee and to assist the institution in making necessary policy and procedural changes to minimize risks of injury to other employees. In order to facilitate reporting, a mechanism should be defined and widely publicized and must be capable of being activated at any time of the day. A number of institutions have implemented 24-hour-a-day hotlines staffed by expert clinicians who can coordinate both exposure reporting and employee management. Clinicians who provide first-line response to employees exposed to patients known or suspected to be HIV-infected should be prepared to provide state-of-the-art medical management of occupational exposures but also must be prepared for and capable of dealing with the extreme anxiety and occasional hysteria associated with these exposures.

Education and counseling are important components of the management of occupational exposures to bloodborne pathogens. Employees sustaining exposures to blood or body fluids from patients known or suspected to be HIV-infected need counseling regarding (a) the epidemiology, routes of transmission, and transmissibility of HIV, (b) the risk for occupational transmission of HIV following such an injury, (c) the importance of notifying the occupational health service of any acute febrile illness, and (d) techniques effective in minimizing the risk for transmission of HIV to sexual partners *(93)*.

Management of employees sustaining exposures to blood or body fluids from patients whose HIV status is unknown is confounded by the problems associated with testing the source patients. Each institution should develop a policy for the management of exposures when the source patient is either unable or refuses to consent to these tests that is consonant with State and/or local laws. Many states have laws that either permit testing of source patients in certain circumstances even if consent is refused or legally require informed consent for testing.

For institutions to achieve and maintain roles as healthcare worker advocates, the medical confidentiality and privacy of healthcare workers who sustain occupational exposures and/or infections must be preserved. Each employee who sustains an occupational exposure must be apprised fully of the procedures used for ensuring confidentiality and reassured that records will not be released without his or her consent. In order to maintain privacy, laboratory samples should never be submitted with identifiers that can be traced to an individual. Additionally, access to records of occupational exposures should be strictly controlled. We recommend that records of HIV, hepatitis B, and hepatitis C testing of employees be maintained separately from routine employee health records. Indeed, the OSHA requires the employer to obtain a copy of the evaluating healthcare professional's written opinion only, which must include a statement that the employee has been informed of the results of the evaluation and told about any medical conditions resulting from exposure that may require further evaluation and treatment. All other medical findings or diagnoses must be kept confidential and not included in the written report provided to the employer *(59)* (see Table 74-2).

Secondary Prevention of HIV Transmission—Postexposure Antiretroviral Prophylaxis Following Occupational Exposures

Ideally, primary prevention of occupational HIV infection would obviate the need for PEP. Unfortunately, neither implementation of Standard Precautions nor use of "safer" devices will prevent all injuries. Postexposure antiretroviral chemoprophylaxis has become the standard of care following at-risk injuries and exposures (*42*,43,*63,97,98*). Currently, the Public Health Service (PHS) recommends that PEP should be available as soon as possible following exposure (43), and the OSHA Final Rule mandates employer compliance with PHS recommendations *(59)*. Basic recommendations for PEP now include a two-drug regimen using two nucleoside analogs (zidovudine plus lamivudine or emtricitabine, or tenofovir plus lamivudine or emtricitabine) for 4 weeks (43). An expanded regimen

incorporating a third drug, usually a protease inhibitor (e.g., lopinavir/ritonavir [Kaletra]), is recommended for exposures that are associated with an increased risk for transmission (43). In instances in which resistance to antiretroviral agents incorporated in the basic regimen is anticipated, CDC has recommended using a combination of three agents to which the source patient's HIV isolate has not been exposed.

Whereas definitive evidence of the efficacy of chemoprophylaxis is still lacking, these recommendations for PEP were based on several pieces of evidence *(63,99)*. The retrospective case-control study results discussed previously in this chapter were initially presented in 1994 *(100)* and then in final form in 1997 (49). This study documented an association between use of zidovudine PEP and an 80% reduction in risk for HIV seroconversion *(101)*. This association was surprising and initially greeted with skepticism *(99)*, particularly since a retrospective case-control study design is not optimal for assessing the efficacy of PEP. Nonetheless, the association held true even with the addition of cases from the United Kingdom, France, and Italy. Although the magnitude of the protective effect may be altered with the future addition of more cases, the conclusion drawn from these data is that "…chemoprophylaxis may well be worthwhile after occupational exposure and may be a reasonable option after any type of exposure to HIV *(99)*." With a risk for infection of 0.2%, the sample-size requirements for a placebo-controlled trial are formidable. For example, assuming that a candidate agent is 80% effective and assuming a power of 80%, 17,110 healthcare workers would be needed for a double-blinded placebo-controlled trial to demonstrate significance at the 0.05 levels. Thus, definitive proof of the efficacy of postexposure, apart from the retrospective case-control study, is unlikely to ever be established.

Zidovudine was demonstrated to decrease the risk of maternal-infant transmission of HIV *(102)*. Only approximately 30% of the decrease in risk of vertical transmission following use of zidovudine prophylaxis was found to be attributable to a reduction in maternal viral burden, suggesting that newborns benefit from a substantial chemoprophylactic effect, effective preemptive therapy for HIV infection, or both *(103)*. Abbreviated zidovudine regimens have also been shown to be effective in decreasing the ratio of prenatal HIV transmission (*104*,105,*106*). Strikingly, in some of these studies, antiviral efficacy was demonstrated in instances in which only the infant received therapy (i.e., true PEP) (105,*107*), although a more recently published study recommends against infant-only treatment *(108)*. In addition, PEP has been shown to prevent or ameliorate retroviral infection in some animal studies *(109)*. Taken together, these pieces of evidence provide the foundation for the current U.S. Public Health Service recommendations (43).

Animal studies have provided insight—both to the safety as well as the efficacy of postexposure chemoprophylaxis regimens. Not surprisingly, given the fact that these agents are active at the level of nucleic acids, long-term studies of the chronic administration of antiretroviral agents to animals have identified toxicities, as well *(110–112)*.

Studies evaluating the efficacy of antiretroviral agents in preventing retroviral infections in animal models provide some of the best available evidence that these agents might, in fact, be of value in preventing occupational HIV infection. Whereas the results of the first such studies were relatively discouraging *(113–125)*, subsequent studies clearly demonstrated that antiretrovirals can prevent infection when the drugs are administered at, or shortly following, infection. Most of the initial studies demonstrated some drug effect (i.e., treated animals fared slightly better than controls, but all animals became infected) *(113–125)*. Beginning in 1992 *(126)*, studies in mouse and macaque models demonstrated the efficacy of chemoprophylaxis (*126–129*,130,*131*). Three sets of studies deserve special mention. The early studies of Ruprecht et al. *(132,133)* using the Rauscher murine leukemia virus (RMLV) model demonstrated as early as 1990 that either zidovudine or zidovudine plus alpha interferon could prevent RMLV viremia. Subsequent studies with this model demonstrated chemoprophylactic efficacy of zidovudine *(129)*. Böttiger et al. *(128)* studied 2,3′-dideoxy-3′-hydroxymethyl cytidine in a macaque model and showed that all treated animals that had been either injected intravenously or exposed intrarectally to either HIV-2 or SIV were protected, irrespective of the viral agent or the route of inoculation. Tsai et al. (130) administered a nucleotide analog agent, (*R*)-9-[2-phosphonylmethoxypropyl] adenine (PMPA, now FDA-approved as tenofovir), to several sets of macaques that had been infected intravenously with SIV. One set of animals was given PMPA at the time of infection, one set was given PMPA 4 hours after infection, and a third set was given the agent 24 hours after infection. All of the untreated control animals became infected, and none of the animals in any of the treatment groups developed any sign of SIV infection.

These animal models have also been used to evaluate factors that might modulate the efficacy of postexposure chemoprophylaxis. In the RMLV model the efficacy of antiretroviral prophylaxis is directly dependent on both the size of the viral inoculum administered and the presence of intact cellular immune mechanisms in the animals studied *(129)*. In the macaque model, Tsai et al. (134) demonstrated the importance of both the timely administration of chemoprophylaxis as well as the importance of the duration of therapy. In their model, all of the animals that were treated for a total of 28 days remained uninfected, whereas only half the animals treated for just 10 days were uninfected. In this model, none of the macaques treated for only 3 days were protected. These investigators also demonstrated that delay of treatment was detrimental in the model. None of the animals that received postexposure chemoprophylaxis within 24 hours of intravenous infection developed productive SIV infection, while only 50% of the animals treated at 48 hours after infection and 25% of animals treated at 72 hours after infection were protected from SIV infection.

The evidence provided by these animal studies is invaluable. The data clearly demonstrate that antiretroviral agents can prevent retroviral infections in these models. They do not, however, assure efficacy of prevention of HIV infection in humans.

Failure of chemoprophylaxis following occupational injuries to healthcare workers has been documented in at least 22 instances (*42*,43,*135*). Fourteen of twenty-three source persons were documented as having been

treated with antiretroviral therapy prior to the exposure. Antiretroviral resistance testing of source patient virus was performed in eight instances, and in four the virus was found to have reduced sensitivity to drug(s) used for PEP. Six additional cases of zidovudine failure following larger or direct intravenous inocula have occurred: two seroconversions occurred after direct intravenous inoculation of HIV-infected blood during nuclear medicine procedures *(136,137)*, another occurred after a deep stab injury inflicted on a prison guard *(138)*, the fourth case occurred following suicidal self-inoculation of blood *(139)*, and the fifth seroconversion occurred after transfusion of an entire unit of contaminated blood *(110)*. An additional case of suicidal self-inoculation was reported in which the exposed individual did not become infected after PEP with zidovudine, lamivudine, indinavir, ritonavir, and nevirapine. The authors suggest that the absence of infection was related to the small size of viral inoculum (2 mL blood with viral load <50 copies/mL), administration of PEP, and development of an HIV-specific T cell response *(140)*. Interestingly, genotypic resistance did not correlate with a lack of protection in the ACTG 076 study of zidovudine administration to attempt to prevent vertical transmission of HIV. Nonetheless, exposure to a strain of HIV with reduced sensitivity to the agents administered may influence the likelihood of failure of postexposure chemoprophylaxis. Other hypothesized reasons for the failure of PEP include a high viral titer or large inoculum exposure, time factors, including delayed initiation or premature discontinuation of PEP, host factors, including cellular immune responsiveness, and the source patient's virus, including the presence of syncytia-forming strains (141). Although anecdotal reports of failure provide useful insight into both injury circumstances and specific issues regarding administration of postexposure chemoprophylaxis, these reports indicate only that the efficacy of chemoprophylaxis is not 100% and do not, in themselves, prove lack of efficacy.

Delayed seroconversion following zidovudine prophylaxis has been a theoretical concern, since some of the animal data indicate that administration of zidovudine may merely delay viremia *(114)*. A review of zidovudine prophylaxis failure determined that 10 of 11 healthcare workers experienced an acute retroviral illness between 13 and 75 days (median 22 days) following the exposure, and all had seroconverted by 6 months following the exposure (141). These data are consistent with seroconversion data from healthcare workers who had not received PEP.

The role of resistant strains of HIV in the failure of chemoprophylaxis is unclear. A few reports of transmission of resistant isolates have been published *(142,143)*. Little et al. *(144)* reported in 2002 that the frequency of high-level resistance to one or more antiretroviral drugs increased from 3.4% (1995–1998) to 12.4% (1999–2000) among 202 subjects in 10 North American cities. Thus, the source patient's treatment history should be taken into account when determining the appropriate antiretroviral drugs for PEP. Data regarding perinatal transmission suggest that perinatal HIV transmission may be established by a relatively restricted number of virus particles and that drug-resistant forms may be less able to establish infection than wild type *(145,146)*. To further support this notion, several groups have found that virus with three-class multidrug resistance is infrequently transmitted which may reflect the poor replication capacity of these extensively mutated viruses *(147–150)*.

Combination regimens, particularly those using three or more drugs, have been proven superior to monotherapy or double nucleoside therapy in HIV-infected patients *(151–154)*. Current guidelines define highly active antiretroviral therapy (HAART) as the cornerstone of care for HIV-infected patients. HAART typically involves three or more drugs that inhibit the replication of HIV by various mechanisms (155). There are no data to address the efficacy of other antiretroviral agents added to the basic single-drug regimen for PEP. Theoretically, a combination of drugs with activity at different stages of viral replication could offer an additive preventive effect, particularly for occupational exposures with increased risks of transmission.

Currently, the routine use of three drugs for all occupational HIV exposures is not recommended (*42*,43). The PHS has concluded that the use of a highly potent regimen (i.e., three drugs) can be justified for exposures that pose an increased risk for transmission but that the additional potential toxicity may not be justified for lower risk exposures (*42*,43). The basic two-drug regimen is recommended for less severe exposures (e.g., solid needle and superficial injury) and HIV-infected sources with asymptomatic HIV infection or known low viral load (<1,500 RNA copies/mL). If the injury is more severe (e.g., large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein) or the HIV-infected source has symptomatic HIV infection, AIDS, acute seroconversion, or known high circulating viral burden, then an expanded three-drug regimen is recommended. The two-drug basic regimens currently recommended by the PHS include: zidovudine plus lamivudine or emtricitabine, or tenofovir plus lamivudine or emtricitabine (see Table 74-3). Regimens including new classes of agents and newly marketed agents have been reported *(156–159)*. The addition of a protease inhibitor as a third drug for PEP following high-risk exposures is based on the demonstrated efficacy of these agents in reducing viral burden, as well as their interference at a different site of viral replication (i.e., after viral integration has occurred) than for nucleoside or nucleotide analog reverse transcriptase inhibitors. However, protease inhibitors have potentially serious drug interactions when used concomitantly with other medications. These agents also have serious side effects when used as an agent for combination PEP, including nephrolithiasis, hepatitis, and pancytopenia (*42*,43). Nonetheless, one analysis determined that triple-drug combination therapy following moderate-to-high risk occupational exposures was cost-effective for society *(160)*. Another analysis determined that the mean cost associated with administration of PEP was $706 (in 2003 dollars), with a reported range of costs to manage reported exposures from $71 to $4,838 *(161)*. If combination PEP is minimally more effective than zidovudine alone, then the added expense of including other drugs in the drug regimen is clearly justified. Mathematical modeling suggests that the optimal regimen would be a dual nucleoside regimen unless the background rate of viral resistance in the source population is >15%, in which case a three-drug regimen including a protease inhibitor would be favored *(162)*.

TABLE 74-3

Summary of Postexposure Prophylaxis Options for Healthcare Workers Exposed to HIV

Basic Regimen		*Expanded Regimen*
Two nucleoside analogs		Two nucleoside analogs plus one additional drug
	Indications	
Occupational HIV exposures categorized as "less severe" (e.g., solid needle and superficial injury) source with asymptomatic infection or low viral load		Occupational HIV exposures categorized as "more severe" (e.g., deep puncture and visible blood on device) source with symptomatic infection or high viral load, or known drug resistance
	Antiretroviral Agents	
Choice of one regimen	Zidovudine + lamivudine Zidovudine + emtricitabine Tenofovir + lamivudine Tenofovir + emtricitabine	*Choice of one regimen*
	Additional Agents for Expanded Regimen	
	Lopinavir/ritonavir or	Primary Choice
	Atazanavir Fosamprenavir Indinavir/ritonavir Saquinavir/ritonavir Nelfinavir Efavirenz	*Alternatives*

A significant number of healthcare workers begin PEP with two or more drugs after exposure to a source patient of unknown serostatus *(163)*. PEP continues until the ELISA result is available, which may take up to 5 days. CDC HIV PEP Registry data indicate that a healthcare worker taking only a few days of prophylaxis pending the source patient HIV test result is as likely as a healthcare worker taking the full 28 day course of prophylaxis to experience toxicity, since the median time to onset of symptoms was 3 to 4 days *(163)*. Use of a rapid HIV screening test (see "Diagnosis and Clinical Manifestations" section) will likely prevent the need for any medication and thus should decrease healthcare worker anxiety as well as drug toxicity, and decrease cost for the institution *(164,165)*.

Whereas studies of the administration of postexposure antiretroviral chemoprophylaxis have identified toxicity as a problem, the same studies have demonstrated a reasonable safety profile for PEP. For example, one multicenter collaborative study demonstrated safety of prophylaxis administered to healthcare workers following occupational exposure *(166)*. The zidovudine regimen used in this study consisted of 1,200 mg/day on days 1 to 3, followed by 1,000 mg/day on days 4 to 28 *(166)*. The study identified a mean decrease in hemoglobin values from 13.9 g/dL at baseline to 13.2 g/dL at 4 weeks for 105 healthcare workers who took zidovudine for at least 22 days. The maximum decrease in absolute neutrophil count was 1,200/mm^3 at week 4 following exposure. In this study, hematologic toxicities correlated neither with body weight nor with reported subjective toxicities. No objective nonhematologic toxicities were identified *(166)*. Symptoms of drug intolerance (nausea, fatigue, and headache) occurred in a substantial number of subjects *(167)*. Forty-nine percent of 674 subjects experienced at least one adverse effect (most commonly nausea) *(168)*; other investigators reported that subjective toxicities were experienced by 69% of 155 healthcare workers who took zidovudine for at least 1 week *(166)*. Despite the symptoms experienced by a majority of healthcare workers, laboratory evidence of significant objective toxicity was rare. The Italian Registry of Antiretroviral Postexposure Prophylaxis observed hemoglobin values in the 9.5 to 11 g/dL range in 3% of healthcare workers and a neutrophil count of <1,000 cells/mm^3 in two healthcare workers *(168)*. These same authors observed a transient increase of serum alanine aminotransferase to three times the upper limit of normal in seven healthcare workers. Prophylaxis was continued in each of these cases and all laboratory values returned to baseline within 1 to 2 weeks after a completed course of prophylaxis *(168)*. More recent studies have suggested improved adherence with the administration of newer regimens *(156,157,169,170)*.

An increasing body of evidence documents the toxicity of antiretrovirals other than zidovudine in uninfected healthcare workers and in patients with early (or primary) HIV infection. One study examined the effects of HAART on patients with primary HIV infection *(171)* Commonly reported side effects for protease inhibitors include nausea, diarrhea, headache, mild liver function test abnormality,

hyperglycemia, and nephrolithiasis *(42,172)*. A multicenter collaborative study for occupational exposures examined the safety and adherence with combination PEP regimens *(173)*. Thirty-six of fifty-four healthcare workers took two drugs (zidovudine plus lamivudine), 16 took three drugs (zidovudine plus lamivudine plus indinavir) and two workers took didanosine plus stavudine. Twenty-eight percent discontinued prophylaxis early because of symptoms. Liver function abnormalities developed in two individuals, and prophylaxis was discontinued in both cases. The first individual was also receiving isoniazid prophylaxis. The second individual was exposed concomitantly to HCV and HIV. This latter exposure resulted in acute hepatitis C infection; HIV was first diagnosed 12 months after the exposure *(173)*. Additional toxicity data are provided by a report of 10 healthcare workers receiving a three-drug combination regimen *(97)*. All 10 workers had some side effects, including gastrointestinal disturbance, fatigue, headache, and confusion. Three workers stopped PEP early because of symptomatology. Wang et al. *(163)* reported on the PEP experiences of healthcare workers enrolled in the HIV PEP Registry. Three hundred and eight of 492 (63%) enrolled healthcare workers took at least three antiretroviral agents. Three hundred and forty (76%) healthcare workers with 6 weeks of follow-up reported some symptoms while on PEP: nausea (57%), fatigue or malaise (38%), headache (18%), vomiting (16%), diarrhea (14%), and myalgias or arthralgias (6%). Median time to onset of each of the five most frequent symptoms was 3 to 4 days. Only 37 (8%) workers with 6 weeks of follow-up were reported to have lab abnormalities, most of which were unremarkable. Similar proportions of workers who took two drugs as compared with three drugs completed regimens as prescribed. However, significantly more healthcare workers taking three drug regimens reported adverse events. An additional report describing healthcare worker PEP experience indicated that 10/46 (22%) stopped treatment secondary to adverse events or symptoms *(174)*. Another review of individuals who received PEP reported that those who received zidovudine, lamivudine, and tenofovir or indinavir had increased rates of nausea and those who received zidovudine, lamivudine, and indinavir were more likely to complete the regimen than those who received a tenofovir-containing regimen *(170)*.

The immediate management of an occupational exposure should include the administration of first aid and rinsing and/or decontaminating of the exposure site as soon as is reasonably possible (i.e., as soon as patient and healthcare worker safety permits). At the Clinical Center of the NIH, we recommend the following management approach for healthcare workers who have sustained occupational exposures to HIV *(93,94)*. Wounds should be washed with soap and water, and then irrigated with sterile saline, a disinfectant or other suitable solution. Healthcare workers who have sustained a mucosal exposure involving the mouth and nose should flush the exposed area extensively with water or sterile irrigants. For exposures involving the eyes, the involved area(s) should be irrigated with clean water, saline, or sterile fluids designed as ocular irrigants. All exposures should be reported immediately to the employee's supervisor and to the institution's Occupational Medical Service. Each institution should work aggressively to develop mechanisms that facilitate both the reporting of exposures as well as the provision of follow-up care. The mechanisms should be widely publicized in the institution. Where feasible, institutions should offer access to consultants who are expert about the pathogenesis of HIV infection, the risk for occupational HIV infection, and the safety, efficacy, and known toxicities associated with the administration of antiretroviral agents. All institutional occupational medical systems must protect the confidentiality and medical privacy of the exposed worker. For healthcare workers who sustain documented occupational exposures to HIV, we advocate serologic studies at or as near to the exposure event as is possible (to document baseline seronegativity), with follow-up studies at 6 weeks, 3 months, 6 months and 1 year following exposure. All exposed workers should be offered the opportunity to take postexposure antiretroviral chemoprophylaxis (described above). Once the baseline serology, hematology, and chemistry studies are drawn, healthcare workers who elect chemoprophylaxis should be followed for signs of drug toxicity while on therapy. Studies that we routinely order for healthcare workers electing postexposure chemoprophylaxis are detailed in Table 74-4. Additional, supplementary studies, including direct measurement of the HIV viremia, are ordered if the healthcare worker develops symptoms suggestive of the seroconversion illness.

MANAGEMENT OF THE HIV-INFECTED HEALTHCARE WORKER

In July 1990, the CDC published a report of possible iatrogenic transmission of HIV to a patient during an invasive dental procedure *(175)* followed 6 months later by another report documenting identification of four additional patients apparently infected with HIV by the same dentist in Florida *(176)*. Two years later, a sixth patient was also identified as having been infected with the same strain of HIV as that from the dentist *(177)*. These events, as well as the drama surrounding the tragic stories of the infected patients of the dentist who have chosen to make their plights public, alarmed the public, and prompted calls for practice restrictions for HIV-infected healthcare workers.

Assessment of Risk for Transmission of HIV from Healthcare Worker to Patient

Discovery of the cluster of patients infected by the Florida dentist highlighted the need for additional data on the risk of HIV transmission from an HIV-infected provider to patients. These anecdotal cases of transmission, similar to the cases of transmission from patient to healthcare worker, indicate that provider-to-patient transmission is possible, but do not quantify the level of risk associated with infected providers. Scrutiny of the procedures that were performed by the dentist on the infected patients also provides little useful information, because some of the patients had no more than what would be considered "routine" (i.e., "noninvasive") dental work.

The second instance of transmission from provider-to-patient was reported from France *(178)*. An orthopedic surgeon most likely was infected with HIV in May 1983. The diagnosis of HIV infection and syndromic AIDS were made

TABLE 74-4

Summary of Laboratory Testing for Healthcare Workers Receiving Postexposure Prophylaxis

	HIV Antibody	*CBC with Differential*[a]	*Chemistry Panel*[b]	*Urine Pregnancy Test for Females*
Baseline	X	X	X	X
2 wk		X		
4 wk		X		
6 wk	X	[c]	[c]	
3 mo	X			
6 mo	X			
12 mo	X			
Suspected acute retroviral syndrome[d]	X	X	X	
Suspected drug toxicity	X	X		

[a]CBC with differential should consist of a basic hematology panel with white blood cell differential and platelet count.
[b]Chemistry panel should consist of routine electrolytes, glucose, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, bilirubin, and amylase.
[c]Only if previous results indicate toxicity.
[d] Direct measurement of HIV by PCR or other technique also indicated in this setting.

simultaneously in March 1994. Nine hundred and sixty eight of 3,004 of the surgeon's patients who had undergone at least one invasive procedure by the surgeon were serologically tested for HIV. One patient, who had undergone two very lengthy hip procedures in 1992 and 1993, was determined to have newly acquired HIV infection. While no specific exposure incidents were recognized during the procedures, the patient was seronegative before the operation performed by the surgeon, and had a particularly prolonged duration of exposure to risk (the initial procedure lasted more than 10 hours). The surgeon's viral load could have been elevated at the time of the operation on this patient, and phylogenetic analysis indicated a close relationship between the patient's and the surgeon's viruses. The French National Public Health Network believes the case for transmission, based on the epidemiologic investigation and confirmed by viral sequencing, to be highly probable *(178)*.

A third possible case of transmission, in this instance nurse-to-patient, was also reported from France in 2000 *(179)*. Phylogenetic analysis strongly suggests an HIV-infected nurse as the source of infection, although the authors do not provide any epidemiological information as to the possible route of infection. The nurse was also co-infected with HCV, and both HIV and HCV were diagnosed 3 weeks after she provided care for the patient and transmission likely occurred. At the time of diagnosis, the source nurse had an HIV viral load of 1.8×10^5 copies/mL; her CD4 count was 94 per mm^3, and she was diagnosed with advanced hepatic cirrhosis with a blood clotting disorder *(180)*. Hepatitis C was not transmitted to the patient. Investigators suggest that the nurse's high viral load associated with severe blood clotting disorders may have enhanced the risk of HIV transmission, although the nurse reported no percutaneous blood injury. A lookback study reported testing 2,310 of 7,580 patients (30%), and no additional cases of HIV infection were identified *(180)*.

A fourth case of provider to patient transmission of HIV apparently occurred in Spain. In this instance a woman was apparently infected with HIV by her obstetrician/gynecologist during a caesarian section. A look-back evaluation identified 275 of the physician's patients on whom the practitioner had performed procedures. Of these, 250 could be tested, and no additional infections were identified *(181)*.

Based on our knowledge of routes of transmission from patients to providers, the primary risk for transmission of HIV is through exposure of the patient's bloodstream to blood from an infected provider *(182)*. Based on this assumption, most authorities have concluded that routine patient-care activities pose no measurable risk for transmission *(72,183)*. The CDC recommends that, if Universal/Standard Precautions and the correct infection control procedures are followed, infected healthcare workers should not be restricted from performance of routine patient-care activities including drawing blood or starting intravenous lines. In order to transmit infection, a sharp object would first have to be contaminated with the provider's blood and then would have to recontact the patient's tissues. Whereas a number of studies have described the risk for surgeons sustaining exposures during surgical procedures *(184–187)*, none of these studies attempted to assess the "recontact" risk. Two direct observational studies have attempted to address the patient's risk for exposure to a provider's blood during a surgical procedure *(188,189)*. In the first study, investigators from the CDC estimated that a surgical "sharp object" that had potentially injured a resident or attending surgeon had approximately a one in three chance of recontacting the tissues of the patient. This estimate was based on 28 "recontacts" following 88 observed injuries in surgeons; other authorities, including surgeons with years of operative experience, feel that this estimate of 32% may substantially overestimate the actual recontact risk. In the second preliminary study addressing potential for "recontact" injuries, occupational injuries during surgery were categorized as "definite" and "possible" *(189)*. These investigators found that three of nine "definite" provider injuries recontacted the patient, while two of seven "possible" injuries recontacted the patient.

In response to the Florida case cluster, CDC issued guidelines for HIV and HBV infected providers in July of 1991 *(72)*. From an implementation perspective, three aspects of these guidelines were challenging: (a) to implement the guideline, one needed to be able to characterize a subset of invasive procedures as "exposure-prone," (b) for infected providers to be able to conduct "exposure-prone" procedures, the provider would be required to notify patients prospectively of the provider's infection status, and (c) the guidelines required the convening of a Expert Review Panel but did not provide administrative or legal guidance about this function. These guidelines have not been modified since they were issued in 1991. The public anxiety associated with the Florida dentist case cluster prompted Congressional passage of a law (Public Law [PL] 102–141) requiring states to certify that they had implemented the July 1991 CDC/U.S. Public Health Service guidelines or their "equivalent." With the consultative assistance of several professional medical associations and professional societies, CDC attempted to develop a list of exposure-prone invasive procedures. Unfortunately no consensus could be reached. Ultimately, in 1992 Dr. William Roper, then the CDC Director, sent a letter to state health departments, noting that the states, not CDC, would certify the equivalency of their guidelines. As a result, substantial variability exists in state guidelines. Although the US guidelines have not been modified since their issuance, other countries have issued new guidances and several manuscripts have been published presenting various perspectives about this complex issue.

Guidelines issued from the United Kingdom provided one possible characterization of "exposure-prone" procedures *(190)*, and a manuscript published from the University of Virginia provided a second interpretation *(191)*. More recently, the Society for Healthcare Epidemiology in America (SHEA) published updated guidelines for managing the provider infected with bloodborne pathogens (192). The UK guidelines recommend that HIV-infected providers have their practices restricted *(72,190)*. Neither the US nor the UK guideline considers either the infected providers' clinical status or the HIV-infected provider's viral burden. The SHEA guideline recommends that HIV-infected providers who have circulating HIV viral burdens of $\geq 5 \times 10^2$ genome equivalents/mL routinely double-glove for all invasive procedures, for all contact with mucous membranes or nonintact skin, and for all instances in patient care for which gloving is recommended, and that they not perform those procedures identified as associated with a risk for provider-to-patient transmission of bloodborne pathogen infection despite the use of appropriate infection control procedures. The guideline recommends that HIV-infected providers who have viral burdens $< 5 \times 10^2$ genome equivalents/mL not be excluded from any aspect of patient care, including the performance of "exposure-prone" procedures, so long as the infected provider: (a) is not detected as having transmitted infection to patients; (b) obtains advice from an Expert Review Panel about continued practice; (c) is followed routinely by Occupational Medicine, who tests the provider twice annually to demonstrate the maintenance of a viral burden of $< 5 \times 10^2$ genome equivalents/mL; (d) is also followed by a personal physician who has expertise in the management of HIV infection and who is allowed by the provider to communicate with the Expert Review Panel about the provider's clinical status; (e) consults with an expert about optimal infection control procedures (and strictly adheres to the recommended procedures, including the routine use of double-gloves and frequent glove changes during procedures, particularly if performing technical tasks known to compromise glove integrity [e.g., placing sternal wires]); and (f) agrees to the information in, and signs, a contract or letter from the Expert Review Panel that characterizes her/his responsibilities (192).

The SHEA guidelines emphasize a "case-by-case" approach to this complex problem and note that whatever institutions decide, their approach has to be consonant with the State laws developed in the 1990s.

Lookback Notifications for Patients of Infected Providers

A series of retrospective "lookback" studies have provided additional, albeit indirect, information about the risk of HIV transmission from provider to patient. In all of these studies, patients have been offered HIV testing retrospectively after a healthcare provider has been determined to be HIV-infected. According to the CDC, 51 HIV-seropositive healthcare workers had prompted HIV antibody testing of 22,171 patients by January 1, 1995 *(193)*. To date, no additional iatrogenic infections have been documented in these studies. In fact, no HIV-infected patients have been identified for 37 of these infected healthcare workers; one or more HIV-infected patients were identified for 14 healthcare workers (the number of HIV-infected patients per healthcare worker ranged from 1–41). Of the 113 infected patients identified in these lookback studies, investigations have been completed for 110 patients. Twenty-eight were known to have been previously infected, 62 had established risk factors other than care by an HIV-infected provider, 15 had other potential chances for exposure (e.g., exchange of sex for drugs or money and/or multiple sex partners), and 5 had no risk identified. Genetic sequencing of the virus in the case of the infected Florida dentist indicated that six of the nine HIV-infected patients in the practice were infected with HIV strains that were closely related to those of the dentist *(194,195)*.

The large series of well publicized lookback studies that have been published from the United States *(196–206)* may imply that lookback studies are now a standard of care whenever an HIV-infected healthcare worker who has performed invasive procedures in his or her practice is publicly identified. Indeed, many of these studies were the response of an institution or public health agency to a public outcry precipitated by discovery of an infected provider. Epidemiologists and other professionals responsible for follow-up of an infected provider must bear in mind that the risk of transmission associated with patient contact and even most, if not all, invasive procedures is negligible, and many experts argue that these studies are of extremely limited utility. The CDC has concluded that the risk for transmission of HIV from a healthcare worker to a patient is very small, and that retrospective patient notification need not be routine *(193)*.

According to guidelines published by the Society for Hospital Epidemiology of America, lookback notification should be considered in the following circumstances: (a) after a proven case of transmission of HIV, hepatitis B, or any other bloodborne pathogen to an index case and (b) following a

serious breach in infection control practices during invasive procedures performed by an infected healthcare worker *(183)*. Lookback studies should not be undertaken for HIV-infected healthcare workers who do not perform invasive procedures. Two of the published lookback studies also detailed the costs incurred. Danila et al. *(198)* estimated that the costs associated with a study of an HIV-infected family physician totaled approximately $130,000, which was one-third of the entire annual Minnesota Department of Health budget for statewide AIDS and HIV surveillance. A second lookback study estimated that the total costs incurred by initial patient notification and testing were $158,500 *(206)*. Given the current efforts to control spiraling healthcare costs, lookback notifications may, in general, be an inappropriate use of diminishing resources.

Similarly guidelines from the United Kingdom National Health Service (*www.doh.gov.uk/aids*) advise that it is no longer necessary to notify every patient who has undergone an exposure-prone procedure by an infected healthcare worker because of the low risk of transmission and the anxiety caused to patients and the wider public. The National Health Service defines three categories of exposure-prone procedures; only for category 3 procedures where fingertips are out of sight for a significant part of the procedure and in which there is a distinct risk of injury (e.g., hysterectomies, caesarian sections, and open cardiac surgery procedures) is patient notification necessary.

Policy Issues

In summary, only four instances (nine patients infected by four healthcare workers) of iatrogenic HIV transmission have been documented in the 25 years since testing for HIV became widely available. Additionally, the published risk estimates, even with their inherent limitations, support the conclusion that the risk of HIV transmission from provider to patient is extremely small, perhaps negligible, even during invasive procedures. Clearly, we all face, and accept, risks of a much higher magnitude each day.

Another traditional concern of the medical establishment is that of *primum non nocere*. This concept is reinforced from each provider's first days as a student in a healthcare profession, yet we all recognize that doing no harm is impossible. The realistic goal is to minimize the harm that we do while keeping risks in appropriate perspective. Other risks, including such issues as the competence levels of practicing providers and provider substance abuse, undoubtedly result in a much higher level of patient morbidity and mortality than the risk associated with competent HIV-infected providers. Thus, to reduce patient risk, one could certainly marshal a cogent argument for implementing routine drug and alcohol testing and mandatory competence reviews of healthcare professionals rather than implementing mandatory HIV-testing programs.

A third issue of concern relates to disability law and the concept of "significant risk." The concept of significant risk was adopted in the School Board vs. Arline case *(207)*, in which the US Supreme Court determined that a disabled teacher who had chronic tuberculosis could not be discharged from her job because she was disabled as a result of her condition and did not present a significant risk for transmission of tuberculosis. This concept has been reaffirmed twice, in the Civil Rights Restoration Act of 1988 (PL 100–259, 134, Congressional Record H.587–8) and, more recently, in the Americans with Disabilities Act of 1990 (PL 101–336, 104 Stat. 327). Mandating practice restrictions in order to reduce a risk that is lower than other accepted risks would essentially undermine current disability law by legally redefining the concept of significant risk *(208)*.

The issues surrounding the management of providers infected with bloodborne pathogens are exceedingly complex. As more knowledge is gained about the risks for iatrogenic spread of hepatitis B, hepatitis C, and HIV, management strategies may become more straightforward. The constellation of problems associated with the management of HIV-infected healthcare workers will undoubtedly continue to haunt the medical profession for years to come. Obtaining data to aid decisions about the most appropriate management of infected providers will be extraordinarily difficult given existing societal perceptions and the magnitude of risk associated with infected providers. Nonetheless, as a discipline, the healthcare epidemiology community must assume leadership through educational efforts and by placing these risks into appropriate perspective with other risks, whether occupational, iatrogenic, or societal (192). Finally, based on our current understanding of the magnitude of risk for provider-to-patient transmission of bloodborne pathogens, we feel that prevention efforts should be focused on strategies to prevent occupational exposures to blood and body fluids. We believe the limited research capital available should be used to develop: (a) devices and procedures that minimize risks of injury, (b) interventions that influence improvements in practitioners' workplace practices, (c) better and more effective approaches to the education of healthcare workers and patients about risks and risk perception, and (d) sensible strategies to manage these risks.

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CHAPTER 75

Vaccination of Healthcare Workers

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It has been said that sanitation and vaccination have made the two greatest contributions to the health of mankind. This importance is mirrored within healthcare institutions. For healthcare personnel (HCP) and for their patients, sanitation (better known within hospitals as hygiene or infection control) may be the first line of defense against infectious agents, but HCP vaccination is an essential second line of defense to prevent spread of infection from patients to HCP, among HCP, and from HCP to patients.

Accordingly, ensuring the immunity of HCP to infection or disease caused by relevant infectious agents is an essential component of any healthcare institution's occupational health program, to accomplish two fundamental legal and moral duties: protection of the workers from the risks of the workplace, and protection of the patients from the risks posed by infectious HCP.

High rates of immunity among HCP are required if patients are to be protected from infection spread by HCP, as even a single infected worker can expose many patients. Unfortunately, it has proven impossible to attain the necessary high vaccination rates through purely voluntary programs. Screening has repeatedly shown substantial proportions of hospital staff to be susceptible to vaccine-preventable diseases, in the absence of a policy requiring immunity. For example, numerous studies of hospital workers in the early 1990s showed that 5% to 10% were susceptible to measles, despite national recommendations regarding measles immunity *(1–5)*. Indeed, the last major outbreaks of measles in the United States were predominantly fueled by spread within healthcare institutions. As cohorts born after the disappearance of epidemic measles enter the workforce, the proportion susceptible will increase unless immunity is confirmed and vaccinations provided to the susceptible. For example, a recent study reported that 9% of adult HCP hired at a cancer hospital between 1998 and 1999 were seronegative for measles antibody, compared with 4% of those of the same age hired between 1983 and 1988 *(6)*.

The problem of continued HCP susceptibility to vaccine-preventable diseases is not, of course, limited to measles. Even following adoption by the Occupational Safety and Health Administration (OSHA) of the Bloodborne Hazard Standard, with its requirement to offer hepatitis B vaccine to all exposed workers, substantial numbers of healthcare workers (HCWs) remain susceptible (particularly physicians, who typically are not employees and thus not subject to the standard). Similarly, surveys of HCP have reported low rates of acceptance of influenza immunization. Selected studies of hepatitis B and influenza vaccine coverage rates are shown in Table 75-1 (*7–23,*24,*25,26,*27).

Many institutions (and some jurisdictions) have adopted policies requiring the demonstration of immunity to selected diseases as a condition of service in various capacities or units. Although the proportion of institutions with such policies continues to increase, as recently as 1995, a survey of children's hospitals showed the following frequency of policies requiring measles, mumps, rubella, and varicella vaccination: medical students, 47% to 74%; resident physicians, 70% to 91%; hospital-based physicians, 40% to 55%; and private or community-based physicians, only 15% to 26% *(28)*.

Although one might argue that it is the worker's right to decline vaccination and accept the risk of infection, no one would argue that the worker has a right to infect patients. Accordingly, we consider "informed refusal" of vaccination to be permissible only for infections that are not expected to place the patient at jeopardy. (For employees, hepatitis B has been placed in this category as a matter of law by the Bloodborne Hazards Standard, despite numerous outbreaks of healthcare provider-to-patient transmission of hepatitis B; but physicians typically are not employees, and vaccination can be made a condition of admitting or other privileges, even if not a condition of employment.) For those vaccine-preventable infections among HCP that place patients at risk, we urge the adoption of policies that make demonstrated immunity (or valid medical waiver) a condition of employment (or privileges) in positions that would place the patient at risk in the event of HCP infection.

ORGANIZATION OF THE IMMUNITY (VACCINATION) PROGRAM

As alluded to above, it is important that the occupational health team understand that they need to operate an immunity program, not simply a vaccination program. The goal is to identify the susceptibilities of the workers to relevant infections and to take such steps (typically, vaccination) as may be appropriate to ensure their continued immunity.

TABLE 75-1

Hepatitis B and Influenza Vaccine Coverage of HCP: Selected Studies

Vaccine	*First Author*	*Year(s)*	*Study Location*	*HCP Evaluated*	*Immunization Rate*
Hepatitis B	Shapiro *(7)*	1991	3,411 orthopedic surgeons	Orthopedics	65%
	Panlilio *(8)*	1991–1992	21 hospitals	Surgical services	55%
	Agerton *(9)*	1992	150 hospitals, United States	All staff	51%
	Cleveland *(10)*	1992	US dentists	Dentists	85%
	Gyawali *(11)*	1994	London teaching hospital	Staff with blood exposure	78%
	Mahoney *(12)*	1994–1995	200 US hospitals	Staff eligible for hepatitis B vaccine	67%
	Simard *(13)*	2002–2003	425 US hospitals	At-risk HCP	81%, MDs/RNs; 71%, phlebotomists
Influenza	Weingarten *(14)*	1986–1987	Los Angeles hospital	House staff and nurses	3.5%
	Nichol *(15)*	1993–1994	Minneapolis hospital	Physicians and nurses	61%
	Zadeh *(16)*	1995–1998	Nursing homes, nine US states	All staff	46%
	Cui *(17)*	1996–1998	43 nursing homes, Hawaii	All staff	38%
	Russell *(18)*	1998	136 nursing homes, Alberta, Canada	All staff	30%
	Stevenson *(19)*	1999	Nursing homes, Canada	All staff	35%
	Seale *(20)*	2007	Two teaching hospitals in Sydney, Australia	1,079 HCP	22%
	Ballestas *(21)*	2008	Five hospitals in Perth, Australia, participating in a vaccination–rate improvement campaign	11,501 HCP	56–77% (29–51% in the precampaign year)
	Caban-Martinez *(22)*	2004–2008	National Health Interview Survey, U.S.	6,349 US HCP	46–49% overall; 38–42% for nurses
	Kent *(23)*	2007–2008	Health department staff, North Carolina	1,653 county public health workers	72%
	Ajenjo (24)	1997–2007	Large US health chain	26,000 workers (voluntary program)	Increased from 45% (1997) to 72% (2007)
	Babcock *(25)*	2008	Same large US health chain	26,000 workers (mandatory program)	98%
	Rakita *(26)*	2005–2009	Teaching hospital, Washington, United States	5,000 employees (mandatory program)	98–99%
	Palmore (27)	2009	NIH Clinical Center, Baltimore	2,754 HCP (mandatory program with exceptions)	88%

The services provided by the institution, and the characteristics of the patient populations served, need to be considered in determining these policies. Some infections (e.g., rubella and varicella) are much more likely to be associated with serious complications in adult HCP, and at the same time some infections that are common and often minor among HCP can be life threatening to patients with underlying chronic illnesses (e.g., influenza), immunosuppression (e.g., vaccinia), etc. The presence of special programs or populations (e.g., transplant units) will further alter the nature and scope of the vaccination and immunity policies. With these considerations in mind, the institution must decide which of the infections with potential for spread to, or through, HCP, warrant monitoring of HCP immunity; which warrant offering of immunization to the susceptible (with the option to decline); and which warrant mandatory immunization (or demonstrated immunity).

The institution has no obligation under the Occupational Safety and Health Act with respect to workers (e.g., volunteers, medical or other students, contract workers, etc.) who are not employees. Unfortunately, because microbes are unaware of this legal nuance, patient protection requires that the institution's vaccination and immunity policy apply to all workers, irrespective of their employment status, including workers with direct patient care responsibilities (e.g., nurses, respiratory technicians,

physical therapists, physicians, students), workers without direct patient care responsibilities (e.g., environmental service workers, security), contract or service workers, and emergency medical personnel.

All HCP new to a healthcare facility should receive a prompt review (within 10 working days) of their immunity with respect to vaccine-preventable diseases. Immunity is most commonly demonstrated by written documentation of immunization; for those persons requesting exemption on the basis of natural infection, serologic documentation of immunity should be required (the predictive value of a physician diagnosis is no longer adequate, given the current rarity of these diseases). Unless immune, the HCP should be appropriately immunized. As a general rule, serologic screening for immunity before immunization is neither necessary nor cost-effective. However, healthcare facilities might find certain screening programs to be cost-effective, given the cost of the screening test, the cost of the vaccine, and the prevalence of immunity in the local HCP population. In addition, facilities might wish to permit screening at the worker's request (either at the institution's or the worker's expense).

The institution may also wish to make available to HCP vaccinations that are not necessary for the protection of patients but that are indicated for other reasons. For example, the establishment and maintenance of immunity to diphtheria and tetanus toxins is universally recommended, and ensuring the timely provision of tetanus and diphtheria toxoid (Td; or, if not previously received, tetanus, diphtheria, and acellular pertussis [Tdap]) boosters through the occupational health service will eliminate concerns about tetanus prophylaxis in the event of (possibly unreported) occupational injury.

When vaccines are provided, appropriate information should be recorded in the employee's medical record (Table 75-2) and tracked electronically (either through a computerized employee vaccination registry or an electronic medical record). Computerized records greatly facilitate recall for boosting and identification of susceptibles in the event of an exposure or outbreak. Signed informed consent (or refusal, if appropriate) specific to each vaccine should be obtained before immunization. Vaccine information statements *(29)* must be provided for vaccines covered by the National Childhood Vaccine Injury Act (including measles, mumps, rubella, polio, diphtheria, tetanus, pertussis, hepatitis A, hepatitis B, *Haemophilus influenzae* type b, influenza, human papillomavirus, meningococcal conjugate, pneumococcal conjugate, and varicella vaccines). Vaccine information statements are also available for yellow fever and smallpox vaccines. Clinically significant or unexpected adverse events occurring after immunization should be reported to the Vaccine Adverse Events Reporting System *(30)*, as should any event listed by the vaccine manufacturer as a contraindication to subsequent doses of vaccine OR any event listed in the Reportable Events Table (available at *http://www.vaers.hhs.gov/reportable.htm*) that occurs within the specified time period after vaccination.

The immunization status of all HCP should be recorded in their employee medical record. A mechanism should be established to track immune status, including the need for and timing of repeat immunization, with effective recall and enforcement provisions.

TABLE 75-2

Data to Record When Providing Vaccines to HCP

Employee name
Employee identification number
Date of birth
Signed informed consent (or refusal, if relevant)
Date of immunization (or refusal)
Vaccine provided (or declined)
Name of vaccine manufacturer
Lot number of vaccine
Site of immunization
Route of immunization
Date of next scheduled dose or booster (if applicable)
Adverse events (if any)
Name, title, and address of person providing vaccine

VACCINES RECOMMENDED FOR HEALTHCARE WORKERS: GENERAL GUIDELINES

Recommendations regarding the vaccination of HCP have been issued by the Centers for Disease Control and Prevention (CDC) and its advisory bodies, the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC) (31–37), the American College of Physicians (ACP) *(38)*, the American Academy of Pediatrics *(39)*, and others (*40–42,*43). Many of these recommendations are updated periodically (see Table 75-3 for online sources of information).

All HCP should be immune to mumps, measles, rubella, varicella, and pertussis, and all HCP with potential exposure to blood or body fluids should be immune to hepatitis B (Table 75-4). Influenza vaccine should be offered to all HCP yearly (and strongly encouraged, if not mandated). In special circumstances, HCP or laboratory personnel should be offered immunization with other vaccines, including (no longer recommended) hepatitis A, quadrivalent meningococcal, inactivated poliomyelitis, rabies, typhoid, and vaccinia (Table 75-5).

Before the administration of any vaccine, the HCP should be evaluated for the presence of any condition that is listed as a vaccine contraindication or precaution *(44)*. If such a condition is present, the risks and benefits of vaccination need to be carefully weighed by the healthcare provider and the employee. The most common contraindication is a history of an anaphylactic reaction to a previous dose of the vaccine or to a vaccine component. Factors that are not contraindications to immunization include the following: breast-feeding or household contact with a pregnant woman (exception: vaccinia); reaction to a previous vaccination consisting only of mild-to-moderate local tenderness, swelling, or both, or fever less than 40.5°C; mild acute illness with or without low-grade fever; current antimicrobial therapy (except for oral typhoid vaccine) or convalescence from a recent illness; personal history of allergies (except a history of an anaphylactic reaction

TABLE 75-3

Online Sources for Current Vaccine Information and Vaccination Recommendations

General Information Concerning Vaccines and Vaccine-Preventable Diseases
CDC: *http://www.cdc.gov/nip/vaccines*
Allied Vaccine Group: *http://www.vaccine.org/*
American Academy of Pediatrics Childhood Immunization Support Program: *http://www.cispimmunize.org/index.html*
ACPs Adult Immunization Initiative: *http://www.acponline.org/aii/?hp*
The Immunization Action Coalition: *http://www.immunize.org/*
Recommendations
ACIP: *http://www.cdc.gov/vaccines/pubs/ACIP-list.htm*
HICPAC: *http://www.cdc.gov/hicpac/*
Major Vaccine Manufacturers (login not required for package inserts and other selected information)
GlaxoSmithKline: *http://gskvaccines.com/*
Merck: *http://www.merckvaccines.com/vaccineInfo_frmst.html*
Novartis: *http://www.novartisvaccines.com/*
Pfizer (Wyeth): *http://www.wyeth.com/vaccines*
Sanofi Pasteur: *https://www.vaccineshoppe.com/*

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; HICPAC, Hospital Infection Control Practices Advisory Committee.

to a vaccine component); and family history of allergies, adverse reactions to vaccination, or seizures *(38)*.

Special Conditions

HCP who are immunocompromised, pregnant, or have certain underlying chronic diseases can pose special considerations in the provision of immunizations (Table 75-6) *(45–59)*. Some routinely recommended vaccines (especially live virus vaccines such as measles, mumps, rubella, and varicella) may be contraindicated, and some vaccines that are not routinely recommended for HCP may be indicated (e.g., pneumococcal, meningococcal, and *H. influenzae* type b vaccines). In addition, for some indicated vaccines, higher antigen doses or postimmunization serologic evaluation may be indicated (e.g., hepatitis B vaccine in people with renal failure). When an otherwise mandatory vaccine is contraindicated for a given HCP, the worker should be individually evaluated for the possibility of altering his or her assignment to reduce risk to patients or to the HCP. The decision to reassign such a worker should be made in consultation with the employee.

Pregnancy Immunization of pregnant HCP raises a number of issues. For some live-attenuated and all inactivated or toxoid vaccines, the risks from immunization during pregnancy are largely theoretical (36,*38*). For such vaccines, the benefit of immunization outweighs the potential risks for adverse reactions, especially when the risk of exposure is high, infection would pose a special risk to the mother or fetus, and the vaccine is unlikely to cause harm. Furthermore, newer information continues to confirm the safety of vaccines given inadvertently during pregnancy.

No reliance should be placed on the presumption that certain vaccines "must have" been given in childhood or adolescence. HCP come from many countries, with differing vaccination programs; many children fail to receive various "routine" vaccinations, either through inadvertence or deliberate avoidance; and even if vaccinated, immunity may not have been produced. Accordingly, reliance should be placed only on objectively verifiable records of vaccination or serological assay. It is especially important that serological proof of immunity be obtained for all HCP without documentation of two separate vaccinations with rubella-containing vaccine, given the concern for both the worker and the patient populations regarding the consequences of this infection on the fetus.

Because of the theoretical risks, live attenuated viral vaccines (mumps, measles, rubella, and varicella) should be deferred for pregnant women. Pregnant HCWs may receive combined tetanus and Td (36,*60*). All women who are pregnant or will be pregnant during influenza season should receive influenza immunization *(61)*. If otherwise indicated, susceptible pregnant women may receive hepatitis A, hepatitis B, inactivated influenza, meningococcal, pneumococcal, rabies, typhoid Vi polysaccharide, and inactivated poliomyelitis vaccines (formulations containing trace or no thimerosal are preferable, when available) (36). Breast-feeding does not adversely affect the response to immunization and is not a contraindication for any of the currently recommended vaccines. The indications for using immune globulins in pregnant women are the same as those for women who are not pregnant.

USE OF VACCINES FOR POSTEXPOSURE PROPHYLAXIS OR OUTBREAK CONTROL

Those who have had to respond to the spread within their institution of a vaccine-preventable illness understand quite clearly how preferable it is to have previously vaccinated their HCP. The virtual impossibility of identifying and immunizing susceptible HCP sufficiently rapidly during an outbreak of measles, mumps, rubella, or varicella to avoid spread to another generation of susceptible HCP or patients offers a powerful inducement for policies requiring immunity before assignment to duty. Moreover, these vaccines are not known to provide protection when given to a susceptible person following exposure. In contrast, tetanus toxoid (Tdap is preferred, if not previously received) (*62*,63), hepatitis B vaccine *(64)*, vaccinia *(53)*, and rabies vaccine *(49)* are effective when given promptly following exposure, and hepatitis A vaccine may provide at least partial protection *(65)*. Varicella vaccine may provide protection if given within 72 hours of exposure, but it should not be relied on to prevent further transmission by exposed HCP because of incomplete efficacy *(66)*. Immunization of HCP with hepatitis A, meningococcal, or acellular pertussis vaccine may be indicated to control an institutional or community outbreak. In the event of widespread influenza activity, additional supplies of influenza vaccine may be difficult to obtain, adding further importance to a robust annual influenza vaccination

TABLE 75-4

Vaccines Strongly Recommended for All Persons Who Provide Healthcare to Patients or Who Work in Institutions that Provide Healthcare

Vaccine	*Recommendation*	*Schedule (Adults)*	*Major Contraindications*	*Special Considerations*
Hepatitis B	All HCPs at risk for exposure to blood or body fluids. Vaccinate unless laboratory evidence of immunity or prior receipt of three doses of vaccine with an appropriate schedule is documented.	1.0 mL IM (deltoid) at 0, 1, 6 mo; booster doses not necessary	Hypersensitivity to common baker's yeast.	Prevaccination serologic screening is not necessary. Perform post-vaccination serologic testing for HCPs at high risk for continued exposure. HCPs who have contact with patients or blood should be tested 1–2 mo after vaccination to determine response (see text).
Influenza	All HCPs should receive annual seasonal influenza vaccine. Consideration should be given to requiring vaccination (unless appropriately exempted) as a condition of presence within the healthcare institution. The Schedule and Contraindications shown are for trivalent inactivated vaccine (see Special Considerations).	0.5 mL IM yearly	Hypersensitivity to eggs (or thimerosal, for formulations containing thimerosal). No evidence exists of risk to mother or fetus when the vaccine is administered to a pregnant woman.	Trivalent inactivated vaccine is preferred over live attenuated intranasal vaccine for immunization of HCPs, due to the theoretical risk of spread to immunosuppressed and other at-risk patients.
Measles	All HCPs (including those born before 1957) who cannot document either receipt of two doses of live vaccine on or after their first birthday or laboratory evidence of immunity should receive a total of two doses of vaccine. MMR is preferred unless immunity to mumps and rubella is documented.	0.5 mL SC, second dose at least 1 mo later	Pregnancy; hypersensitivity to gelatin, neomycin, or eggs; immunocompromised state[a]; recent receipt of immunoglobulin.	Persons vaccinated during 1963–1967 with a killed measles vaccine alone, killed vaccine followed by live vaccine, or with a vaccine of unknown type should be revaccinated with 2 doses of live measles virus vaccine.
Mumps	Vaccinate (2 doses) unless born before 1957, laboratory evidence of immunity or laboratory confirmation of disease, or prior receipt of 2 doses of vaccine is documented. MMR preferred unless contraindicated or immunity to measles and rubella is documented.	0.5 mL SC, no booster	Pregnancy; hypersensitivity to gelatin, neomycin, or eggs; immunocompromised state[a]; recent receipt of immunoglobulin.	For unvaccinated personnel born before 1957 who lack laboratory evidence of mumps immunity or laboratory confirmation of disease, healthcare facilities should consider (and during an outbreak should require) 2 doses of vaccine.

(*Continued*)

TABLE 75-4

Vaccines Strongly Recommended for All Persons Who Provide Healthcare to Patients or Who Work in Institutions that Provide Healthcare (*Continued*)

Vaccine	*Recommendation*	*Schedule (Adults)*	*Major Contraindications*	*Special Considerations*
Pertussis	Recommended for all persons aged 11–65 who have not yet received a dose. All HCP with direct patient contact should receive Tdap as soon as feasible.	0.5 mL IM. Booster schedule not yet determined, but likely will be similar to Td.	Hypersensitivity to any component of the vaccine.	
Rubella	Vaccinate unless male born before 1957[b], laboratory evidence of immunity or laboratory confirmation of disease, or prior receipt of vaccine. MMR is preferred unless contraindicated or immunity to measles and mumps is documented.	0.5 mL SC, no booster	Pregnancy; hypersensitivity to gelatin or neomycin; immunocompromised state[a]; recent receipt of immunoglobulin.	For unvaccinated personnel born before 1957 who lack laboratory evidence of rubella immunity or laboratory confirmation of disease, healthcare facilities should consider (and during an outbreak should require) 1 dose of vaccine.
Varicella	All personnel should have evidence of immunity (see Special Considerations). Vaccinate unless physician-diagnosed disease, laboratory evidence of immunity or disease, or prior receipt of vaccine is documented. A personal history of disease is not acceptable unless reviewed and confirmed as unambiguous by a healthcare professional.	0.5 mL SC, second dose 4–8 wk later if ≥13 y of age	Pregnancy; hypersensitivity to gelatin or neomycin; immunocompromised state[a]; recent receipt of immunoglobulin. Avoid salicylate use for 6 wk after vaccination.	Susceptibles can be identified by serotesting all HCPs or only those with a negative or uncertain history of chickenpox; or, institutions may simply immunize all those with a negative or uncertain history.

Note: The package insert and ACIP recommendations should be consulted for specific guidance regarding indications, storage, administration, precautions, and contraindications.
[a]Persons immunocompromised because of immune deficiency diseases, human immunodeficiency virus infection, leukemia, lymphoma or generalized malignancy, or immunosuppressed as a result of therapy with corticosteroids (i.e., ≥2 mg/kg body weight or 20 mg/day of prednisone for ≥2 wk, alkylating drugs, antimetabolites, or radiation). Also see Table 75-6.
[b]Many authorities would also vaccinate males born before 1957 unless immunity is demonstrated.
IM, intramuscularly; MMR, measles, mumps, and rubella vaccine; SC, subcutaneously.
(Data from references 32, 33, 34, and 43.)

program. Outbreaks of measles or polio are now highly unlikely (except, perhaps, in distinct communities that reject vaccination), but either would trigger large-scale immunization drives. Finally, passive vaccination with immunoglobulin is useful for postexposure prophylaxis for hepatitis A, hepatitis B, measles, rabies, tetanus, varicella, and vaccinia. Unfortunately, postexposure prophylaxis (vaccine and/or immunoglobulin) is not available to prevent rubella or mumps following an exposure.

GUIDELINES FOR THE USE OF SELECTED VACCINES

The following subsections provide additional information regarding the vaccine-preventable diseases for which immunization of HCP is recommended, either universally (Table 75-4) or in special circumstances (Table75-5). For each vaccine, administration schedules and contraindications

TABLE 75-5

Vaccines that May Be Indicated for HCP or Laboratory Personnel

Vaccine	*Recommendation*	*Schedule*	*Major Contraindications*	*Special Considerations*
BCG (for tuberculosis prevention)	Indicated for HCPs only in localities where (a) multidrug-resistant tuberculosis is prevalent; (b) ongoing transmission to HCPs exists; and (c) full implementation of infection control precautions has been inadequate in controlling the spread of infection.	One percutaneous dose of 0.2–0.3 mL, given by multipuncture device; no booster recommendation	Immunocompromised state[a] or pregnancy	BCG vaccination of US HCP is discouraged as it would interfere with subsequent PPD screening programs and can result in complications.
Hepatitis A	Not routinely indicated for HCP. Persons who work with HAV-infected primates or with HAV in a research laboratory setting should be vaccinated.	Two 1.0-mL doses IM, 6–18 mo apart (*Vaqta*) or 6–12 mo apart (*Havrix*)	History of anaphylaxis to a previous dose; hypersensitivity to latex or neomycin.	
Meningococcal (serogroups A, C, Y, W135)	Not routinely indicated for HCP except personnel with laboratory or industrial exposure to *N. meningitidis* aerosols. May be useful during an outbreak due to a type included in the vaccine. Conjugate preferred (see Special Considerations).	0.5 mL IM; consider booster dose within 3 (polysaccharide) to 5 (conjugate) y if exposure continues	Conjugate: known history of Guillain-Barré Syndrome or latex allergy. Polysaccharide: Sensitivity to thimerosal (used in multidose presentation only) or to latex.	Although conjugate vaccines are not yet licensed for those >55 y, they have important immunological advantages and off-label use should be considered.
Poliomyelitis	All persons should be immune. Immune status should be confirmed for HCPs in close contact with people who may be excreting wild virus and laboratory personnel handling specimens that may contain wild virus.	Unimmunized adults: two doses of IPV given SC 4–8 wk apart, followed by a third dose at 6–12 mo	Hypersensitivity to 2-phenoxyethanol, formaldehyde, neomycin, streptomycin, or polymyxin B.	Use only IPV. OPV can, rarely, result in paralysis of recipients or their contacts (OPV is not available in the United States).
Rabies	Not routinely indicated for HCP except personnel working with rabies virus or infected animals in diagnostic or research activities	Preexposure: 1.0 mL IM on days 0, 7, and 21 or 28. Follow standard guidelines for postexposure prophylaxis	*Imovax*: None. *RabAvert (PCEC)*: Hypersensitivity to bovine gelatin, chicken protein, neomycin, chlortetracycline, or amphotericin B.	Postexposure prophylaxis boosters may be required despite primary immunization
Typhoid	Not routinely indicated for HCP except laboratory personnel who frequently work with *Salmonella typhi*	One 0.5-mL dose IM (Vi polysaccharide vaccine); booster doses of 0.5 mL every 2 y; *or* Four oral doses (Ty21a) on alternate days; revaccinate with the entire 4-dose series every 5 yr	History of severe local reaction or anaphylaxis to a previous dose of vaccine. Ty21a should not be administered to immunosuppressed[a] persons or to persons receiving antimicrobials.	Do not use the killed whole-cell vaccine. The Vi polysaccharide vaccine (*Typhim VI*) may be preferable because Ty21a (*Vivotif*) is a live attenuated product that poses a theoretical risk of transmission to patients by recently immunized HCPs.

(*Continued*)

TABLE 75-5

Vaccines that May Be Indicated for HCP or Laboratory Personnel (*Continued*)

Vaccine	*Recommendation*	*Schedule*	*Major Contraindications*	*Special Considerations*
Vaccinia	Not routinely indicated for HCP except personnel who directly handle cultures or animals contaminated with recombinant vaccinia or orthopox viruses (monkeypox, cowpox) that infect humans, or as part of "Pre-Event Vaccination Program" (see Special Considerations).	One dose administered with a bifurcated needle; boosters every 10 y	Pregnancy; breastfeeding; history of eczema in worker or close family contacts; other acute, chronic, or exfoliative skin conditions; immunosuppression in vaccine recipient or household contact; hypersensitivity to polymyxin B, streptomycin, tetracycline, neomycin, glycerin, or phenol.	Vaccine is available only from CDC Drug Services. A bioterrorism-related "Pre-Event Vaccination Program" was conducted among HCP in 2002 and early 2003 but is currently inactive.

Notes:
1. Excluded are vaccines not currently available in the United States for civilian use (e.g., anthrax, plague).
2. This table only considers indications related to occupational exposures of HCPs; these and other (e.g., Td, pneumococcal, etc.) vaccines may be indicated for persons, whether HCP or not, who meet certain exposure or risk criteria.
3. ACIP recommendations and the current package insert for the selected product should be consulted for specific guidance regarding indications, storage, administration, precautions, and contraindications.
[a]Persons immunocompromised because of immune deficiency diseases, human immunodeficiency virus infection, leukemia, lymphoma or generalized malignancy, or immunosuppressed as a result of therapy with corticosteroids (i.e., ≥2 mg/kg body weight or 20 mg/day of prednisone for ≥2 wk, alkylating drugs, antimetabolites, or radiation).
BCG, Bacille Calmette-Guerin; HDCV, human diploid cell vaccine; IM, intramuscularly; IPV, inactivated poliovirus vaccine; OPV, oral poliovirus vaccine; PCEC, purified chick embryo cell culture rabies vaccine; PPD, purified protein derivative (tuberculin); SC, subcutaneously.
(Adapted from Centers for Disease Control and Prevention. Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 1997; 46(RR-18):7–9.)

are summarized in these tables, and recommendations concerning immunization of healthcare workers with special conditions are provided in Table 75-6. Management of the vaccine-preventable diseases themselves and management of exposures to those diseases (other than postexposure vaccination) are covered in detail in other chapters, to which readers will be referred.

In addition to those vaccines discussed below, there are other vaccines that are indicated only in certain parts of the world (e.g., Japanese encephalitis, tick-borne encephalitis, yellow fever) or that have no recognized application for HCWs (Hib, HPV, rotavirus); they are not discussed further.

Hepatitis A Vaccine

Background Hepatitis A virus (HAV) is highly endemic in the United States, with 13,397 cases (4.91 cases per 100,000) reported to the CDC in 1999 *(67)*, a figure that probably represents <10% of actual infections. The incidence of HAV varies by race (among US residents highest in Native Americans and Native Alaskans), location (in the United States higher west of the Mississippi River), and age. Globally, incidence and median age of onset are closely related to socioeconomic and developmental status, with higher rates and lower median ages of onset in less-developed countries. In the United States, schoolchildren 5 to 14 years of age have the highest reported incidence. However, infection in infants and young children often is asymptomatic, so the age distribution of reported cases may not be representative of the underlying age distribution of infection. Sources of infection include household or sexual contact with a person with HAV (22–26% of reported cases), with a child or employee in a day-care center (14–16%), or with an international traveler (4–6%) *(68)*. The majority of cases are sporadic, with no identified source. Food- or waterborne outbreaks classically account for only 2% to 3% of cases, but are becoming more common with globalization of the US food supply.

Hepatitis A results in substantial morbidity with significant costs caused by medical care and lost work time. Approximately 11% to 22% of people who develop recognized hepatitis A require hospitalization *(54)*. In the United States, an estimated 100 deaths per year are attributable to acute hepatitis A (there is no chronic infection).

Healthcare-Associated Outbreaks Although several cohort studies have failed to demonstrate HCP to be at increased risk for hepatitis A compared with control populations *(69–72)*, some European researchers have reported that HCP had higher than expected rates of seropositivity to hepatitis A *(73,74)*. A number of healthcare-associated outbreaks of HAV have been reported *(75–91)*. These reports suggest a common set of circumstances: a source patient who was not jaundiced, in whom hepatitis was not suspected, and who had fecal incontinence or diarrhea. Risk

TABLE 75-6

Recommendations Concerning Immunization of HCP with Special Conditions

Vaccine	*Pregnancy*	*HIV Infection*	*Severe Immunosuppression*[a]	*Asplenia*	*Renal Failure*	*Diabetes*	*Alcoholism and Alcoholic Cirrhosis*
BCG	C	C	C	UI	UI	UI	UI
Hepatitis A	UI	UI	UI	UI	UI	UI	R[b]
Hepatitis B	R	R	R	R	R	R	R
Influenza, inactivated	R[c]	R	R	R	R	R	R
Influenza, live attenuated[d]	C	C	C	C	C	C	C
Measles, mumps, rubella	C	R[e]	C	R[b]	R	R	R
Meningococcus	UI	UI	UI	R	UI	UI	UI
Pertussis (as Tdap)	UI	R	R	R	R	R	R
Poliovirus, inactivated[f,g]	UI	UI	UI	UI	UI	UI	UI
Pneumococcus	UI	R[b]	R[b]	R[b]	R[b]	R[b]	R[b]
Rabies	UI	UI	UI	UI	UI	UI	UI
Tetanus/diphtheria[f]	R[b]	R[b]	R[b]	R[b]	R[b]	R[b]	R[b]
Typhoid, Vi polysaccharide	UI	UI	UI	UI	UI	UI	UI
Typhoid, Ty21a[d]	UI	C	C	UI	UI	UI	UI
Varicella	C	C	C	R	R	R	R
Vaccinia	C	C	C	UI	UI	UI	UI

Note: The package insert and ACIP recommendations should be consulted for specific guidance regarding indications, precautions, and contraindications.

[a]Severe immunosuppression can be the result of congenital immunodeficiency; HIV infection, leukemia, lymphoma, generalized malignancy, or therapy with alkylating agents, antimetabolites, radiation, or large amounts of corticosteroids.

[b]Recommendation is based on the person having the indicated underlying condition, not their status as HCP.

[c]Recommended for all women who are pregnant or will be pregnant at any time during the influenza season.

[d]Because of the theoretical risk of transmission to patients of the live attenuated agent contained in this vaccine, use of the alternative inactivated vaccine is preferred.

[e]Generally contraindicated in persons with HIV infection; recommended for children (no official recommendation for serosusceptible adults) with CD4+ >200/μL; consider reimmunization if initial immunization was given when CD4+ <200/μL and if CD4+ increases to ≥200 μL due to highly active antiretroviral therapy.

[f]All persons, whether HCP or not, should be immune unless specifically contraindicated.

[g]Immunization with IPV is recommended for unvaccinated HCP who have close contact with persons who may be excreting wild poliovirus. HCP who have a primary series of OPV or IPV who are directly involved with the provision of care to patients who may be excreting poliovirus may receive another dose of IPV. Except in the context of mass immunization to control circulating wild polio, use only IPV; OPV can, rarely, result in paralysis of recipients or their contacts (OPV is not available in the United States).

BCG, bacille Calmette–Guérin; HIV, human immunodeficiency virus; IPV, inactivated poliovirus vaccine; MMR, measles-mumps-rubella vaccine; R, recommended; C, contraindicated; UI, use if indicated.

(Adapted and expanded from Centers for Disease Control and Prevention. Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR Recomm Rep* 1997;46(RR-18):30.)

factors for HAV transmission to personnel include activities that increase the risk of fecal–oral contamination, including caring for a person with unrecognized HAV infection *(77–84)*; sharing food, beverages, or cigarettes with patients, their families, or the staff *(78,84–86)*; nail biting; handling bile without proper precautions *(84)*; and not washing hands or wearing gloves when providing care to an infected patient *(81,82,84,85)* (see also Chapters 46 and 73).

Vaccination Although current recommendations do not support routine immunization of United States HCP except in areas where hepatitis A is highly endemic (31), cost-benefit analyses have suggested that the cost of hepatitis A vaccination in HCP, per life-year saved, was similar to that of other standard medical interventions *(92)*. As with other special use vaccines, HCP should be encouraged to review with their local medical provider their own risks and benefits for hepatitis A vaccine.

Hepatitis B Vaccine

Background Exposure to blood-borne pathogens via parenteral or mucosal contact can expose HCP to the risk of acquiring numerous infections, foremost among these (in terms of risk, prevalence, and aggregate burden) being hepatitis B. Seroprevalence surveys conducted prior to the availability of hepatitis B virus (HBV) vaccine showed HCP to be at threefold to fivefold higher risk of HBV infection than the general US population *(93–96)*, with the risk of infection proportionate to the extent and duration of blood contact. The use of HBV vaccine among HCP, coupled with the institution of Universal (now Standard) Precautions and other preventive measures such as needleless devices and safety needles and syringes (e.g., self-sheathing needles), has markedly reduced that risk. Mahoney et al. *(12)* reported that HBV infection among HCP declined from 17,000 in 1983 to 400 in 1995. This 95% decline in incidence observed among HCP was 1.5-fold greater than the

reduction in incidence in the general US population during the same time period.

Healthcare-Associated Exposures HCP are at risk of hepatitis B acquisition for several reasons. First, HCP have high rates of exposure to blood *(97)*. For example, a 1988 survey of New York City surgeons found that 86% had at least one puncture injury in the preceding year *(98)*. A survey of US and Canadian orthopedic surgeons in 1991 found that 87.4% had a blood–skin contact and 39.2% a percutaneous blood contact in the previous month *(99)*. Second, the virus can persist in the environment, being able to survive drying and storage at 25°C and 42% relative humidity for at least 1 week *(100)*. Third, HBV is highly transmissible; the titer of infectious particles is extraordinarily high in the blood of actively infected persons. Consequently, rates of disease transmission after a percutaneous injury with a contaminated sharp range from 6% to 30% *(101–103)*. HBV infection also can be acquired via mucosal exposure, exposure to nonintact skin, or ocular exposure *(68)*, and has been transmitted to patients by a worker with severe exudative dermatitis while obtaining arterial blood gases *(104)*. Fourth, a substantial number of patients have inapparent infections; for example, a study of consecutive blood samples submitted to the chemistry laboratory of an urban hospital in 1987 revealed that only 28% of hepatitis B surface antigen (HBsAg)-positive specimens were labeled with a biohazard label as required *(105)*. Finally, many HCP remain unimmunized.

Many outbreaks of healthcare provider–to-patient transmission of hepatitis B have been described *(106–110)*. Transmission typically occurs during an invasive procedure, with the most important risk factors being e-antigen positivity of the HCP, degree of invasiveness of the procedure, the infected HCP not wearing gloves, or injury (often inapparent) to the infected HCP (see also Chapters 46, 73, and 76).

Vaccination OSHA has mandated since 1991 that all healthcare employees be offered hepatitis B immunization. Employees may refuse immunization but must sign a declination form. Employees who decline hepatitis B vaccine cite a desire to avoid medications, the perception that they are at low risk for occupationally acquired HBV infection, and concern about side effects *(111)*. Availability of educational materials directed at these issues may be helpful in minimizing refusals.

Protective serum titers of anti-HBsAg (≥10 mIU/mL) develop in 90% of healthy adults who receive three intramuscular (IM) doses of hepatitis B vaccine *(112–114)*. Independent risk factors for failure to seroconvert following HBV vaccine include smoking, female gender, higher body mass index, and older age *(115)*. The two currently available hepatitis B vaccines, Recombivax HB and Engerix-B, are equally immunogenic and are interchangeable; either can be used (in its recommended dose) to complete an immunization series begun with the other *(112)*. Immunogenicity is not reduced when hepatitis B vaccine is given with other vaccines. Pregnancy is not a contraindication to hepatitis B vaccine. All injections should be provided in the deltoid because gluteal injection can result in poor immunogenicity *(116)*.

The usual vaccination schedule consists of three doses administered at 0, 1, and 6 months. Acceptable alternative adult schedules include 0, 1, and 4 months and 0, 2, and 4 months. A schedule of 0, 1, 2, and 12 months should be considered for unimmunized HCP at high risk of HBV (e.g., hemodialysis workers, cardiac surgeons) *(117,118)*. All HCP at ongoing high risk for percutaneous or mucosal exposures should have an anti-HBsAg titer obtained 1 to 2 months after the third immunization *(119)*. HCP with postimmunization titers <10 mIU/mL should receive up to three additional IM doses of hepatitis B vaccine; serum antibody can be checked 1 to 2 months after each dose, with vaccination terminated if immunity is achieved. (Laboratories using test kits that simply report "positive" or "negative" must consult the product literature or manufacturer to determine the minimum antibody level able to return a positive result.) If protection is not achieved following the third additional (sixth total) dose, the HCP should be considered a nonresponder. Persons who are nonresponders after receiving the vaccine series should be tested for HBsAg (after the third or sixth dose of hepatitis B vaccine), as one of reasons for failure to respond to vaccine is active infection. This is especially a problem in HCP born in HBV-endemic countries who acquired hepatitis B perinatally or at a young age. HCP found to be HBsAg positive should be referred for care to a hepatologist or infectious diseases physician specializing in the care of chronic hepatitis B. In addition, current recommendations should be followed for managing and reporting HCP personnel who are HBsAg positive and perform invasive procedures (120). Following a blood-borne or mucous membrane exposure to an HBsAg positive source, nonresponding HCP should be tested for the presence of HBsAg and given hepatitis B immune globulin as indicated for postexposure prophylaxis.

Symptomatic hepatitis B is rare in immunized people who developed protective levels of antibody, even though there is eventual loss of detectable antibody in up to 50% of those people 5 to 10 years after immunization. For this reason, there is currently no recommendation for periodic boosting of HCP who have responded to hepatitis B vaccine *(66,121)*. Nonetheless, many institutions provide postexposure serologic testing of exposed HCWs and offer a booster dose of vaccine for those with antibody levels <10 mIU/mL, not because of medical need but in consideration of the anxieties of the exposed worker.

Influenza Vaccine

Background Influenza is characterized by the abrupt onset of fever, myalgia, sore throat, and nonproductive cough. During influenza epidemics, the hospitalization rate for the elderly and for persons with underlying health problems (especially cardiopulmonary) may increase twofold to fivefold compared with nonepidemic periods *(122)*. Of the 23 influenza seasons between 1972 and 1992, 19 were associated with excess mortality, 9 with more than 20,000 influenza-associated excess deaths, and 4 with more than 40,000 excess deaths *(123,124)*.

Influenza is a single-stranded RNA virus that occurs in three basic antigen types (A, B, and C) based on nuclear material. Type A infects humans and other animals (especially fowl, other birds, and pigs) and is antigenically characterized by two surface proteins, hemagglutinin (associated with cell attachment), and neuraminidase (associated with cell penetration). In recent years, most

influenza A human disease has been caused by viruses expressing hemagglutinin types H1, H2, or H3 and neuraminidase types N1 or N2. Infection with a strain expressing a given hemagglutinin and neuraminidase reduces the likelihood and severity of subsequent infection by strains expressing those types, but confers little or no protection against viruses expressing other types. Influenza A hemagglutinins and neuraminidases of given types undergo continual antigenic modification (antigenic drift, due to point mutations) that can reduce, sometimes markedly, the protection conferred by infection with an earlier strain of the same subtype, leading to epidemics. At unpredictable intervals, an influenza A strain undergoes a genetic shift (probably due to recombination events within an avian or porcine host that is simultaneously infected with a human and an animal strain) and produces a new subtype, to which there is no protection from infection with previous strains, leading to pandemics. In the past 125 years, there have been five pandemics, due to H3N2 in 1889, H1N1 in 1919 (the "Spanish flu"), H2N2 in 1957 (the "Asian flu"), H3N2 in 1968 (the "Hong Kong flu"), and novel H1N1 in 2009. In recent years, both H1N1 and H3N2 have circulated *(124)*. In addition, there have been isolated instances of human infection due to human–animal recombinant influenza A viruses (e.g., the Hong Kong chicken-market outbreak of H5 virus or the Netherlands H6 cases), but (perhaps due to aggressive containment efforts, or perhaps due to inherent characteristics) none have spread widely.

Influenza B infects only humans, predominantly children, and typically causes milder illness than does influenza A. Influenza B is genetically more stable than influenza A.

The composition of each year's influenza vaccine is determined about 6 months before influenza season each year (to allow time for manufacture), based on recommendations by the World Health Organization (WHO) and national advisory groups that monitor strains circulating worldwide. Unfortunately, new strains sometimes arise too late to be included in that year's vaccine.

Influenza virus appears to spread from person to person by small-particle aerosol transmission. Although aerosol transmission is well established, healthcare-associated transmission via fomites and contaminated hands remains possible. Influenza virus is shed for 1 to 2 days prior to onset of symptoms and for up to 5 days after onset of illness among adults and up to 7 days among children.

Healthcare-Associated Exposures Healthcare-associated acquisition of influenza is common *(125–146)*, typically in association with community outbreaks; HCP acquire infection from patients or in the community, and then spread infection to other HCP and patients, endangering patients and disrupting the provision of care *(125–129,147)*. Influenza infection among staff is common during the winter season and results in substantial absenteeism. Attack rates of 25% to 80% are often observed among both patients and staff during outbreaks. Similarly, healthcare-associated outbreaks within extended-care facilities (e.g., for the elderly) can result in substantial morbidity and mortality *(147–165)*.

The healthcare-associated spread of influenza cannot be prevented with measures instituted only when influenza is known to circulate, because identification of all patients with influenza is unlikely to be accomplished *(129)* and community indicators of influenza activity (e.g., visits to acute ambulatory care centers for upper respiratory illness) cannot be relied on to provide warning of influenza among hospitalized patients *(127)*.

On the other hand, a high influenza immunization rate among HCP has been shown to result in a decrease in the attack rate of influenza among patients *(166,167)*. For example, patients in facilities with more than 60% of the staff immunized experienced less influenza-related mortality and illness compared with patients in facilities without immunized staff *(166)*.

For all these reasons, routine annual influenza immunization of HCP is essential and has been recommended for many years. Recommendations for prevention and control of healthcare-associated influenza have been published and are summarized in Table 75-7 *(130,131,168–174)*. (see also Chapters 42 and 76).

Vaccination Influenza vaccine is recommended for all persons aged 6 months and older without specific contraindication (new ref), and a randomized, controlled trial in a general working population has demonstrated that providing influenza vaccine is cost-effective *(175)*.

Those who are at increased risk for complications of influenza because of age or underlying medical condition include all persons aged 6 through 23 months; all persons aged 50 years or older; residents of extended-care facilities or long-term-care facilities that house people of any age who have chronic medical conditions; adults and children who have required regular medical follow-up or hospitalization during the previous year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; persons aged 6 months to 18 years who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye syndrome after influenza; and women who will be in the second or third trimester of pregnancy during the influenza season *(61)*.

Most pertinently, influenza vaccine is strongly recommended and is the standard of care for HCP, because they can transmit influenza virus to people at high risk, and moreover are needed for patient care during influenza outbreaks. The CDC specifically recommends immunization for the following HCP: physicians, nurses, and other personnel in both hospital and outpatient care settings; medical emergency-response workers; employees of nursing homes and long-term-care facilities who have contact with patients or residents; and providers of home care to people at high risk (e.g., visiting nurses and volunteer workers) *(61)*. Unfortunately, despite these recommendations, many HCP choose not to take influenza vaccine *(175–177)*. Reasons offered by HCP who decline influenza immunization have included desire to avoid medications, inconvenient vaccine administration, concern about side effects, belief that influenza can be caused by the vaccine, and belief that the vaccine is ineffective *(14,15,111)*. Institution-wide influenza immunization programs that are highly publicized, bring the program to the worker, take advantage of social or peer pressure, and reward participation have shown the greatest success, but still often struggle to vaccinate even half of the HCP having direct patient contact.

TABLE 75-7

Recommendations for the Prevention and Control of Healthcare-Associated Influenza

Prevention

1. Educate personnel about the epidemiology, modes of transmission, and means of preventing the spread of influenza;
2. Establish mechanism(s) by which hospital personnel are promptly alerted of an increase in influenza activity in the local community;
3. Establish protocols for intensifying efforts to promptly diagnose cases of healthcare-associated pneumonia;
4. Arrange for laboratory tests to be available to clinicians, for use when clinically indicated, to confirm the diagnosis of influ enza and other acute viral respiratory diseases promptly, especially during November through April;
5. Offer vaccine to outpatients and inpatients, beginning in September and continuing throughout the influenza season;
6. Vaccinate HCPs before the influenza season each year, preferably between mid-October and mid-November;
7. Isolate patients with known or suspected influenza in a private room, preferably under negative pressure;
8. Institute masking of individuals who enter the room of a patient with influenza;
9. Evaluate HCPs with febrile upper respiratory illnesses and consider removal from duties that involve direct patient care (use more stringent guidelines for staff working in high-risk areas, such as intensive care units, nurseries, or with severely immunocompromised patients); and
10. During community or hospital outbreaks, restrict hospital visitors who have a febrile respiratory illness.

Control of Healthcare-Associated Influenza Outbreaks

1. Early in the outbreak, perform rapid influenza virus testing and/or viral cultures on nasopharyngeal swab or nasal-wash specimens from patients with recent onset of symptoms suggestive of influenza;
2. Administer current influenza vaccine to unvaccinated patients and staff;
3. Administer antiviral prophylaxis to all uninfected patients in an involved unit for whom it is not contraindicated;
4. Administer antiviral prophylaxis to all unvaccinated staff members for whom it is not contraindicated and who are in the involved unit or taking care of high-risk patients;
5. If the cause of the outbreak is confirmed to be influenza and vaccine has been administered only recently to susceptible patients and personnel, continue antiviral prophylaxis until 2 wk after the vaccination;
6. To the extent possible, do not allow contact between those at high risk of complications from influenza and patients or staff who are taking antiviral treatment for an acute respiratory illnesses. Prevent contact during and for 2 d after the latter discontinue treatment; a failure to isolate patients treated with amantadine or rimantadine may result in the dissemination of drug-resistant strains; and
7. Consider restricting or curtailing visitation, elective admissions, and nonemergent cardiovascular or pulmonary surgery.

(Data from references 37 and *168*.)

In recognition of this dismal fact, there is an increasing trend of medical organizations recommending, and healthcare institutions requiring, mandatory influenza vaccination of HCP unless there is a medical contraindication to immunization *(178,179)*. As of early 2010, those recommending such policies include the Infectious Diseases Society of America, the ACP, the Association for Professionals in Infection Control and Epidemiology, and the New York State Department of Health. Institutions that have implemented such requirements include Virginia Mason Medical Center, the Clinical Centers of the National Institutes of Health, the Department of Defense, Hospital Corporation of America, Johns Hopkins Health System, University of Iowa Hospitals, Hospital of the University of Pennsylvania, Children's Hospital of Philadelphia, and the Cook County Health and Hospitals System *(180)*. Several institutions have published their experience and demonstrated achievement of vaccination rates exceeding 98% (*25*,*26*,27).

In light of these successful initiatives, institutions are encouraged to consider mandatory vaccination of HCP with direct patient contact. Institutions unable or unwilling to do so should consider introducing innovative methods of taking vaccine to workers, such as provision by mobile carts on hospital wards, offering vaccine to house staff and students in clinics and conferences, etc. *(169)*.

In June 2010, CDC published notice of the intent to provide an updated guidance that will emphasize a prevention strategy to be applied across the entire spectrum of healthcare settings, including hospitals, nursing homes, physicians' offices, urgent-care centers, and home healthcare. It will focus on the importance of vaccination, steps to minimize the potential for exposure such as respiratory hygiene, management of ill healthcare workers, droplet- and aerosol-generating procedure precautions, surveillance, and environmental and engineering controls *(181)*.

Measles-Mumps-Rubella Vaccine

Background The widespread use of measles-mumps-rubella (MMR) vaccine in the United States, coupled with the hemisphere-wide measles eradication program, led to record-low incidences of measles, mumps, and rubella. However, all three diseases continue to be reported, including small outbreaks of measles and large outbreaks of mumps, reflecting ongoing importations combined with pockets of susceptible populations (measles, mumps) or waning vaccine-induced immunity (mumps).

All three diseases are transmitted by the droplet route; measles, perhaps the most contagious disease known, also is transmitted by the airborne route. All three infections are contagious prior to development of clinically

recognizable illness. Moreover, a history of prior disease does not reliably predict prior infection and immunity, and consequently, many unimmunized HCP may falsely believe themselves immune.

Measles is highly dangerous; during the last major US outbreak, one of every 500 infected persons died. Rubella is less serious, but is of special concern because of its ability to cause congenital abnormalities in the fetuses of up to 90% of women with confirmed infection in the first trimester of pregnancy. Mumps is typically a mild illness in children, but meningoencephalitis, oophoritis, pancreatitis, and nephritis can occur, especially in adults, and epididymo-orchitis occurs in 20% to 40% of postpubertal men and may eventuate in testicular atrophy. Orchitis has been reported among male HCP who developed mumps as a result of hospital exposure *(182)*.

Healthcare-Associated Exposures Healthcare-associated measles is well documented in the literature *(183–215)* and has played an important role in the propagation of community outbreaks *(183–185)*. Measles was acquired in a medical setting by 1.1% of all cases between 1980 and 1984 *(186)* and 3.5% of all cases between 1985 and 1989 *(187)*, representing up to 53% of the cases in certain outbreaks *(184,188–193)*. Spread of measles has also occurred in outpatient settings, including emergency departments and physician offices, with transmission occurring even 75 minutes after the departure of the index case *(189,194–199)*. People who visited an emergency department have been shown to have a 4.9-fold *(200)* to 5.2-fold *(185)* higher risk of developing measles one incubation period later compared with those who did not have such visits. Healthcare-associated outbreaks have led to hospitalization of infected staff *(201)*, severe complications in infected patients *(202)*, and occasionally death of patients *(183,201)*. The cost of controlling a single outbreak has ranged from $28,000 to more than $100,000 *(183,201)*.

Healthcare-associated outbreaks of mumps have been reported infrequently *(182,216–220)*, but transmission from patient to patient *(216–218)* and from patient to healthcare provider *(182,217–219)* has been reported. In one case, it was suggested that an asymptomatically infected hospital nurse introduced mumps into a children's hospital *(216)*. During the 1986 to 1987 Tennessee mumps epidemic, six HCP in three different hospitals developed mumps after healthcare-associated exposure *(217)*. Healthcare-associated rubella also is well documented in the literature *(221–238)*. Sources of rubella infection have included both people with acute infection and infants with congenital rubella *(221–223)*. Healthcare-associated infection of pregnant staff members has led to the termination of pregnancy *(223,225)*.

Absence of a mandatory program requiring MMR immunity results in a subpopulation of susceptible HCP capable of propagating epidemics. Although these diseases presently are uncommon or rare, they are not eradicated, and introductions and local outbreaks of measles and mumps occur with regularity. These viruses are so communicable—especially measles—that rapid healthcare-associated spread will inevitably occur following each index case, unless exceptionally high vaccination rates are maintained (see also Chapters 51 and 76).

Vaccination All HCP should be immune to mumps, measles, and rubella. Immunity may be demonstrated through laboratory evidence of immunity (people with indeterminate levels should be considered susceptible) or evidence of appropriate immunizations *(239)*. Traditionally, birth before 1957 has been considered adequate for the presumption of immunity, but a recent study of healthcare workers born before 1957 who were newly hired in the period 2006 to 2008 revealed the following rates of serosusceptibility: measles 1.3%, mumps 3.7%, and rubella 2.9% (43). Given the consequences of rubella infection during pregnancy, hospitals should require proof of rubella vaccination or immunity even if birth before 1957 is accepted in lieu of proof of measles vaccination or immunity *(39)*. Moreover, hospitals that accept birth before 1957 as proof of measles immunity should assess the immunity of HCP born before 1957, in the same manner as for younger HCP, during a community or institutional outbreak of measles.

About 95% of subjects respond to a first dose of measles vaccine. However, measles is so contagious that it can propagate in a population that is 95% immune. Because nearly 95% of initial nonresponders will respond to a second dose, two doses of measles vaccine (MMR is preferred) are recommended to reduce the pool of susceptibles. Revaccination with MMR is also advisable for mumps control, because experience has shown that mumps outbreaks can propagate even in a highly vaccinated population *(240)*.

Meningococcal Vaccine

Background *Neisseria meningitidis* is responsible for 1,000 to 3,000 cases of invasive meningococcal disease annually in the United States, the majority of these in persons over 18 years of age (*241*,*242*,243). This relatively uncommon disease is notorious for its high rates of morbidity and mortality, and its ability to maim or kill a healthy person overnight. Even with the best medical care, fatality rates are 9% to 12% (up to 40% for meningococcal sepsis), and 11% to 19% of survivors of meningococcal disease experience serious sequelae such as hearing loss, neurologic disability, or amputation *(242)*.

There are five serogroups of *N. meningitidis* that are important in human disease (based on the capsular polysaccharide and denoted A, B, C, Y, and W-135). Humans are the only natural reservoir for *N. meningitidis*. The microorganism colonizes the nasopharynx and is carried by 5% to 10% of the population at any given point in time; carriage can give rise to type-specific antibody. Transmission is by droplet or nasopharyngeal secretions. Disease arises from invasion of capsule-producing strains in persons lacking specific anticapsular antibody.

In the United States, nearly all cases of invasive meningococcal disease are sporadic, but certain populations (including military recruits, college freshmen living in dormitories, and persons with terminal complement deficiencies or asplenia) are at elevated risk of invasive meningococcal disease, and small outbreaks occur regularly. Household or other close contacts are at 200 to 1,000 times the risk of developing meningococcal disease as is the general public *(244)*, and secondary attack rates in households average 2% to 5% *(245)*.

Effective vaccines exist for four of the five common serogroups (all but B). In developed countries, the older

polysaccharide vaccines have largely been replaced by newer, more effective conjugate vaccines. Two different quadrivalent conjugate vaccines are available in the United States and some other countries, and bivalent, trivalent, and quadrivalent polysaccharide vaccines and monocomponent (type C) conjugate vaccines are available in many countries. Polysaccharide vaccine should not be used if conjugate vaccine with equal or broader serogroup coverage is available.

Healthcare-Associated Exposures Although person-to-person transmission of *N. meningitidis* appears to require relatively prolonged close contact *(245,246)*, the existence of epidemics, the elevated secondary attack rates in households, the known elevated risk of disease among social clusters (military recruits, college freshmen, concertgoers, bar patrons, etc.) *(242)*, and especially the fearsome consequences of invasive meningococcal disease give rise to substantial anxiety among HCP caring for patients diagnosed with the disease. And indeed, healthcare-associated *(245,247–249)* and laboratory-based *(250)* transmission have occurred, but sufficiently uncommonly that vaccination is not routinely recommended for HCP *(247)* (see also Chapters 47 and 76).

Vaccination The ACIP has recommended that all adolescents aged 11 to 18 receive quadrivalent conjugate meningococcal vaccine, as should all persons aged 2 to 55 years at elevated risk of meningococcal infection (e.g., those with persistent complement deficiencies or asplenia, laboratorians or others with routine occupational exposure, travelers to or residents of endemic areas, military recruits, etc.) and any other persons wishing to avail themselves of this protection *(251,252)*. Persons who are at continued high risk and who were vaccinated at least 5 years previously should be revaccinated at 5-year intervals (253). In addition, institutions might elect to immunize selected staff members who have heightened likelihood of (or anxiety concerning) caring for patients with invasive meningococcal disease.

Pertussis Vaccine

Background In the United States, the reported annual incidence of pertussis declined from a high of 260,000 cases prior to routine vaccination to a low of some 1,300 cases in 1977 *(254)*. Subsequently, however, pertussis has progressively increased, with 13,506 cases reported in 2009 *(255)*. Most of this increase has occurred among adolescents and adults (due to waning vaccine-induced immunity). Heightened community prevalence of pertussis has led to dangerous increases in disease among infants too young to be fully vaccinated; it is in this group that most hospitalizations and fatalities occur *(256)*.

Because the initial phase of the disease resembles many viral respiratory infections and the classic whoop often is not seen with adult pertussis, the disease is commonly misdiagnosed (e.g., as bronchitis). However, studies using sophisticated diagnostic methods have demonstrated that *Bordetella pertussis* is a common cause of prolonged cough illness in adults *(257–259)*. Deville et al. *(260)* followed HCP for 5 years and found that 90% of subjects had serologic evidence of new infection during that period; 55% had evidence of two infections, 17% had evidence of three infections, and 4% had evidence of four infections.

Healthcare-Associated Exposures Many healthcare-associated pertussis outbreaks have been reported (*261–270,*271,*272*). Although the source case most commonly was an infected patient in whom pertussis was unrecognized *(261–263)*, infected HCP *(264,265)* and visitors *(266)* have also served as sources. Secondarily infected HCP, in turn, serve as the source for additional cases in the institution (*264,265,270*,271) or their own households *(262,264)* (see also Chapter 76). Costs associated with such outbreaks can be substantial (271).

Vaccination Pertussis immunization classically ceased around age 6 years, because adverse reactions to whole-cell vaccine among older persons were not tolerable. However, the development and worldwide licensure of highly effective adult-formulation tetanus, diphtheria, and acellular pertussis (Tdap) vaccines that are little more reactogenic than a standard tetanus-diphtheria booster has enabled a major expansion of the fight against pertussis *(273–280)*.

Tdap is recommended by ACIP for routine administration at age 11 to 12 years and for all persons aged 11 to 65 who have not yet received a dose, except during pregnancy; pending further data, it is recommended that Tdap be administered prior to pregnancy or immediately following delivery (63,*281*,282). It is particularly recommended that those who will have close contact with an infant receive Tdap. In addition, ACIP and HICPAC recommend that all HCPs with direct patient contact receive Tdap as soon as feasible (63).

In the event of a healthcare-associated outbreak, consideration should be given to administration of Tdap to all potentially exposed persons who have not yet received a dose (63,*280*).

Typhoid Vaccine

Background Typhoid fever now is relatively rare in the United States, with fewer than 500 cases reported annually. The disease remains common, however, in areas of the world where fecal contamination of food or drinking water occur. The majority of cases in Western countries occur among travelers to other countries *(283)*.

Healthcare-Associated Exposures Although *Salmonella* is a common cause of healthcare-associated infectious diarrhea, such cases in the United States usually involve the animal serotypes *(284–289)* rather than *Salmonella typhi (290–298)*. Transmission to HCP other than laboratorians working with *S. typhi* is distinctly uncommon (see also Chapter 76).

Vaccination Two modern vaccines exist, a live-attenuated oral vaccine (not recommended for HCWs, due to the theoretical risk of spread to patients) and a killed parenteral vaccine based on the capsular polysaccharide. A conjugate version of the latter vaccine has been developed but is not licensed. Vaccination is recommended for microbiology laboratorians who work frequently with *S. typhi*.

Vaccinia (Smallpox Vaccine)

Background Smallpox, one of the greatest killers of mankind, was eradicated as a natural disease in 1977 *(299)*. Unfortunately, it is now known that the Soviet Union weaponized smallpox during the 1980s, stockpiling enormous quantities of the virus whose present whereabouts are not known with certainty *(300)*. The consequent fear that smallpox might be used as a bioterror agent spurred efforts by the United States and other governments to reestablish stockpiles of smallpox vaccine (vaccinia). In addition, in 2002 to 2003 the United States promulgated a pre-event vaccination program designed to ensure the availability of immunized cadres that could respond to a smallpox release *(301)*. However, due primarily to concerns about vaccine adverse events *(299)* but also, perhaps, to doubts as to the likelihood of such an event, vaccine uptake among HCP was so low that the program was functionally suspended in 2003. Routine vaccination continues among deploying military personnel, certain rapid-response public health teams, and other select groups.

Healthcare-Associated Exposures Prior to the eradication of natural smallpox, the threat of healthcare-associated spread of infection was averted through universal vaccination. Subsequently, until the issue of bioterror protection arose, the only indication for the (somewhat hazardous) vaccination of HCP was to prevent the potentially more hazardous consequences of inadvertent infection with vaccinia among laboratorians and HCP occupationally exposed to vaccinia, recombinant vaccinia viruses, and other orthopoxviruses that can infect humans *(302)* (see Chapters 76, 101, and 104).

Vaccination In the United States, vaccinia is available to civilians only through the public health authorities. Vaccination against smallpox is recommended by the CDC only for laboratorians (or, presumably, other HCP) who work with orthopoxviruses (for this indication, contact CDC) and for public health and healthcare response team members (for this indication, contact your state or local health department). In addition, as noted, the Department of Defense routinely vaccinates deploying military personnel.

Varicella Vaccine

Background Varicella zoster virus (VZV) is the causative agent of varicella (chickenpox). Following acute infection, the virus remains latent in the trigeminal and dorsal root ganglia for life, and from there may erupt on occasion to cause herpes zoster (shingles) *(303)*. Although varicella is generally a mild disease in children, it is often more serious in adults, and substantial morbidity and mortality are common if infection occurs in neonates, pregnant women, or the immunocompromised *(303)*. VZV is most commonly transmitted from person to person by the droplet route, but true airborne transmission may also occur. The secondary attack rate of varicella among susceptible people in the household setting has ranged from 61% to 87% *(304–306)*. Herpes zoster is also infectious, although analysis of households suggests that the risk of transmission is lower than for varicella.

Varicella disease has declined sharply in the United States following incorporation of the varicella vaccine into the childhood vaccination schedule, with decreases in varicella-related hospitalizations and deaths *(307)*. Paradoxically, this heightens the importance of an institutional varicella immunity program, as those who escaped infection in childhood [in the prevaccine era, at least 5% of persons aged 20 to 29 *(308)*] and were left susceptible are likely to remain so, absent vaccination.

Healthcare-Associated Exposures Control of varicella is important in healthcare facilities because varicella and zoster are highly contagious, with many reported healthcare-associated outbreaks *(306,309–329)*; infection in adults frequently results in complications, including hospitalization *(310,330,331)*; infection in pregnant women is particularly dangerous, and may lead to both maternal *(303)* and fetal *(332–334)* complications; and immunosuppressed persons, who make up a progressively larger proportion of hospital inpatients, are at high risk of complications *(310,335–342)*.

Studies conducted prior to widespread varicella vaccination have indicated that a report of prior varicella by an HCP is predictive of immunity as measured by serology *(343)*. However, as exposure opportunities are reduced by childhood immunization programs, the proportion of such reports that are false positive must inevitably rise, and active screening will increasingly be necessary. A history of prior household exposure to VZV is not predictive of immunity *(344)*. Overall, a median of 3% of HCPs are susceptible to varicella *(312–314,329,345–349)*, absent an institutional immunization program. Among HCP with a negative or uncertain history of VZV infection, serosusceptibility has ranged as high as 47% *(309,312,313,346–350)*. Following healthcare-associated exposure to VZV, 2% to 16% of susceptible staff will develop clinical varicella *(309,310,312)* (see Chapters 43 and 76).

Vaccination Due to its high communicability and potential for serious consequences, the appearance of active varicella infection within a healthcare institution is an infection control emergency. In the absence of assurance of HCP immunity, the management of such VZV exposure incidents is burdensome and expensive. Accordingly, many institutions (particularly those with pediatric, obstetric, transplant, chemotherapy, or similar programs) have elected to require demonstrated immunity among HCP working with such patients. Decision and cost-effectiveness analysis methods have been used to demonstrate that immunization of HCP susceptible to varicella is cost-effective for healthcare facilities *(351–354)*.

We recommend that HCP be screened for VZV immunity at the time of initial employment (or, for current employees, at time of next tuberculosis or similar screening). HCP with a reliable history of VZV infection may be considered immune; all others should undergo serologic testing and, if negative, be considered for immunization with two doses of vaccine at least 4 weeks apart. Postimmunization serology is not recommended.

There appears to be virtually no risk of transmission of the vaccine virus from healthy people who do not develop

a rash postimmunization. HCP who develop an injection site rash may continue to work with nonimmunocompromised patients, provided that the lesions are covered. HCP with a generalized rash should be furloughed until the rash is resolved. In the authors' experience, this has been approximately 5 days. The rash should not automatically be assumed to be due to vaccine, especially if exposure to a case of chickenpox has occurred in the preceding 3 weeks.

CONCLUSION

All HCP should be immune to measles, mumps, rubella, and varicella. All those with the potential for exposure to blood or potentially contaminated body fluids should be immune to hepatitis B. Absent specific contraindication, those who are susceptible should be offered the appropriate vaccines; prevaccination serologic testing is not medically required but may be offered at the institution's discretion.

In addition, all HCP should be immunized annually against influenza. HCP also should receive Tdap (at least once), tetanus-diphtheria (thereafter), and pneumococcal vaccines as recommended for the general public. Hepatitis A vaccine may be indicated based on local or regional epidemiology. Finally, selected HCP may be candidates for other available vaccines, including meningococcus, polio, plague, rabies, typhoid, and vaccinia.

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CHAPTER 76

Prevention of Occupationally Acquired Diseases of Healthcare Workers Spread by Contact, Droplet, or Airborne Routes (Other Than Tuberculosis)

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By virtue of their profession, healthcare workers are at greater risk of acquiring certain illnesses than are non–healthcare workers. This chapter discusses diseases spread by the contact or airborne routes for which healthcare workers are at elevated risk or that pose a particular problem for infection control and employee health staff. Notwithstanding the occasional healthcare-associated report, diseases that occur in the healthcare setting incidentally (e.g., food-borne illness arising in the hospital's cafeteria) are not considered. Similarly, only those diseases to which the immunologically normal healthcare worker is susceptible are covered.

Issues posed by the viral hepatitides and the human immunodeficiency virus (HIV) are covered in Chapters 73 and 74, respectively; tuberculosis is discussed in Chapter 38; infections of particular pertinence to laboratory workers are discussed in Chapter 77; infections pertinent to prehospital and posthospital healthcare workers are reviewed in Chapters 78 and 79; and issues consequent to bioterrorism are found in Chapters 101 to 104. Vaccinations of healthcare workers are detailed in Chapter 75. This chapter enumerates the remaining healthcare-associated airborne and contact-spread diseases for which healthcare workers are at elevated risk, reviews their epidemiology and prevention in healthcare institutions, and discusses some of the special challenges they pose for the infection control team. Pathogenesis, diagnosis, and therapy of these diseases are not addressed in detail, because they are discussed in other chapters of this text and elsewhere.

METHODS OF SPREAD

As Brachman *(1)* and others have pointed out, contact and airborne spread represent two ends of a spectrum. The spectrum begins with direct physical contact, as seen with bacterial pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA). Such person-to-person spread also includes most fecal–oral transmission. Disease may be transmitted by indirect contact, in which the victim encounters an intermediate object that previously was in contact with the source, as may occur, for example, through careless handling of contaminated equipment or used dressings. Disease can be spread via respiratory droplets expelled by a cough or sneeze; the cloud of expelled particles can impact persons or other objects within several feet, but the droplets do not travel farther before they settle to the ground. Finally, if respiratory droplets are sufficiently small, their moisture entirely evaporates while airborne, leaving any contained infectious particles suspended in the air. These droplet nuclei can be transported in the air over substantial distances. Under appropriate circumstances, other tiny particles (e.g., desquamated skin squames, fungal spores) may also be spread afar on the wind. Many diseases are spread by more than one of these routes. Additional pathways for the spread of disease include the blood-borne, common-source, and vector-borne routes. The diseases of transcendent importance that are spread by the blood-borne route are hepatitis B and C (Chapter 73) and HIV infection (Chapter 74). In the United States, healthcare workers generally are not at elevated risk of common-source or vector-borne diseases because of their occupation.

Humans long have pondered the origins of disease, and through the ages, the issue of airborne contagion has been raised many times. The Greek physician Galen stated, "When many sicken and die at once, we must look to a single common cause, the air we breathe" *(2)*. Hamlet bemoaned "this foul and pestilent canopy, the air," but 1,500 years after Galen, Sydenham said it was not the air itself, but "pestilential particles" carried by the air that conveyed disease *(2)*. Despite these prophetic speculations, Galen was responsible for establishing the dominance of the theory that deranged humors were responsible for disease, a belief to which Sydenham subscribed and which persisted until overthrown by the discoveries of the anatomists, pathologists, and microbiologists of the nineteenth century.

The discoveries of Louis Pasteur and others refocused attention on the possible spread of disease through the

air to such an extent that Tyndall was moved to write "the floating dust of the air … mingled with it the special germs which produce the epidemic, being thus enabled to sow pestilence and death over nations and continents" *(3)*. But soon, belief in the airborne spread of disease ebbed again because of the elucidation of the causes and modes of transmission of fecal–oral diseases, such as cholera; vector-borne diseases, such as malaria; and venereal diseases, such as syphilis. These discoveries had so reduced the attraction of the concept of airborne spread that by 1910, Chapin *(4)* stated in his *Sources and Modes of Infection*, "Bacteriology teaches that former ideas in regard to the manner in which diseases may be airborne are entirely erroneous; that most diseases are not likely to be dust-borne, and they are spray-borne only for 2 or 3 ft."

There opinion lay for 20 years, not overturned even by the great influenza pandemic until Wells *(5)* articulated the concept of droplet nuclei, infectious particles that can remain suspended in the air for many hours after the droplet itself has evaporated and that can be carried a considerable distance on air currents. Wells promptly proceeded to test his theory by placing ultraviolet lights in selected classrooms of two schools *(6)*. In a subsequent measles epidemic, the attack rate was dramatically higher in the control classes. Riley later collaborated with Wells to demonstrate the airborne transmission of tuberculosis *(7,8)*. Similar experiments, coupled with more sophisticated epidemiologic observations of outbreaks, have established the importance of the airborne route of spread for many diseases.

VIRAL INFECTIONS

Common Respiratory Viruses

Few healthcare workers would rank the common respiratory viruses first on a list of the diseases to which their work exposes them, but we would speculate that these illnesses cause more disruption and lost productivity than all the others we discuss combined.

Influenza The prototype of these illnesses is influenza. Influenza epidemics occur with distressing frequency within healthcare institutions, with predictable consequences; increased absenteeism or reduced efficiency of staff members and increased mortality, morbidity, and length of stay among the patients. Indeed, immunization of healthcare workers results in significantly reduced morbidity (43% reduction in influenza-like illness) and mortality (44% reduction) among geriatric patients in long-term-care facilities *(9)*.

The capacity of influenza for explosive spread was demonstrated by an outbreak among 53 persons stranded aboard a grounded airliner for 3 hours: within 3 days, 72% of the passengers were ill with influenza A *(10)*. When the "Asian" influenza A pandemic of 1957 reached the Oklahoma City Veterans' Hospital, 19 (39%) of 49 patients on the neurologic ward were affected, three of whom died; all but one of the physicians on the ward were "incapacitated" *(11)*. During the same epidemic, eight (62%) of 13 unvaccinated staff members studied at the New York Hospital developed influenza, as compared to 7 (35%) of 20 vaccinated staff *(12)*. Influenza A/Bangkok (H3N2) produced illness in one third of patients and staff members on affected wards at a Chicago hospital *(13)*. The same strain of influenza caused a 70% increase in absenteeism during a 2-week period among employees of a Winnipeg, Canada, hospital, which incurred excess sick-leave costs of $24,500 (1,980 Canadian dollars) *(14)*. Reports of healthcare-associated outbreaks of influenza B appear to be less common than reports of influenza A. This finding may merely reflect the greater prevalence of influenza A, although one report of hospital surveillance during an influenza B epidemic found no clusters of disease despite 25 cases detected by culture *(15)*.

Influenza is spread via infected nasopharyngeal secretions. Attempts in 1918 to transmit the pandemic strain failed because of improper technique; it was not until 1937 that Smorodintseff and associates demonstrated experimental transmission by droplets *(16)*. Spread is believed predominantly to involve respiratory droplets, as well as direct person-to-person spread through contact with infected secretions. Airborne spread is possible, but not as well documented as with such diseases as tuberculosis and varicella. Mingling of the occupants, a vigorously coughing source patient, and a nonfunctioning ventilation system were associated with the airliner outbreak, and thus, it may have been entirely caused by droplet spread.

Given the opportunities for exposure to influenza during a community outbreak, the only realistic approach to prevention among healthcare workers is through immunization. Unfortunately, achieving high immunization rates among healthcare workers has proven difficult *(17–19)*, with rates often less than 50% (20). Hospital-wide influenza immunization programs that are highly publicized, bring the program to the worker, take advantage of social or peer pressure, and reward participation find greater success, but still fail to maintain vaccination rates above 90%. Mandatory influenza vaccination programs appear to have the greatest effect on sustaining acceptable influenza vaccination rates among healthcare personnel (21). In an established outbreak, cohort isolation may help prevent spread to other patients *(22)* but likely would be of little benefit to the work force, given the ubiquitous opportunities for exposure during an outbreak. The neuraminidase inhibitors have traditionally afforded protection against influenza A (H1N1, H3N2) and influenza B, should a worker at high risk of complications be unable or unwilling to participate in the immunization program. In recent years, however, some influenza A (H1N1) strains have become resistant to oseltamivir. A combination of oseltamivir with an adamantine or zanamivir alone may be used if prophylaxis is indicated. Current recommendations for the prevention and treatment of influenza are available from the Centers for Disease Control and Prevention (CDC) and should be consulted prior to prescribing antiviral therapy *(23)*. Infected employees should not work in order to prevent spread to patients and others. (For more information on influenza, see Chapter 42.) (Note: All references to specific forms of isolation precautions, such as Standard, Droplet, or Airborne Precautions, refer to the "2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings," by the Hospital Infection Control Practices Advisory Committee of the United States Public Health Service (24)) (see also Chapter 90).

Parainfluenza Parainfluenza infections are most problematic among infants and young children, and spread on pediatric wards is well documented. These outbreaks often involve the staff *(25,26)*; an outbreak investigated at the Children's Hospital National Medical Center was shown to affect six of 17 neonates along with 18 of 52 nursing personnel *(26)*. Although the disease is relatively mild among older children and healthy adults, it can be a problem in long-term-care facilities, affecting both patients and staff, with patient deaths reported *(27)*. Of the various strains of parainfluenza virus, type 3 appears to be implicated more often in healthcare-associated outbreaks. The spread of parainfluenza often is indolent *(28)*, and the virus appears to be relatively hardy; droplets may contaminate environmental surfaces with virus that survives for many hours *(29)*.

Spread of parainfluenza virus is by direct contact and by large droplets, which may create the potential for indirect contact spread. Airborne spread is plausible but has not been demonstrated. Immunity is not durable and reinfection occurs throughout life. Thus far, efforts to develop vaccines have not been fruitful. Thus, protection of the healthcare worker rests on identification and isolation of cases with use of Contact and, perhaps, Droplet Precautions.

Respiratory Syncytial Virus Respiratory syncytial virus (RSV) is the most important respiratory pathogen of infants and young children, in whom it is the predominant cause of bronchiolitis and pneumonia *(30,31)*. Community-based outbreaks occur every winter and spring, and essentially the entire population has serologic evidence of infection by age 3 years. Immunity is short-lived and reinfection can occur annually. Thus, RSV spreads readily to healthcare workers. The disease is mild in previously infected adults, who may be asymptomatic or experience symptoms of the common cold *(31)*. Despite their mild illness, however, infected healthcare workers can serve as a source of infection for pediatric *(32,33)* and other *(27,34–37)* patients in whom infection may be dangerous.

Hall et al. *(32)* studied healthcare-associated RSV during a community outbreak and found that 45% of infants hospitalized 1 week or more acquired infection as did 10 of 24 staff members. Indeed, in the absence of effective barrier precautions, 30% to 60% of healthcare workers caring for RSV-infected children acquired infection *(38,39)*.

RSV infection appears to be acquired through inoculation of the eyes or nose by direct and indirect contact with infectious respiratory secretions *(31,39)*. Use by caregivers of eye–nose goggles markedly reduces spread of the disease *(38,40)*, probably by preventing self-inoculation via contaminated hands; others have shown similar benefit through use of gloves and gowns *(41)* or gloves, gowns, and masks *(42)*. To curtail both direct and indirect contact spread, use of Standard and Contact Precautions is appropriate. As is so often the case, scrupulous hand washing is the key to prevention of infection (see also Chapter 91).

Adenovirus The adenoviruses are responsible for a variety of syndromes: typical upper respiratory infections (e.g., cough, coryza, pharyngitis), particularly of children; febrile acute respiratory disease of military recruits; epidemic keratoconjunctivitis; pharyngoconjunctival fever; and, uncommonly, pneumonia *(43)*. Spread can be explosive, particularly in closed groups, such as military recruits or shipyard workers.

A number of outbreaks of epidemic keratoconjunctivitis have been documented in healthcare facilities. Most often, these outbreaks involve spread to patients exposed to contaminated ophthalmologic equipment or solutions or to a caregiver's unwashed hands *(44–52)*. Healthcare workers have acquired conjunctivitis not only through care of patients with conjunctivitis but also through care of patients with other adenovirus infections such as pneumonia *(53)* when appropriate isolation precautions were not observed (see also Chapter 90).

Although less common, outbreaks of respiratory disease resulting from adenovirus are more serious. A 1980 outbreak at Children's Hospital in San Diego, California, involved six patients (of whom four died) as well as 300 (78%) of 383 employees, of whom 15% developed conjunctivitis, 28% diarrhea, and 72% upper respiratory symptoms *(53a)*. The outbreak was terminated by strict isolation, cohorting, furlough of ill employees, and closure to new admissions. A smaller but similar outbreak in a neonatal intensive care nursery resulted in two patient deaths and infection of nine patients and ten staff members *(54)*. An outbreak in a pediatric long-term-care facility resulted in 11 deaths and 28 cases (46% attack rate) among patients; 22% of staff members (23 of 106) acquired illness *(55)*. An outbreak in another pediatric long-term-care facility following infection in one infant spread to involve two staff members and 10 (30%) of 33 patients, of whom two died *(56)*.

Although respiratory illness is rarely serious among adults, it may be more severe among residents of long-term-care facilities *(27,57)*. The infection can be fatal among the immunocompromised *(58)*. Serotype 14 has recently emerged and may be associated with more severe respiratory illness, even among the less infirm. An outbreak of severe respiratory disease in a military training facility affected 48% of trainees (551/1147), resulting in 23 hospitalizations (4 requiring admission to an intensive care unit [ICU]) and one death *(59)*.

Good evidence supports the spread of adenovirus by direct contact, indirect contact, droplets, and (predominantly among children) the fecal–oral route. Airborne spread is plausible, but we are not aware of a healthcare-associated outbreak that cannot be explained by contact or droplet spread. Airborne spread does not appear to be necessary to explain epidemics among military recruits *(59,60)*, given their prolonged close contact and the opportunity for droplet spread. Contact Precautions should be used for patients with adenovirus conjunctivitis; Droplet Precautions should be added for those with adenovirus respiratory infection. Environmental decontamination can be difficult, because the adenovirus is unusually hardy; alcohol and chlorhexidine are not reliable agents for disinfection *(61)*. A variety of vaccines have been used with success in the military, but none is available for civilian use (see also Chapter 48).

Rhinovirus and Coronavirus The rhinoviruses and coronaviruses cause the common cold—coryza, with variable cough, and pharyngitis. More than 100 serotypes of

rhinovirus are known (virtually ensuring the opportunity each year to encounter a virus to which one is not yet immune), as well as an as-yet-undetermined number of coronaviruses. Although the rhinoviruses and the usual coronaviruses are virologically distinct, they are clinically and epidemiologically similar enough to be considered together. Widespread community outbreaks caused by these viruses occur every winter, with low-level spread throughout the year. As every parent knows, incidence rates are highest among young children and decline with increasing age among adults (apart from a higher incidence among adults with young children). Schools and homes are the major foci of dissemination *(62)*. Given the ubiquitous opportunities for exposure and the usually benign outcome, healthcare workers may not view the common cold as a target for infection control. The frequency of infection, though, is not trivial. In a prospective analysis of healthcare workers with respiratory illness, nearly 40% were found to be infected with rhinovirus. Of those infected employees, one quarter provided care for high-risk patients *(63)*.

Transmission does occur between patients and caregivers, however, with outcomes that are burdensome for caregivers and potentially serious for selected patients, such as the immunocompromised, the very young *(30)*, or the elderly *(64)*. For example, Valenti et al. *(33)* investigated an outbreak of viral respiratory disease in a neonatal intensive care unit (NICU) and determined that one half of the cases were caused by RSV and one half were caused by rhinovirus; respiratory illnesses were similarly serious in the two groups of infants *(33)*. The investigation showed that the infants acquired their infections from their caregivers, 31% of whom had been ill in the preceding week. Unlike other viral respiratory infections, rhinovirus infections do not appear to be significantly more dangerous among the healthy elderly *(27)*, although lower respiratory tract involvement has been seen *(65)* and can have severe consequences among those with chronic pulmonary disease *(64)*.

During infection, rhinovirus is present in high titer in nasal secretions but only in low titer, if at all, in oral or pharyngeal secretions *(62)*. Volunteer studies have shown that infection is acquired readily via the nose or conjunctiva but poorly via the oral route. Although the virus is relatively hardy and can survive drying on environmental surfaces for several hours, the overwhelmingly most important route of spread is nose to hand to nose or eye. Prevention of spread of infection to or from workers is best accomplished through use of Standard Precautions, with particular attention to hand washing. Workers should be encouraged to stay home at times of profuse catarrh.

Severe Acute Respiratory Syndrome (SARS) Coronavirus

Severe acute respiratory syndrome (SARS) emerged in southern China late in 2002 and spread rapidly to Hong Kong, Singapore, Taiwan, Vietnam, and Canada *(66)*. Few cases were documented in the United States. A new coronavirus was quickly established as its cause. Although definitive information concerning the nuances of transmission is lacking, it is clear that droplet and close contact spread occur, sometimes with astounding efficiency from so-called super-spreaders. Aided by a large, distinctive, and malfunctioning sewage system, transmission from virus excreted in feces may have occurred in a high-rise housing complex in Hong Kong. The role of conventional fecal–oral transmission and the role of environmental contamination remain uncertain.

Healthcare-associated transmission to healthcare workers (with some fatal results) was a prominent feature in virtually every country experiencing the disease *(66–71)*. The United States was spared almost all healthcare-associated spread. This may have been the happy consequence of intensive education by the CDC, the good fortune of not having a super-spreader enter the country, or other unknown factors.

Much of the healthcare-associated spread of SARS was attributed to inconsistent observance of strict Airborne Precautions and inconsistent use of personal protective equipment, particularly during aerosol-generating activities. Droplet Precautions have been shown to be effective in reducing transmission risk. If SARS recurs, the fastidious use of isolation and personal protective equipment will be critical to avoiding spread of the virus to healthcare professionals.

Enteric Viruses

Coxsackievirus, Echovirus, Poliovirus, and Miscellaneous Enteroviruses The enteroviruses cause a variety of syndromes, including aseptic meningitis, encephalitis, poliomyelitis, herpangina, epidemic myalgia, upper and lower respiratory disease, hand–foot–mouth disease, conjunctivitis, pericarditis, and myocarditis *(72)*. In the United States, enterovirus infections occur almost exclusively between May and November, peaking in the summer months *(73)*. Many enterovirus infections are associated with exanthems. These viruses are so common, and their manifestations so varied, that recognition of transmission or identification of the causative agent often occurs only when a distinctive outbreak occurs.

Enterovirus infections are common in children, for whom they are generally mild. Infections are more likely to be serious among infants and adults, who experience a greater frequency of cardiac or neurologic involvement *(72)*. For example, an outbreak of echovirus 30 in a day-care center came to attention when 13 parents developed aseptic meningitis *(74)*. Similarly, in an outbreak of coxsackievirus B5 infection in a newborn nursery, illness was sporadic and mild among full-term infants but more prevalent and severe among premature infants; two nurses developed severe pleurodynia and fever *(75)*. A New Zealand hospital experienced a dual outbreak involving echovirus 11 and coxsackievirus B3 *(76)*. Eleven infants and 12 staff members developed meningitis; about one-half the infections were healthcare associated. Modlin *(77)* reviewed 16 nursery outbreaks of echovirus and found hospital personnel to be involved in nine cases. In a unique outbreak of hand–foot–mouth disease in Utah, 17 (13%) of 136 operating suite personnel—but no patients—developed clinical disease resulting from contact spread following illness in an index surgical technician *(78)*.

All enteroviruses reside in the gastrointestinal tract, and thus most spread is by direct contact involving the fecal–oral route. Standard Precautions should be supplemented by Contact Precautions for diapered or fecally incontinent individuals. Although many of these viruses

can be recovered from the oropharynx during illness and have been experimentally transmitted by coughing *(72)*, use of Droplet Precautions is not routinely recommended. As always, hand washing is likely the most important single preventive strategy.

Poliovirus infection has been eradicated from the Western Hemisphere *(79)*. Until worldwide eradication is achieved, occasional imported cases may be seen in the United States. However, the risk of spread will remain confined to sects that shun immunization unless immunization efforts wane in this country. The use of live attenuated oral poliovirus vaccine (OPV) has been abandoned in the United States. The risk of vaccine-associated disease was once seen at a rate of about one case per 2.6 million doses *(80)*. In countries where OPV is still used, a risk of vaccine-associated paralytic disease exists in contacts of OPV recipients, raising a theoretical concern of infection in a healthcare worker, although we find no evidence that such an event has ever occurred. In addition, transmission should be prevented by Standard Precautions. Thus, verification of primary poliovirus immunization of healthcare workers is recommended only for (a) those working with poliovirus in the laboratory; (b) those who might care for, or handle specimens from, a patient excreting wild poliovirus; or (c) in the event of an outbreak (see also Chapters 24 and 50).

Rotavirus, the Norovirus, and Related Viruses Rotavirus is the principal etiologic agent of infantile diarrhea and is responsible for up to one half of all episodes of acute diarrheal disease in infants and young children. The Norwalk-like viruses, a growing group of similar yet genetically diverse members of the Caliciviridae, consist of Norovirus (formerly, Norwalk virus) and a host of other small (27 nm, as compared to 70 nm for rotavirus) round-structured viruses (SRSVs) such as the Snow Mountain, Hawaii, and Marin County agents *(81)*. These agents appear to be responsible for two-thirds of all nonbacterial gastroenteritis *(82)*. An additional but much smaller proportion of viral gastroenteritis is attributable to the astroviruses, other caliciviruses, and minireoviruses. The coronaviruses (especially including the toroviruses *(83)*), adenoviruses, enteroviruses, and parvoviruses, discussed elsewhere in this chapter, can also cause gastroenteritis.

Several healthcare-associated outbreaks of rotavirus have been documented in neonatal or pediatric units, usually initiated by admission of children involved in a community outbreak *(84–91)*. Although each of these outbreaks involved substantial healthcare-associated spread of infection to hospitalized infants and children, no healthcare workers were reported to acquire illness. Several rotavirus outbreaks among geriatric populations have also been reported *(92–94)*. In contrast to the experience with pediatric outbreaks, infection and illness occurred among staff members in each of these geriatric outbreaks. Another outbreak, involving somewhat less-elderly patients on a cardiology ward, also involved the staff *(95)*, as did an outbreak on an obstetrics unit *(96)*. Whether this difference in likelihood of illness among staff members reflects random chance, differing host adaptation of viral strains, or systematic differences in infection control practices is unclear. Routine use of rotavirus vaccine in infancy will reduce the likelihood of the introduction of these viruses into healthcare facilities.

Rotavirus is spread by the fecal–oral route, principally via the hands of healthcare workers. The virus is highly stable, but environmental contamination does not appear to be an important pathway of transmission in an outbreak. Similarly, despite occasional isolation of the virus from pharyngeal secretions, airborne spread does not appear likely. Standard Precautions should be sufficient, supplemented by Contact Precautions for diapered or incontinent patients. Of interest, quaternary ammonium disinfectants appear to be ineffective against rotavirus; bleach or phenolics should be used if rotavirus environmental contamination is a concern *(97)*. (For additional information on enteric viruses, see Chapters 24 and 50.)

Noroviruses and other SRSVs cause explosive outbreaks of gastroenteritis in the home, school, community, and nursing home settings, particularly in the winter and spring. The gastroenteritis is marked by sudden onset of vomiting and diarrhea. Rates of secondary spread are high, and disease often involves school-aged children, parents and caregivers, and some young children. Of 270 outbreaks reported to the CDC from July 2000 to June 2004, 31% involved nursing homes and hospitals *(98)*. In a Tennessee outbreak, 55% of patients and 61% of the nursing staff in a long-term-care hospital became ill in a 10-day period *(99)*; an outbreak in a similar facility in Los Angeles involved 55% of residents and 25% of staff members *(100)*. Although attack rates have been higher among patients than staff in most outbreaks, this outcome is not always the case. In a recent North Carolina outbreak, 31% of staff and 11% of patients were ill *(101)*. A 3-week outbreak at a 600-bed Toronto, Canada, hospital involved 27% of the 2,379-person staff, as well as 10% of their household contacts *(102)*. The outbreak appeared to be centered in the emergency room, where 69% of the staff and 33% of visitors acquired illness; an extensive investigation suggested spread of infection by the airborne route. Investigation of a cruise-ship outbreak the following year similarly suggested a role for airborne or droplet spread *(103)*. Investigators of several subsequent outbreaks have concluded that airborne or droplet transmission occurred *(100,104–106)*, although some commentators remain skeptical *(81,107)*. Caul *(108)* has pointed out that, based on electron micrographic studies, each ounce of vomitus contains 30 million viral particles; only 10 to 100 are required to cause infection. Projectile vomiting associated with Norovirus gastroenteritis may aerosolize infectious droplets. This view is supported by data such as those of Chadwick and McCann *(104)*, who found that staff members exposed to nearby vomiting had a fourfold elevated risk of illness; nearby vomiting and close patient contact remained as the only significant independent predictors in a multiple logistic regression. Numerous outbreaks were reported to the CDC in 2006 to 2007, especially in long-term-care facilities. Two newly identified cocirculating norovirus strains that emerged in 2006 likely accounted for the increased burden of disease *(109,110)*.

The appropriate choice of isolation precautions for Norovirus and related gastroenteritis is somewhat contentious; Standard Precautions may not be sufficient. Although unproven, the plausibility of Droplet spread and the epidemiologic evidence supporting that route of transmission appear to be sufficient to warrant Droplet Precautions when confronted by forceful vomiting caused

by Norovirus-like agents. The evidence that environmental contamination plays a role in disease transmission is insufficient to recommend Contact Precautions, although, as is recommended for rotavirus, Contact Precautions should be considered in the event of fecal incontinence or other gross soiling. Healthcare-associated outbreaks may require cohorting and furloughing of involved staff members until they are well; most affected institutions have employed elaborate environmental decontamination, the need for which is unproven, but perhaps prudent (see also Chapters 24 and 50).

Hepatitis A The hepatitis A virus causes an acute, self-limited infection whose clinical manifestations vary with age. Children typically experience mild or no illness; adults commonly develop malaise, nausea, vomiting, and icterus. Fulminant hepatitis and death are rare (0.1–0.5%) *(111)*. The disease is clinically indistinguishable from several other viral hepatitides, and serologic diagnosis is required.

Healthcare-associated transmission is thought to be unusual. Most healthcare-associated outbreaks arise following admission of a patient not suspected to have hepatitis A, who either has subclinical infection, is in the prodrome, or is serologically false negative because of immune deficiency *(112)*, emphasizing the need to follow Standard Precautions for all patients. For example, three physicians caring for a 21-month-old girl with unsuspected anicteric hepatitis A became infected and ill; another developed subclinical infection *(113)*. Of 58 susceptible workers exposed to a patient who had vomiting, diarrhea, and fecal incontinence during the 8 days preceding jaundice, six (10.3%) acquired infection *(114)*. An outbreak in one NICU affected 13 infants, 22 nurses, 8 other staff, and four household contacts *(115)*; an outbreak in another NICU involved four infants and ten staff members. Investigations of such outbreaks have repeatedly identified two sets of behaviors as risk factors for worker infection: (a) a failure to wash hands, wear gloves, or both *(114–116)*; and (b) eating, drinking, or smoking in the patient care unit *(115,117,118)*.

Hepatitis A is transmitted almost exclusively by the fecal–oral route. A brief viremic phase occurs, during which blood-borne transmission is possible; airborne transmission has been alleged in at least one report *(119)* but is unlikely. The virus is present in high concentrations in the stool, and Standard Precautions should be supplemented with Contact Precautions in the case of fecal incontinence (including diapered infants).

Excellent vaccines have been developed and licensed. Although considered indicated among US healthcare personnel only for susceptible individuals in areas where hepatitis A is highly endemic *(120)*, cost-benefit analyses have suggested that the cost of hepatitis A vaccination in healthcare workers, per life-year saved, was similar to that of other standard medical interventions *(121)* (see also Chapter 46).

Herpes Viruses

Infections caused by the herpes viruses are among the most common diseases of humans. The herpes viruses are not cleared following primary infection but, rather, reside permanently in target tissue. The viruses remain capable of reactivation, which might result in clinical disease on a regular basis (herpes simplex), occasionally (varicella zoster virus [VZV]), or only in the face of immune compromise (cytomegalovirus [CMV]). The herpes viruses have been incriminated as risk factors for several neoplasms, and those that are lymphotropic alter immune function during active infection.

Herpes Simplex Virus Herpes simplex virus (HSV) infection is common. In the United States, by age 45, 70% to 80% of the population has acquired antibody to HSV-1, the strain associated with oral lesions; 15% to 20% of whites and 40% to 60% of blacks have antibody to HSV-2, the strain associated with genital lesions. Infection with either strain is lifelong; following primary infection, the virus travels along sensory nerves and becomes latent within sensory ganglia. In a recurrence, the virus reactivates, travels peripherally from the ganglia along the nerves, and reestablishes cutaneous infection *(122)*. Of importance to the healthcare worker, active virus can also be demonstrated in oral or genital secretions when no cutaneous or mucosal lesion is evident.

Although herpes virus can cause a variety of clinical syndromes, only one is routinely of pertinence to the healthcare worker: whitlow, a term derived from the middle-English whit flaw, or a flaw in the quick of the nail. Both HSV-1 and HSV-2 can cause whitlow; prior oral or genital infection does not necessarily protect one from acquiring a new infection of the finger *(123)*. Workers with frequent exposure to oral secretions, such as dental workers, respiratory care personnel, and anesthesia staff members, are at greatest risk *(124–128)*. Oral transmission can occur during mouth-to-mouth resuscitation *(129)*, and at least one outbreak has been reported involving transmission between nurses and patients in a pediatric ICU with further household spread *(130)*.

Under most circumstances, compliance with Standard Precautions should ensure protection from infection with HSV. Workers should glove (both hands) before contact with any oral secretions, including before airway suctioning. Contact Precautions should be considered when dealing with neonatal, disseminated, or severe primary herpes infection (see Chapter 44). Workers with whitlow should be restricted from contact with patients or their environment, and restriction from contact with high-risk patients may be appropriate for workers with orofacial herpes lesions.

Varicella Zoster Virus The VZV is the etiologic agent of chickenpox; reactivation of the latent virus in previously infected persons produces the disease known as herpes zoster (shingles). Chickenpox is common among children, in whom the disease is generally mild; severity of illness increases with age of the subject. Despite repeated epidemics in schools, a small proportion of adults escape childhood infection and remain susceptible. Nearly all healthcare workers (98–100%) with a clinical history of chickenpox are immune as measured by serology *(131)*, but 4% to 47% (median, 15%) of those with a negative or uncertain history of prior chickenpox are susceptible *(131)*. In one study, the rate of susceptibility was higher among those <35 (7.5%) than those more than 35 years of age (0%) *(132)*. Primary infection in susceptible adults can (but usually does not) cause serious disease, including varicella pneumonitis,

which can be fatal. Two groups are at special risk from primary varicella infections: the immunocompromised, among whom the mortality rate may approach 20%; and newborns whose mothers develop primary infection from 5 days before to 2 days after giving birth. The combination of absent transplacental antibody and massive exposure places these infants at high risk, and the mortality rate can approach 30% *(133)*.

Countless healthcare-associated outbreaks of VZV infection have been reported; indeed, it would be surprising to learn of a hospital caring for pediatric patients that has been spared. The high communicability of VZV, the routine presence in the hospital of immunocompromised patients at risk of serious or fatal disease if infected, and the presence of a core of susceptible healthcare workers make the management of VZV exposure one of the most challenging tasks of the infection control worker. This task is complicated by the fact that VZV is one of the few agents of healthcare-associated infection capable of true airborne spread *(134–142)*. Airborne spread of VZV can arise from patients (or personnel) with primary infection *(141)*, from patients with disseminated zoster *(136–138)*, or rarely from patients with localized zoster *(140)*. Of course, the infection can be transmitted by contact as well as through the air.

Management of VZV exposure incidents is burdensome and expensive. In a 1-year period at their hospital, Krasinski et al. *(143)* recorded 95 VZV infections (93 inpatients, two staff members), resulting in six exposure incidents involving 156 patients and 353 staff members. Fifty-one patients and 101 staff members denied prior VZV infection, but serology confirmed 5 and 11, respectively, to be susceptible. Three secondary infections occurred, six courses of varicella zoster immune globulin (VZIG) were administered, and 13 staff members were furloughed, at a cost of 356 hours of infection control staff time and $41,500. Similarly, Weber et al. *(144)* documented exposures in 121 patients and more than 300 staff members in a single year, of whom 11 and 49, respectively, were serosusceptible; costs of managing these exposures totaled $55,934. Given the frequency of VZV exposure incidents and the burden they impose, it is not surprising that the appropriate management of exposure events has been much debated *(137,145–154)*.

Immunization of susceptible employees is now the cornerstone of the varicella control program and is cost effective *(131,155,156)*. Susceptible employees can be identified by serotesting all employees, serotesting only those with a negative or uncertain history of chickenpox, or by foregoing serotesting and simply immunizing all those with a negative or uncertain history; the choice of strategy will depend on the institution's assessment of the relative costs of vaccine and serology, the rate of seronegativity in its employees, and the risk it is willing to accept of missing the detection and vaccination of a susceptible person *(131,157)*.

Immunization of staff does not address all concerns. Although seroconversion is not ensured following vaccination, postvaccination serology is not helpful and is not recommended *(120)*. In addition, vaccinees can develop a mild generalized rash and may pose a risk of infection to susceptible patients. The institution should develop policies concerning management of vaccinated employees who develop a rash illness or who are subsequently exposed to varicella. Employees with chickenpox, as well as immunosuppressed employees with zoster, must be excluded; otherwise, healthy employees with covered zoster lesions may work, except with high-risk patients.

When an exposure event occurs, unvaccinated susceptible employees with exposure (i.e., those who have provided care without the required precautions) are furloughed from the 8th to the 21st days following exposure *(120)*. Only employees known to be immune are assigned to care for patients with active VZV infection. Contact Precautions are used for all patients with VZV infection, and Airborne Precautions are added for those with primary varicella or disseminated zoster. Finally, exposed susceptible patients are discharged as soon as possible; if not discharged by the 8th day following exposure, they are placed in isolation through the 21st day or until discharged. VZIG is considered for exposed susceptible persons with impaired immune responses, including pregnant females (see also Chapter 43).

Epstein–Barr Virus The Epstein–Barr virus (EBV) is the principal causative agent of infectious mononucleosis and has been implicated as a cause of Burkitt's lymphoma and nasopharyngeal carcinoma. From 30% to 95% of children have antibodies to EBV by age 6; the proportion is higher in less-developed countries. After children, young adults are the most commonly infected group, in whom infection is more likely to be symptomatic *(158)*.

Transmission appears to require exchange of saliva and otherwise does not occur even with prolonged close contact. Few reports suggest healthcare-associated spread. Ginsburg et al. *(159)* reported an outbreak of infectious mononucleosis at an outpatient clinic in which five (17%) of 29 staff members developed clinical disease with serologic confirmation of recent EBV infection. The only possible route of transmission identified by the authors was the communal use of poorly washed coffee cups. One additional report noted the development of mononucleosis, reported to be serologically confirmed, in five (17%) of 29 laboratory workers; three had been involved in performing mononucleosis tests on serum specimens.

EBV is apparently transmitted rarely, if ever, in the healthcare setting, and no supplement to Standard Precautions is indicated in the care of patients infected with EBV.

Cytomegalovirus Nearly everyone acquires CMV infection at some point in life; age at first infection follows a pattern similar to that previously described for EBV, with larger proportions of children infected earlier in life in less-developed countries. Infection is most often asymptomatic or associated with nonspecific symptoms, but in less than 1% of cases may cause mononucleosis, hepatitis, or respiratory, gastrointestinal, or neurologic disease. As with the other herpes viruses, CMV infection is lifelong, and subsequent immunocompromised permits the virus to reactivate and cause respiratory, gastrointestinal, ophthalmologic, or other disease. In addition, CMV is one of the five classic teratogenic infections; primary or subclinical recurrent maternal infection during pregnancy can cause transplacental infection and neurologic damage to the fetus. Most fetal infections result from recurrent, rather than primary,

maternal infection; the risk of fetal infection is about 1% for pregnant women with CMV antibody *(160)*.

Concern regarding fetal CMV infection has stimulated substantial anxiety among healthcare workers, although to our knowledge, no healthcare-associated outbreak of CMV has ever been reported. Numerous studies of seroprevalence and seroconversion rates have been performed among nurses and other staff members who care for young children (*161,162,*163,*164–171)*; although some studies found some elevation in risk (often not reaching statistical significance), none concluded that healthcare workers incurred a material additional risk as compared to the risk associated with routine home and community life. In recent years, anxiety concerning CMV appears to have subsided. This reaction may reflect reassurance by the cited data and by the adoption of Standard Precautions—or perhaps distraction by other concerns such as HIV and pandemic influenza. CMV is excreted in urine and saliva, as well as stool, tears, breast milk, semen, and cervical secretions *(160)*. Droplet or airborne spread does not appear to occur, even during mechanical ventilation *(172)*. Adherence to Standard Precautions is adequate to protect the worker (see also Chapter 45).

Human Herpesviruses 6–8 Human herpesvirus 6 (HHV-6) has been identified as the causative agent of *roseola infantum* (also known as exanthem subitum and sixth disease). Roseola, the last of the classic exanthems of childhood to be differentiated, occurs commonly in children between the ages of 6 months, after waning of maternal antibody, and 4 years, by which age almost all children are seropositive. Within this age range, HHV-6 is a common cause of febrile illness, accounting for 20% of emergency room visits by infants 6 to 12 months old *(173)*. Reactivation during the year or two following primary infection was found in 16% of subjects *(173)*, and the occurrence of occasional outbreaks *(174)* suggests that reinfection of children is possible. Primary infection of adults is rare, because most acquire immunity in childhood, but when it occurs, it can produce lymphadenopathy, hepatitis, or a mononucleosis-like syndrome *(175)*. Serious or fatal HHV-6 reactivation has been demonstrated in recipients of bone marrow and, to a lesser extent, liver transplants. However, no evidence of transmission to healthcare workers exists as yet; thus, no infection control measures beyond Standard Precautions are needed. Serologic studies show that infection with human herpesvirus 7 is widespread in childhood. The virus may be another cause of *roseola infantum*; otherwise, its clinical significance is uncertain. Human herpesvirus 8 seems to resemble EBV in its ability to transform lymphocytes, and appears to be important in the cause of Kaposi's sarcoma *(176)* and has produced bone marrow failure in patients with kidney transplants *(177)*. Standard Precautions are indicated.

Herpesvirus Simiae Herpesvirus simiae, also known as simian herpesvirus B, is enzootic in rhesus, cynomolgus, and other macaque monkeys in whom it behaves much as HSV-1 does in humans. The disease can be transmitted to humans by the bite of a monkey; of 23 patients known to have symptomatic infections prior to 1987, 18 died of encephalitis. Only one known instance of spread from human to human has been reported, but it is noteworthy for occurring in the course of providing nursing care: the wife of a monkey handler repeatedly applied cortisone cream both to her husband's wound and to her own excoriated dermatitis; he died, but she received acyclovir and her disease did not progress *(178)*. Standard Precautions appear to be sufficient to prevent transmission to the healthcare worker *(179)*.

Other Major Childhood Viruses

Measles Measles, perhaps the most contagious disease extant, is an acute exanthematous infection caused by the rubeola virus *(180)*. It has been known since ancient times and was ranked first among the exanthems by the 19th-century nosologists *(181)*. Illness begins with cough, coryza, and fever; an enanthem (Koplik's spots) and a maculopapular exanthem follow. Measles is the most dangerous of the common exanthematous diseases of childhood. Even in healthy children, the disease can progress to pneumonia or, less commonly, encephalitis; bacterial pneumonia can also complicate the course. Chronic complications include subacute sclerosing panencephalitis. Measles infection is more serious in adults and in immunocompromised individuals. A safe, effective live attenuated vaccine exists, and its widespread use has interrupted the endemic transmission of measles in the United States *(182)*.

The exceptional communicability of measles permitted continued epidemics in past years, despite relatively high immunization levels. Measles outbreaks typically involve one or both of two groups: (a) infants too young to be immunized and young children who escaped immunization, and (b) young adults (including healthcare workers) with primary vaccine failure (about 2–5% of vaccinees). These problems have been addressed with substantial success by vigorous immunization campaigns *(183)* and by implementing a two-dose immunization schedule, which gives a second opportunity to immunize those who failed to seroconvert when first vaccinated (184,*185*). History makes it clear, however, that any slippage in immunization rates will lead to a resurgence of measles consequent to importations from areas of the world where active transmission continues *(182)*.

Reports of measles infections among healthcare workers caused by healthcare-associated outbreaks once were frequent *(185–195)*, and the frequency of such events climbed during the 1980s. For the 5-year period 1980 to 1984, 241 cases of measles (1.1% of all cases from 1980 to 1984) were acquired in healthcare settings; of the 241 cases, 24% were among staff members *(188)*. In the next 5-year period, 1,209 medical-setting cases were identified (3.5% of all cases during the period); 28% of the infections occurred in staff members *(187)*. Most of these cases represented a failure to immunize, not a failure of vaccine; only 20% of staff members for whom immunization status was known were documented to have received even one dose of vaccine. From 1985 through 1991, 2,997 measles cases were acquired in medical facilities, representing 4% of the total in that period *(196)*. As measles has been brought under greater control, the mean age of patients has shifted upward (27% of cases from 1993 to 1995 were in persons older than 20 years of age), and the proportion of cases acquired in medical settings increased (to 14% for the

period 1992–1995) *(197)*. In the United States, healthcare-associated acquisition of measles by healthcare workers in the 21st century has been essentially eliminated.

Healthcare-associated measles was a serious matter, involving substantial risk to patients and staff. During 1988, Children's Hospital in Los Angeles admitted 37 patients with measles *(193)*. Six cases were unsuspected, exposing 107 patients and 24 staff members. Twelve patients and seven employees developed measles; one patient died, and two workers were hospitalized with pneumonia. Eight hundred workers required vaccination, and 211 workdays were lost. Others have recounted the disruption and expense associated with these outbreaks *(190,192,198)*. In addition to jeopardizing healthcare workers and inpatients, healthcare-associated outbreaks can play an important role in propagating measles in the community (*191,193,199,200)*.

Like varicella, measles is spread readily by the airborne route. In 1937, Wells placed ultraviolet lights in selected classrooms of two schools *(6)*. In a subsequent measles epidemic, the attack rate was dramatically higher in the control classrooms, indicating causation of measles by an airborne agent susceptible to inactivation by ultraviolet light. Analyses of other outbreaks have confirmed the potential for airborne spread (*194,201,202)*, and Airborne Precautions should be used for patients known or suspected to have measles. Isolation strategies, however, clearly do not eliminate the risk of healthcare-associated measles; healthcare workers must be immune. Authorities now are willing to categorize as immune all persons born before 1957 *(196,197,203–205)*. From 1985 through 1991, 29% of healthcare workers reported with measles were born before 1957. Numerous serosurveys support the view that persons in this older group are less likely to be susceptible than younger persons *(206–212)*. Thus, because of the absence of endemic measles in the United States today, the 1957 demarcation is practical.

Immunization program costs can be minimized by devising program strategies that optimize the balance between obtaining preimmunization serology (to immunize only the susceptible) and immunizing without serology (a less expensive alternative if most will need immunization) (*180,207,213,214)*. The ideal measles prevention program would require that regardless of age, every worker with patient contact show documentation of receipt of two doses of measles vaccine after the first birthday, at least 1 month apart, or serologic evidence of immunity. Immunization would be required, as necessary, to satisfy this standard. However, substantial practical difficulties are encountered with this approach. Many workers properly immunized in childhood cannot document that fact and, thus, would require either serologic screening or two immunizations. If serologic screening is pursued, rubella immunity also should be assayed; more workers are susceptible to rubella than to measles (*205)*, and primary vaccine failure could have occurred with either antigen. Finally, a program incorporating serologic screening incurs substantial overhead associated with tracking of results and recall of employees.

The CDC's Advisory Committee on Immunization Practices (ACIP) recommended in June 2009 that all healthcare workers born after 1956 be required to provide laboratory evidence of immunity, laboratory confirmation of disease, or documented proof of receipt of two doses of vaccine; those born before 1957 should be considered for two doses of vaccine without proof of immunity (215). In an outbreak of measles, two doses of MMR vaccine is recommended for those born before 1957 who lack laboratory evidence of immunity. A simpler alternative approach is to give one injection of combined measles-mumps-rubella (MMR) vaccine to every employee who cannot document immunity or adequate prior immunization. Although this approach is not as comprehensive as the ideal program, the shortfall in immunization coverage would be limited to those persons who were susceptible to measles prior to this immunization, who failed to respond to this immunization, and who would have responded to a second injection given a month later. Data from Willy et al. (*211)* suggest that this strategy would leave 0.7% more of the work force susceptible (or equivocal) than would the ideal program (6.1% initially susceptible, 14.1% nonresponders to first vaccination, 81.8% responders to second vaccination). In comparison, programs that do not immunize persons born before 1957 leave 1.6% (*211)* to 6.4% *(206)* of employees susceptible; those that immunize only new hires can be expected to have substantial numbers of susceptible employees for many years.

Regardless of program strategy, MMR vaccine should be used. As discussed later, the consequences of healthcare-associated rubella can be disastrous, and many healthcare workers remain susceptible to mumps. No ill effects ensue from immunizing those already immune, and persons not yet immune require immunization. Individuals responsible for employee immunization programs will find helpful the previously cited program analyses *(209,210,216,217)*, the analysis of vaccine response by Willy et al. *(211)*, and the detailed recommendations published in a 1994 consensus paper *(218)* and recommendations provided by the ACIP (215) (see also Chapter 75).

Rubella Rubella (German measles) is another of the common exanthematous infections of childhood. Categorized as "third disease" when it was clinically differentiated from measles and scarlet fever 100 years ago, rubella is less contagious than measles and substantially less dangerous (except to the fetus). Postnatal acquired infection is commonly mild, and complications are rare apart from arthritis or arthralgia, which can affect up to one third of women (children and men are relatively spared). The arthritis may take several months to resolve and rarely may become chronic (*219)*.

The importance of rubella derives from its potential for devastating damage to the fetus. Depending on fetal age, infection may result in fetal death, heart defects, deafness, cataracts or glaucoma, retardation, and a host of other congenital maladies. The risk of fetal damage declines with maturity, from a high of 60% during the first 2 months of pregnancy. Once a susceptible woman is exposed, no intervention is likely to alter subsequent events favorably. Prevention of congenital rubella syndrome depends on establishing prior immunity.

Several healthcare-associated rubella outbreaks have involved staff members and patients *(214,220–229)*; Hispanic patients and staff are apparently particularly susceptible.

Such outbreaks can have substantial consequences. For example, a healthcare-associated outbreak in Boston involved 47 healthcare workers, one of whom terminated her early pregnancy *(227)*; rubella in an obstetrics clinic nurse exposed 151 obstetrics patients and 44 employees *(224)*; an obstetrician and two other staff members of a prenatal clinic developed rubella, exposing 56 susceptible pregnant women and infecting 2 *(223)*; 15 cases of rubella among staff members of an obstetrics service led to exposure of 231 pregnant women, of whom 25% were susceptible *(229)*. The national immunization program has substantially curtailed circulation of wild rubella virus, and such outbreaks have become rare. At the same time, however, the reduced circulation of wild virus has reduced the opportunity for women who escaped childhood immunization to acquire natural immunity prior to entering the childbearing years. The potential for rubella outbreaks among hospital personnel clearly remains should a case be introduced; serosurveys indicate that 4% to 6% of new hires are susceptible *(230,231)*, and 19% of practicing obstetricians surveyed in 1994 had neither been immunized nor been demonstrated to be immune by serology *(232)*.

Persons infected with rubella are infectious from 10 days before until 5 days after rash onset. Rubella is believed to be spread by respiratory droplets; airborne spread is plausible but has not been demonstrated. Droplet Precautions are recommended for management of patients with rubella, but as with measles, infections can be expected among employees despite isolation precautions unless the employees are immune. Pregnant, nonimmune workers should not care for patients infected with rubella (24).

A safe, effective live attenuated virus vaccine was introduced in 1969. Although the vaccine can cause a febrile illness as well as transient arthritis, these effects are less common, milder, and shorter-lived than with natural infection. Congenital rubella syndrome has not been demonstrated following vaccination, but the vaccine virus can cross the placenta; therefore, the vaccine should not be given to women who might be pregnant or become pregnant within 3 months. As discussed with respect to measles, employee health programs likely will find it more cost-effective to immunize with MMR all those who cannot document prior immunization than to perform serology for both measles and rubella *(196)*. Either approach, however, is less expensive than managing the consequences of an outbreak such as those previously described *(209,227)* (see also Chapter 51).

Mumps Mumps is an acute viral infection that, in unimmunized populations, occurs predominantly among school-aged children. Illness begins with nonspecific symptoms of a viral syndrome, followed by acute nonsuppurative parotitis that may be unilateral or bilateral. The swelling may be painful and accompanied by fever, but it resolves within a week. Other glands may be affected; epididymo-orchitis occurs in 20% to 40% of postpubertal men and may eventuate in testicular atrophy. Rarer manifestations include meningoencephalitis, oophoritis, pancreatitis, and nephritis *(233)*. A safe and effective live attenuated virus vaccine has been available since 1967. However, use of mumps vaccine was not required in many jurisdictions until relatively recently, and a substantial population escaped immunization *(203,234)*. Mumps is much less contagious than measles, varicella, or rubella, and many adults remain susceptible. Outbreaks of mumps have occurred in healthcare facilities with transmission from patient to worker *(235–237)* and from healthcare worker to patient *(238)*. Mumps is spread by droplets and by contact with saliva, which is infectious for up to 9 days prior to the parotitis. Droplet Precautions are recommended and should be implemented for 9 days after swelling onset. Prevention of healthcare-associated transmission is best accomplished by an immunized population, including healthcare workers. A policy of immunizing with MMR all persons who cannot document adequate prior immunization would obviate the need to perform yet another serology (see also Chapter 51).

Parvovirus The parvoviruses cause infections marked by bone marrow suppression and reductions in blood cell counts in a number of species. Parvovirus B19 is the cause of (a) erythema infectiosum, the fifth of the classic exanthems of childhood; (b) transient aplastic crisis in patients with chronic anemias; and (c) fetal infections, leading to hydrops or abortion. Erythema infectiosum is a generally mild illness marked by a "slapped cheek" facial rash and variable, often lacy, extremity rash. Arthritis and arthralgia may occur, most often in adults *(239)*.

Outbreaks in schools and the community are common. Patients with erythema infectiosum are no longer infectious by the time the rash appears, but patients with transient aplastic crisis or immunodeficiency are viremic while ill. Healthcare-associated outbreaks with spread to healthcare workers have been described *(240–242)*, but the risk to healthcare workers is low *(243)*, particularly as compared to school or day-care employees *(244,245)*, who are more commonly in contact with children incubating erythema infectiosum. Indeed, apparent healthcare-associated outbreaks may merely reflect transmission outside the hospital during a community-wide outbreak *(246)*. Parvovirus is believed to be spread by direct contact, blood, and respiratory droplets; true airborne spread has not been demonstrated, and the possible role of fomites is undefined. Standard Precautions are sufficient for care of uncomplicated erythema infectiosum but should be supplemented by Droplet Precautions for patients with transient aplastic crisis or other parvovirus syndromes (see Chapter 51).

Rare and Exotic Viruses

In this section, we briefly consider a number of viral infections that rarely, if ever, are encountered in US hospitals. Some are relatively benign but might be capable of spread to healthcare workers. Others have frightening reputations that are undeserved, because they have no demonstrated potential for spread to healthcare workers. A few have earned their formidable reputations and require caution, particularly including some of the hemorrhagic fever (HF) viruses.

Hemorrhagic Fever Viruses The viruses known to cause HF in humans differ in their structure and genetics but share the ability to cause a generalized illness that can be severe, marked by involvement of visceral organs (e.g., hepatitis, nephritis, carditis) and by thrombocytopenia or other coagulation defects that lead to disseminated intravascular

coagulation or other bleeding diatheses. Humans likely are not the primary hosts for any of these viruses, with the possible exception of dengue. The two most important routes of exposure are insect bites (yellow fever, dengue, Rift Valley fever, Crimean-Congo HF, Kyasanur Forest disease, and Omsk HF) and exposure to infectious rodent urine either directly or, more often, via contaminated airborne dust (Lassa fever, Argentine HF, Bolivian HF, and Hantaan and related HFs); the natural route of exposure is not known for Marburg and Ebola HFs *(247–251)*. Laboratory-acquired infections have been reported for Hantaan HF *(252)* and Kyasanur Forest disease *(253)*, but person-to-person transmission is not known to occur with yellow fever, dengue, Argentine HF, Bolivian HF, Rift Valley fever, Hantaan HF, Kyasanur Forest disease, or Omsk HF, and these diseases are not discussed further here (the hantavirus group is discussed in the next section).

Lassa Fever Of the four HFs with known potential for healthcare-associated spread, the best known is Lassa fever. The disease was first recognized following infection of three nurses at a missionary hospital in Nigeria, of whom two died *(254)*. The next year, an outbreak in the same community led to the death of a missionary physician who became infected through a cut received while performing an autopsy on a presumed Lassa fever patient *(255)*. Two years later, an outbreak in a Liberian missionary hospital led to illness in three patients and seven staff members; one nurse and all three patients died, for a case fatality rate of 36% *(256)*. However, subsequent studies have shown that the disease is endemic in West Africa, with infection rates of 10% to 20%, and that 90% to 95% of these infections are mild or inapparent *(257)*. Thus, the extraordinary precautions recommended and implemented by the CDC with the first case imported to the United States *(258)* were significantly relaxed in later recommendations *(259–261)*, because it became apparent that attention to barrier precautions prevented healthcare-associated infections *(259,261,262)*.

Outcome of Lassa fever is correlated with the degree and persistence of viremia; exceptionally high titers of virus can be found in blood. Prevention of healthcare-associated transmission must focus on avoidance of inoculation or aerosolization of blood. Primary human infection arises from inhalation of dust or aerosols contaminated with infected rodent urine. Person-to-person transmission of Lassa fever has occurred both in the household and the hospital setting, but initial fears of droplet or airborne transmission have not been substantiated. Because spread by direct contact is a possibility, it is appropriate to supplement Standard Precautions with Contact Precautions (see also Chapters 47 and 103).

Marburg Virus In 1967, several hundred African green monkeys imported from Uganda for medical research arrived in Marburg, Germany. Subsequently, 25 researchers working with monkey kidneys or tissue cultures became ill with a viral HF; seven died, as did 13 of the monkeys *(250,251)*. Six close contacts of the researchers also acquired illness; none died. The causative agent was determined to be a unique filamentous virus (filovirus). The virus has been identified in only a few subsequent sporadic cases of infection in Africa, several of which involved person-to-person transmission to medical staff members *(263,264)*. The natural reservoir and routes of transmission remain unknown *(265)*. The disease is clearly transmissible by the respiratory route from laboratory specimens, but person-to-person infection appears to require close contact. In the first known case of Marburg HF imported into the United States, none of the approximately 260 contacts (220 of whom were healthcare personnel) had evidence of a compatible illness. Six of the index patient's travel companions had serologic testing performed, which failed to reveal evidence of disease, supporting the notion that close, prolonged personal contact is likely necessary for person-to-person transmission, at least for sporadic disease *(266)*. During an epidemic of Marburg HF in the Democratic Republic of the Congo, between October 1998 and September 2000, 6 of 48 healthcare workers who cared for patients infected with Marburg virus were later discovered to be seropositive *(267)*. However, poor adherence to Standard Precautions was noted to be widespread. Pending further data, use of Contact Precautions and careful attention to Standard Precautions (especially with respect to blood) appear appropriate. Tissue and laboratory specimens should be handled with caution and processed so as to ensure containment (see also Chapters 47 and 103).

Ebola Virus Two simultaneous outbreaks of viral HF in neighboring regions of Sudan and Zaire in 1976 heralded the existence of yet another African HF virus *(268)*. Of the identified cases in Sudan and Zaire, 55% and 88%, respectively, died, reflecting substantial differences in the two viral subtypes *(250)*. The outbreaks were accompanied by healthcare-associated and household spread, but investigation of the only other known human outbreak, 2 years later, showed that person-to-person transmission required blood exchange or close personal contact *(269)*.

The Ebola virus is similar to the Marburg virus, joining it as the only other member of the filovirus family. As with Marburg virus, the natural reservoir of Ebola virus remains unidentified. Monkeys are susceptible and experience a high mortality rate *(270)*, which suggests that they are not among the natural hosts. The discovery of Ebola virus epidemics among medical research monkeys held in United States and Philippine primate centers caused considerable alarm and prompted strict new screening and quarantine regulations *(271,272)*. This Reston subtype of Ebola virus was highly virulent for monkeys, but it produced only subclinical infection among the exposed humans *(273)*.

More than 25 years had passed since the last recognized outbreak of human disease caused by Ebola virus when a large new outbreak involving the Zaire subtype began in early 1995 in Kikwit, Zaire. As in previous outbreaks, provision of medical care without use of standard infection control precautions led to an explosive healthcare-associated outbreak, with many worker and patient deaths at Kikwit General Hospital; job-specific attack rates ranged from 31% for physicians to 10% for nurses to 4% for other workers *(274)*.

Disease is spread by contact with infected blood or tissues; parenteral exposure is particularly lethal. Although epidemiologic and pathologic evidence suggest that aerosol

spread is possible *(273)*, the importance of this route is uncertain. Standard Precautions should be supplemented with comprehensive Contact Precautions; Droplet Precautions are not known to be necessary but their use, particularly when dealing with the highly lethal Zaire subtype, should depend on the clinical circumstances (see also Chapters 47 and 103).

Both Ebola and Marburg virus can persist in tissues for several months following acute infection, emphasizing the need for careful handling. As with Lassa and Marburg viruses, it is recommended to supplement Standard with full Contact Precautions.

Crimean-Congo Hemorrhagic Fever The fourth of the HFs shown to spread from person to person, Crimean-Congo HF, was first described among Russian troops in Crimea in 1944. Found in the Balkans, Siberia, China, the Middle East, and Africa, the virus is normally transmitted by ticks but can be spread by close contact, and several healthcare-associated outbreaks have occurred *(248,251,275–277)*. Healthcare-associated transmission can be prevented by attention to barrier precautions *(276)*; Contact Precautions should also be used (see also Chapters 47 and 103).

Other arenaviruses have been associated with sporadic secondary transmission *(278)*. For example, Sabiá virus has infected at least two laboratory workers *(279)*; although transmission to healthcare workers as a consequence of clinical duties has not been reported, enhanced infection control precautions have been proposed for care of such patients *(279)*.

Hantavirus Group Hantaan and related viruses are the etiologic agents of the HF with renal syndrome seen in Korea (Korean HF), China, Siberia, and southeastern Europe. Spread is through inhalation of dust or aerosols contaminated with infected rodent urine or, rarely, a rodent bite; person-to-person transmission is unknown. In June 1993, a previously unrecognized syndrome consisting of nonspecific viral symptoms progressing rapidly to respiratory failure, interstitial pulmonary edema, and death was described among residents of the southwestern United States *(280)*. Investigation showed the causative agent to be a previously unrecognized hantavirus (now named the Sin Nombre virus). Although the syndrome is new, the reservoir (the deer mouse) and route of transmission appear to be typical of the hantavirus family *(281)*. The deer mouse resides in much of the United States, and cases of hantavirus pulmonary syndrome have been described in various locales *(282,283)*. Little evidence supports healthcare-associated spread, and Standard Precautions should be sufficient.

Human Papillomavirus A large number of papillomaviruses produce various forms of warts and other epithelial tumors. Spread is believed to be by close contact and would be prevented by Standard Precautions. However, one interesting report showed the presence of intact papillomavirus deoxyribonucleic acid (DNA) in the vapor produced by laser treatment of warts and other verrucae *(284)*. Whether human infection at any site could arise from such an exposure is speculative, but prudence suggests ensuring proper exhaust of the vapor.

Pox Viruses Smallpox, a colossus of death, no longer strides the earth but lies imprisoned under heavy guard in Russia and Atlanta, awaiting final destruction *(285)*. Only as smallpox neared defeat by the milkmaid's friend, vaccinia, did smallpox reveal beyond doubt its ability to attack not only those nearby, via contact, but also distant victims through the air; to prove its prowess, it claimed as its final victim, a photographer infected in her office, by air wafted from a nearby research laboratory *(286,287)*.

Vaccinia too, its task completed, had largely disappeared, although vaccination continued for laboratorians working with orthopox and vaccinia viruses *(288)*. After the terrorist attacks of September 11, 2001, smallpox bioterrorism preparedness activities included a program of vaccinating public health workers and some hospital workers. This program is further discussed in Chapter 103.

Vaccinia can be passed from person to person by contact with the active vaccinial lesion, but no viremia is present in the normal host *(289)*, and respiratory spread does not occur; Contact Precautions are sufficient. The theoretical possibility of airborne spread exists with the progressive vaccinia that can occur in the immunocompromised, although it has not been demonstrated; should such a case be encountered (or smallpox be unleashed once again), Airborne Precautions would be indicated.

The large genome of vaccinia makes it attractive as a carrier of inserted genetic material, the hybrid then being used to infect a patient and thereby accomplishing gene therapy. This process raises numerous infection control issues, which are discussed in detail elsewhere *(290)* (see also Chapter 69). Vaccination of clinical staff working with patients given vaccinial recombinants may be appropriate.

Monkeypox produces a disease that is similar in appearance to smallpox but is not readily transmitted from person to person *(289)*. During the summer of 2003, an outbreak of monkeypox occurred in the United States among persons who had purchased imported exotic pets (Gambian giant rats among them) and prairie dogs that had become cross-infected at the animal distribution facility *(291)*. No transmission to healthcare providers was detected. CDC's ACIP suggested that vaccinia vaccine (smallpox vaccine) might be a useful preventive measure among potentially exposed healthcare workers. Not much, if any, vaccine was used for that purpose. Molluscum contagiosum and orf require close contact for transmission *(292)*; Standard Precautions are sufficient.

Rabies and the Other Encephalitis Viruses Vector-borne encephalitis viruses include (a) eastern, western, and Venezuelan equine encephalitis virus; (b) St. Louis and tick-borne encephalitis viruses; (c) the California encephalitis virus group (including La Crosse and Jamestown Canyon viruses); (d) Powassan, Louping Ill, and Negishi viruses as well as West Nile virus. Most strains are spread by mosquitoes, some by ticks; primary host species include horses, birds, deer, rodents, and pigs. None of the viruses are transmitted from person to person, although some have infected laboratory workers exposed to aerosols *(247,248,293)*.

West Nile virus arrived in the United States in 1999, causing an outbreak of meningoencephalitis among largely elderly residents of New York City *(294)*. Over succeeding

mosquito transmission seasons, it has spread stepwise across the entire United States. Although the vast majority of human infections are acquired from mosquito bites, transplacental transmission to a fetus, transmission via breast milk, and acquisition from an infected organ donor as well as from transfused blood have been documented. No special risk to healthcare workers has been shown.

Lymphocytic choriomeningitis (LCM) virus, related to the Lassa fever virus, shares its characteristic of being spread by exposure to infectious rodent urine; rodent bites have also been implicated. Unlike Lassa virus, LCM virus is not known to spread from person to person. Several outbreaks of LCM have affected medical center staff, but all have been attributable to contact or presence in the same room with rodents being used in research *(249,295–298)*.

Rabies, one of the most feared diseases, is a viral zoonosis transmitted to humans through the bite of an infected mammal. Rabies is the most uniformly fatal infection known; survival is nearly unprecedented once symptoms begin. Consequently, anxiety among healthcare workers is intense once a patient has been diagnosed with rabies, and scores or even hundreds of healthcare workers are commonly administered rabies prophylaxis following diagnosis of a patient. Although rabies virus can be isolated from a variety of human tissues and fluids, including saliva, a well-documented instance of person-to-person transmission of rabies has never occurred, apart from corneal transplantation *(299,300)*. One report describes two possible cases in Ethiopia of human-to-human transmission (both involving saliva: one bite and one kiss), but these cases were not laboratory confirmed *(301)*.

No evidence supports droplet, airborne, or environmental transmission from human sources for any of these agents; therefore, Standard Precautions are sufficient. Healthcare workers involved with a rabies case do not need prophylaxis unless mucous membranes or nonintact skin were exposed to potentially infectious body fluids *(299)*. Preexposure immunization is indicated for those working with rabies virus or likely to come into contact with potentially rabid animals (see also Chapter 47).

Prions

Prions are poorly understood, small, protein-containing particles that can be detected in the brain in certain pathologic states and appear to be responsible for a number of slowly progressive neurodegenerative diseases. These transmissible spongiform encephalopathies include Creutzfeldt–Jakob disease (CJD), kuru, Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia in humans, and scrapie, bovine spongiform encephalopathy (mad cow disease), transmissible mink encephalopathy, and related diseases in animals. Purified prion material derived from the aforementioned diseases can induce the disease in a healthy host when injected (or, in the case of kuru, when ingested). No one has been able to demonstrate nucleic acids in prions, and their reproduction might involve an alteration in a protein normally encoded by the host *(302)*.

Person-to-person spread of CJD has occurred in connection with corneal transplants *(303)*, dural grafts *(304)*, contaminated neurosurgical instruments *(305)*, and cadaver-derived growth hormone *(306)* or gonadotropin *(307)*. Kuru is acquired by ingestion of infected human brain, and new-variant CJD is a rare sequela to ingestion of beef products from cattle with mad cow disease *(308)*. The evidence strongly indicates that CJD and related diseases do not spread by the airborne or contact routes, and Standard Precautions are sufficient when caring for patients with these diseases. However, prions are extremely resistant to inactivation and retain infectivity even in formalin-fixed tissue. Patient specimens and contaminated equipment (e.g., needles, surgical instruments) must be handled with particular care, and detailed recommendations have been offered for their decontamination *(309)* (see also Chapters 47 and 80).

CHLAMYDIAL, RICKETTSIAL, AND MYCOPLASMAL INFECTIONS

Chlamydiae

Like the viruses, members of the order Chlamydiae are obligate intracellular parasites. Three species have been identified: *Chlamydia trachomatis,* the cause of trachoma and lymphogranuloma venereum; *Chlamydia psittaci,* the agent of psittacosis; and *Chlamydia pneumoniae,* previously called the TWAR agent, which causes an atypical pneumonia. (The first two recognized isolates were identified at the University of Washington and were obtained from a Taiwanese child in 1965 and a student with acute upper respiratory infection in 1983.) Humans are the natural hosts of *C. trachomatis* and *C. pneumoniae,* whereas *C. psittaci* is a pathogen of animals, particularly psittacine birds (parrots), and infects humans only secondarily. *C. trachomatis* is spread by contact with infected secretions, and Standard Precautions are sufficient to protect healthcare workers.

C. psittaci is spread through the air, but it is uncertain whether person-to-person transmission occurs. Several healthcare-associated outbreaks have been described in the literature that were attributed at the time to psittacosis *(309a,309b,313)*, but they either antedated the recognition of *C. pneumoniae* (to which bird owners are as susceptible as anyone else) and might well have been caused by the latter agent *(310)*, or rested on serologic results that were less than fully conclusive *(311,312)*. *C. pneumoniae* has been implicated in outbreaks of pneumonia in various closed communities such as classrooms and military barracks; healthcare-associated outbreaks appear to be very rare. In at least one outbreak, serologic data support the impression of healthcare-associated spread of chlamydial pneumonia, but whether the species was accurately identified is unclear (*313*).

Although droplet spread of chlamydial pneumonia cannot be excluded, current evidence does not appear to justify imposition of Droplet Precautions; Standard Precautions should suffice (24).

Rickettsiae

The rickettsiae are also obligate intracellular parasites. Those of the genus *Rickettsia* all have nonhuman mammalian reservoirs, are transmitted to humans by insect vectors, and survive only briefly outside a host. The lone member of the genus *Coxiella* behaves quite differently. *C. burnetii*,

the etiologic agent of Q fever, is a gram-negative coccobacillus that can sporulate and thereby survive outside the host for extended periods *(314)*. Q fever (so named because its cause was a query) is a zoonosis of ungulates (e.g., sheep and cattle) that can cause an acute and chronic febrile illness in humans. Humans are highly susceptible; a single microorganism can cause disease. Outbreaks of Q fever have occurred not only among those who work with ungulates but also those nearby. Included among the latter group have been a number of healthcare workers exposed to sheep used in research at their medical centers *(315–320)*. Laboratory workers are also at risk *(321)*; indeed, the first recognized case of Q fever in the United States was acquired occupationally by a National Institutes of Health physician *(322)*. However, despite the fact that *C. burnetii* can be isolated from human milk, placenta, and blood, no evidence indicates transmission to healthcare workers during normal clinical duties, and Standard Precautions are sufficient.

Mycoplasmas

The members of the *Mycoplasma* and closely related *Ureaplasma* species are the smallest free-living microorganisms known. Because they have fastidious growth requirements, they are difficult to culture on artificial media and are found in nature only in close relation with their hosts. Of the numerous mycoplasmas isolated from humans and potentially involved in human disease, only one has been associated with outbreaks among healthcare workers: *Mycoplasma pneumoniae,* a prominent cause of the atypical pneumonia syndrome.

M. pneumoniae infections occur sporadically or as outbreaks in closed populations such as families, schools, and military barracks *(323)*. Younger persons are more susceptible and tend to have milder disease. Outbreaks among staff members have been described in healthcare institutions in Finland, Ohio, Texas, and New York *(324,325)*. Transmission is believed to be by respiratory droplets, and Droplet Precautions should be followed.

BACTERIAL INFECTIONS

Bacterial Enteric Infections

Salmonellae The salmonellae are aerobic gram-negative bacilli that inhabit the intestinal tracts of humans and animals. Some strains are specific to humans or other species, whereas others have a broad host range. Salmonellae routinely cause gastroenteritis but can induce a wide variety of diseases in humans. *Salmonella typhi,* the causative agent of typhoid fever, produces the most serious illness in humans, but many of the animal salmonellae can produce serious or fatal disease, particularly in the elderly *(326)*.

Salmonella was once a common cause of healthcare-associated infectious diarrhea, particularly in newborn and pediatric units, which accounted for 50% of reported healthcare-associated cases *(327)*. Between 1963 and 1972, 28% of reported *Salmonella* outbreaks in the United States occurred in healthcare institutions *(328)*; case–fatality ratios were <1% in most hospital units but rose to 3% in pediatric units, 7% in nurseries, and 9% in nursing homes.

Healthcare-associated outbreaks often involve healthcare workers *(329–332)*, who occasionally become chronic carriers. One unusual healthcare-associated outbreak involved spread of *Salmonella* infection from patients to nursing home laundry workers who handled soiled sheets without use of gloves or other barrier precautions and who routinely ate in the laundry room *(333)*.

Salmonella is spread by the fecal–oral route and, notwithstanding the rare report suggesting alternative routes of spread *(334)*, Standard Precautions are sufficient to protect the worker. In addition, soiled laundry must be handled in accord with established recommendations, and food should not be consumed in work areas (see also Chapters 24, 34, and 50). Two excellent typhoid vaccines, one oral, one parenteral (as well as an older parenteral vaccine that should no longer be used), are now available, and immunization is indicated for laboratorians working with *S. typhi*.

Shigella *Shigella* species are the principal etiologic agents of bacillary dysentery; *S. dysenteriae* causes the most severe disease, whereas *S. sonnei* has been the most common isolate in recent years. Shigellosis is easily transmitted, because the infective dose is 100 microorganisms or fewer. The disease is marked by abdominal cramping and watery diarrhea that becomes bloody or mucoid, usually accompanied by fever. Illness typically lasts 1 week but can be prolonged *(327,335)*. Healthcare-associated outbreaks of *Shigella* are much less common than are *Salmonella* outbreaks but can be a particular problem in long-term-care and custodial institutions for children and for the elderly *(336–340)*. In each of the cited outbreaks, staff members acquired infection from patients and often facilitated the spread of infection.

Shigella species are transmitted solely by the fecal–oral route, and Standard Precautions normally are sufficient to protect the worker. Because of the low infective dose, Contact Precautions should be used when managing diapered or incontinent patients.

Cholera *Vibrio cholerae* causes cholera, a toxin-mediated profuse watery diarrhea that can cause prostration in the first hour and death from dehydration in the second. Cholera, described in ancient Greek and Sanskrit texts, circled the globe in six successive epidemic waves during the19th and early 20th centuries. Epidemic cholera returned in 1991 in South America, establishing a new endemic focus *(341)*.

Spread of cholera is by the fecal–oral route. On rare occasions, humans may become carriers. Healthcare-associated transmission to patients has occurred *(342,343)*, but little evidence indicates transmission to healthcare workers. As with other highly transmissible gastroenteritides, Standard Precautions should be supplemented with Contact Precautions when caring for diapered infants or fecally incontinent patients (see Chapter 50).

Other Bacterial Agents of Diarrhea *Clostridium difficile* secretes a toxin that causes pseudomembranous colitis. Risk of the disease is substantially elevated in patients whose normal bowel flora have been depleted by treatment with antibiotics, particularly broad-spectrum cephalosporins *(344). C. difficile* is an important healthcare-associated pathogen spread by direct and indirect contact *(345,346)*, and

Standard Precautions should be supplemented with Contact Precautions. Healthcare workers might acquire the microorganism occupationally, but normally would not be expected to manifest illness. However, full-blown pseudomembranous colitis has been reported in staff members who were taking a bowel-active antibiotic during a healthcare-associated outbreak of disease *(347,348)* (see Chapter 37).

Escherichia coli is the most common of the aerobic enteric bacteria that colonize the normal intestinal tract. There are numerous strains, some of which can be important causes of enteric disease. Enteroinvasive *E. coli* microorganisms behave like *Shigella* and cause dysentery; enterotoxigenic strains cause a cholera-like illness; the enterohemorrhagic *E. coli* O157:H7, often associated with undercooked ground beef, causes bloody diarrhea. All strains are spread by the fecal–oral route and require Contact Precautions only when managing diapered or incontinent patients. Similar precautions are recommended for the bacterial diarrheas not discussed here.

Bacterial Diseases Spread by the Respiratory Route

Diphtheria Diphtheria, described by Hippocrates, has been a fearsome disease; an epidemic in New England in the early 18th century killed one third of all children, and in the early 1920s diphtheria was the leading cause of death of Canadian children aged 2 to 14 years *(349)*. Epidemics occurred at approximately 25-year intervals until modern times; the disease has nearly been eradicated through use of diphtheria toxoid vaccines. The causative microorganism is *Corynebacterium diphtheriae,* a gram-positive bacillus for which humans are the only known reservoir. The microorganism colonizes the respiratory tract or skin wounds, where it may be asymptomatic or produce mild inflammation. The microorganism does not invade, but if it is infected by the toxin-encoding bacteriophage, it can liberate a toxin that interferes with ribosomal protein synthesis, causing local accumulation of killed cells and inflammatory residue (the pseudomembrane), myocarditis, neuropathies, and nephritis. Skin carriage can be common in certain groups; for example, 86% of diphtheria cases among urban alcoholics in Seattle, Washington, were cutaneous *(350)*. Spread of the microorganism to others occurs more readily from those with skin carriage than from those with pharyngeal carriage *(351)*.

Adequate antibody to the toxin largely protects from the serious consequences of infection but does not eradicate carriage of the microorganism. Because introduction of toxigenic strains into the community can result in disease if immunization levels are inadequate, it is pertinent that 22% to 62% of US adults under 40 years of age and 41% to 84% of persons 60 years and older lack protective levels of diphtheria antitoxin *(352)*. The possible consequences of widespread adult susceptibility to diphtheria were illustrated in Russia and other former Soviet states, which experienced a massive outbreak of diphtheria in the 1990s following decreased childhood immunization programs, resulting in 140,000 cases and 4,000 deaths *(353)*. Although diphtheria has become rare in the United States and Western Europe, outbreaks involving patients and staff members have occurred in healthcare institutions *(354,355)*. Serotesting during one hospital outbreak found 37% of staff members to be susceptible. Diphtheria is spread both by respiratory droplets and by direct contact. Droplet Precautions are appropriate for cases with respiratory tract disease, and Contact Precautions should be implemented for those with cutaneous diphtheria. Employee health programs should ensure that employees have been immunized within the past 10 years with tetanus and diphtheria toxoids (Td) adsorbed, for adult use (184).

Pertussis Guillaime Baillou described an outbreak in Paris of a disease he called "quinta" in 1578; in 1679, Thomas Sydenham renamed the disease pertussis, meaning violent cough. The disease is highly contagious and spreads via respiratory droplets. When *Bordetella pertussis* microorganisms enter the respiratory tract, they attach via their fimbriae to cilia, causing ciliary stasis, cell death, and shedding of respiratory mucosal cells. Because they do not invade, they largely escape cellular host defenses, continuing to produce local damage and, through their toxins, systemic disease, until the host finally is able to clear the microorganisms. The onset is insidious, seeming like a typical cold or upper respiratory infection with little fever. Within a week or so, a cough appears that progresses within another week or two to paroxysms. In a paroxysm, the patient may produce up to a dozen short coughs with no intervening inspiration; cyanosis and vomiting often occur. Finally, after perhaps expelling some thick mucus from the bronchial tree, a desperate inspiration through a narrowed glottis produces the characteristic whoop. This phase continues for up to 4 weeks and then gradually subsides; nonparoxysmal cough may persist for as long as 6 months. Pertussis is one of the most contagious of the infectious diseases, and is a significant health problem worldwide, with more than 60 million cases and 500,000 to 600,000 deaths annually *(356)*.

Pertussis can be an important cause of respiratory disease in adults *(357–364)*, who experience a less severe syndrome marked by a debilitating cough that persists for many months. One quarter to one-fifth of adults with persistent cough have laboratory evidence of recent pertussis infection *(365,366)*. A number of hospital outbreaks have been reported in which staff members became infected by symptomatic patients and subsequently spread disease to other patients and adult contacts *(367–373)*, and studies have demonstrated both the prevalence and the incidence of pertussis among healthcare workers *(374–376)*. Unfortunately, adverse reactions to conventional whole-cell pertussis vaccine are common and severe among adults; for example, significant local reactions were noted in as many as 97% of adult recipients of whole-cell pertussis vaccine in one hospital outbreak *(371)*. Because standard pertussis vaccine is not given beyond age 6, antibody wanes with age, and adolescents and adults become increasingly susceptible to pertussis. In turn, they act as a reservoir of disease able to expose and infect infants not yet immunized *(373,374,377)*. These factors are thought to be important in the current epidemic of pertussis: there were 7,796 cases of pertussis reported in 1996, the highest total in nearly 30 years *(378)*.

Acellular pertussis vaccines have been available for use in children and are now licensed for adult use. To mitigate the healthcare worker's role in pertussis epidemics,

employee health programs should utilize tetanus-diphtheria acellular pertussis (Tdap) vaccine. It is recommended that adults substitute a one-time dose of Tdap for a Td booster, providing at least 2 years have elapsed since the prior Td immunization (184). In the event of an outbreak, consideration should be given to mass immunization with Tdap of all potentially exposed persons who cannot document prior receipt of Tdap.

Droplet Precautions should be used when managing known or suspected pertussis infection. Erythromycin or its more recent derivatives (e.g., azithromycin) can be used for prophylaxis of exposed healthcare workers and others *(373)*, but may fail (*379)*; work restrictions are appropriate for symptomatic employees (380).

Streptococcus *Streptococcus pyogenes* (group A *Streptococcus*) is one of the most common and dangerous bacterial pathogens. Group A streptococci colonize the throats of 15% to 20% of schoolchildren; anal, vaginal, scalp, and other cutaneous carriage also occurs. The microorganism commonly causes acute pharyngitis and cutaneous infections, including erysipelas, and was the most common cause of puerperal sepsis in the days before Semmelweis. The group A streptococcus can cause fatal deep infections, including pneumonia, sepsis, myositis, and necrotizing fasciitis, and it can cause nonsuppurative sequelae, including rheumatic fever and nephritis *(381)*.

Streptococcal toxins are responsible for streptococcal toxic shock syndrome and for scarlet fever (second disease, the only classic exanthematous disease of childhood caused by a bacterium). Most reported healthcare-associated outbreaks of group A streptococcal disease have involved transmission from healthcare workers to patients, resulting in wound (382) or skin and soft tissue *(383)* infections. Healthcare workers can acquire colonization or infection from patients, most commonly resulting in pharyngitis *(384–386)*. Invasive disease resulting from patient to healthcare worker transmission has also been reported, resulting in toxic shock syndrome with associated pneumonia *(387)* or necrotizing fasciitis *(388,389)*.

Group A streptococcus is spread by respiratory droplets, as well as by direct and indirect contact with contaminated sources such as respiratory secretions, food, and drink *(384)*. Reports have also apparently documented the airborne spread of group A streptococci *(16)*, but such events are probably rare. Contact Precautions should be used for persons with purulent wound infections (including burns), unless the infections are minor and well contained by bandages. Droplet Precautions should be implemented until completion of the first 24 hours of effective antibiotic therapy in patients with severe group A streptococcal wound infection and those with respiratory tract infection, including pharyngitis, pneumonia, or scarlet fever (which is most commonly associated with pharyngeal infection). Infected workers should be excluded from patient care and treated, as should asymptomatic carriers who have been epidemiologically implicated in transmission (24,*390,391*).

Pneumococcus *Streptococcus pneumoniae* is a major cause of bacterial pneumonia, sinusitis, otitis media, and meningitis, and can cause a host of other serious infections. Previously uniformly susceptible to penicillin, pneumococci increasingly manifest reduced susceptibility or resistance to penicillin, erythromycin, and even third-generation cephalosporins *(392–394)*. Unlike group A streptococci, pneumococci elaborate few toxins; their ability to cause disease resides in their capacity to reproduce in host tissues and to stimulate a vigorous inflammatory response.

The pneumococcus colonizes the nasopharynx in 5% to 10% of adults and 20% to 40% of children *(395)*. Infection is seasonal, increasing in the winter months, and more likely at the extremes of age. Outbreaks of pneumococcal disease usually occur in circumstances of prolonged close contact *(396–401)* and are uncommon but not unprecedented in hospitals *(396)*; several nursing home outbreaks have been documented *(402–406)*. Spread is by respiratory droplet but, as noted, usually requires prolonged close contact. In most cases, Standard Precautions will be sufficient, but Droplet Precautions are recommended when the infecting pneumococcus is resistant to antibiotics.

Healthcare workers are not a group recommended to receive the present polysaccharide polyvalent pneumococcal vaccine. Conjugate pneumococcal vaccines, which link the capsular polysaccharide to a carrier protein and thereby stimulate the T-cell–dependent arm of the immune system, are used routinely in young children *(402)*.

Meningococcus *Neisseria meningitidis* has a fearsome reputation as the causative agent of epidemic cerebrospinal fever and, indeed, is capable of producing rapidly fatal sepsis or meningitis. However, the microorganism is not nearly as communicable as fables (and television) portray. Epidemics of meningococcal disease occur throughout the world, and transmission undoubtedly occurs with prolonged close contact *(407,408)*. Household or other close contacts are at 200 to 1,000 times the risk of developing meningococcal disease as is the general public *(409)*; secondary attack rates in households average 2% to 5% *(407)*. However, although healthcare-associated *(407,410–412)* and laboratory-based *(413)* transmission has occurred, such transmission is distinctly unusual and appears to be more likely to occur with meningococcal pneumonia *(410,412,414)* than with meningitis or sepsis *(407)*.

Transmission is by respiratory droplets, and Droplet Precautions are appropriate for patients with invasive meningococcal disease, particularly pneumonia, until 24 hours after institution of effective therapy. Chemoprophylaxis should be offered to workers having prolonged close contact or contact with respiratory secretions without appropriate barrier protection and might consist of orally administered ciprofloxacin (or equivalent), 500 mg once, or rifampin, 600 mg twice daily for 2 days. Chemoprophylaxis is not recommended for those individuals who have had only casual contact with an infected patient. Healthcare workers are not a group routinely recommended to receive the meningococcal vaccine, unless at persistent risk of exposure (e.g., certain laboratorians) (415) (see also Chapter 47).

Haemophilus Influenzae *Haemophilus influenzae* is a gram-negative bacillus indigenous to humans, commonly carried in the pharynx and, less often, the conjunctivae and genital tract. In past years, *H. influenzae* type b (Hib) was the most common cause of meningitis among children

between 1 month and 2 years of age. However, following licensure of the conjugate Hib vaccines *(416)*, invasive Hib disease among children has virtually disappeared *(417)*. Pneumonia caused by *H. influenzae* occurs among adults but tends to be restricted to those with lung disease, alcoholism, or other compromise. Healthcare-associated outbreaks of type b and nontypable *H. influenzae* have been reported *(418–422)*, but spread to healthcare workers appears to be unlikely. Use of Droplet Precautions for patients with invasive *H. influenzae* infections is recommended to prevent spread of the microorganism to other patients, particularly unimmunized children, the elderly, and the immunocompromised.

Plague "The hand of the Lord was against the city with a very great destruction: and he smote the men of the city, both small and great, and they had emerods in their secret parts." 1st Samuel 5:9

Yersinia pestis, the causative microorganism of plague, is a gram-negative bacillus that is zoonotic among rodents. Although some of the pestilences described in First Samuel and other books of the Bible may have been the disease we now know as plague, the first epidemic ascribed with confidence to that disease was the Great Epidemic of Justinian, which took the lives of 25% of the population of the Roman Empire in 542 A.D. *(423)*. Two more great epidemics swept the world in the 14th (the "Black Death") and late 19th (the "Bombay Plague") centuries. In modern times, plague persists in endemic foci in the western United States, Southeast Asia, east Africa, and South America. In the United States, 362 cases of human plague were reported from 1944 to 1993. The disease is slowly becoming more widespread and, in the last decade, has been reported from Texas, Oklahoma, and every contiguous state in or west of the Rockies. As suburban development has extended, the household has become the most common site of exposure, and domestic cats allowed to roam in endemic areas have become important sources of transmission to cat owners and veterinarians *(424)*.

There are three distinct forms of plague. Bubonic plague is characterized by markedly swollen and tender inguinal, axillary, or other lymph nodes (buboes), and is typically spread by the bite of a flea (or similar pest). Bubonic plague commonly eventuates in sepsis. However, septicemia can occur directly, without development of a bubo, and is called septicemic plague. Finally, pulmonary involvement permits direct human-to-human spread of the disease, causing pneumonic plague. In the absence of prompt antibiotic therapy, fatality rates for bubonic, septicemic, and pneumonic plague are 70%, 100%, and 100%, respectively; even with antibiotics, 33% of patients with septicemic plague die, three times the rate of those with bubonic plague *(425)*. The outbreak of pneumonic plague in India in late 1994 served as a reminder that the disease remains dangerous; of 276 persons hospitalized in the first 3 weeks of the outbreak with a diagnosis of plague, 56 (20%) died *(426)*.

Pneumonic plague is spread by respiratory droplets. Because any case of plague may progress to pulmonic involvement, all patients with plague should be placed on Droplet Precautions until the patient has received an effective antibiotic for 24 to 48 hours *(427)*; persons known to have respiratory tract disease should remain on Droplet Precautions for at least 72 hours following initiation of effective therapy. Care should be taken with laboratory specimens not to create aerosols, but otherwise they may be handled normally (see also Chapter 47).

Brucellosis Brucellosis is a zoonosis due to any of several species of *Brucella*. Like typhoid fever, brucellosis is an enteric fever characterized by fever (undulant if untreated), malaise, headache, and possibly, lymphadenopathy, visceromegaly, and depression; most organ systems can become involved. Nearly all cases occur in persons with close contact with infected animals. Airborne transmission in the laboratory *(428,429)* is a potential problem if proper safeguards are not followed (see Chapter 77), and transmission to nurses and physicians caring for infected patients has occurred *(429)* but is rare. Standard Precautions are sufficient to prevent transmission during clinical care.

Legionellosis Healthcare-associated outbreaks of legionellosis (either pneumonia or Pontiac fever) attributable to environmental sources have been reported on multiple occasions, as detailed in Chapter 36. Although the exposure of staff members to these environmental sources is often similar to that of patients, overt disease is rare among staff members even when common among patients, reflecting the relationship between pulmonary or other compromise and development of clinical disease. Nonetheless, serologic surveys of hospital staff members support the hypothesis that subclinical or mild disease occurs among healthy staff members in an outbreak resulting from an environmental source *(430–432)*. Despite suggestions in the early literature *(432)*, no good evidence supports person-to-person spread of *Legionella* infection, and cautious prior CDC recommendations for "secretion" precautions *(433)* have been withdrawn; Standard Precautions suffice (24).

Bacterial Diseases Spread by Contact

Staphylococcus aureus *Staphylococcus aureus* is a gram-positive microorganism that intermittently colonizes normal human skin and, particularly, the nares. The microorganism is hardy and survives well on environmental surfaces. Healthy mucous membranes and skin are adept at preventing invasion by *S. aureus,* but a break allows invasion that can lead to serious local, metastatic, or systemic infection. The increasing prominence of MRSA has heightened concern among clinicians, infection control workers, and other staff members. Transmission of MRSA is not considered to differ from that of methicillin-susceptible *S. aureus*.

Colonization with *S. aureus* becomes more likely as exposure and opportunities increase *(434)*. Colonization of healthcare workers with MRSA is likely in direct proportion to its prevalence in their environment *(435,436)*, except when contact precautions are followed (437). In turn, the likelihood that healthy workers will acquire staphylococcal infection of minor wounds, or that staphylococci will invade through minor wounds to cause serious illness, increases with their prevalence of carriage *(434,438–441)*.

Spread of staphylococci is almost exclusively by direct and indirect contact, notwithstanding demonstration of the possibility of airborne spread *(442,443)*. Prevention of spread depends on appropriate attention to Standard

Precautions supplemented by Contact Precautions when environmental contamination is likely (e.g., staphylococcal scalded skin syndrome; exfoliative dermatitis; furunculosis, especially in children; infected burns, especially if large) or when dealing with MRSA (see also Chapters 28 and 29).

Vancomycin-Resistant Enterococcus Infection control workers who once had MRSA nightmares now dream about vancomycin-resistant *Enterococcus* (VRE). Indeed, VRE is a legitimate source of anxiety (see also Chapter 33), and it can be transmitted readily from patient to patient on the hands of healthcare workers, but it poses no personal threat to the workers themselves.

Syphilis *Treponema pallidum*, the causative agent of syphilis, is a spirochete for which humans are the only known natural host. The microorganism causes a complex and chronic infection that begins with the primary skin or mucosal lesion (chancre), progresses to secondary dissemination throughout the body, and then becomes latent. Ten to 30 years later, 10% to 20% of patients with untreated disease will progress to tertiary disease with cardiovascular, neurologic, gummatous, or other complications *(444)*.

T. pallidum is a fragile microorganism that survives poorly apart from the body. Transmission is by contact with the chancre, mucous patches, condylomata lata, nasal discharge of babies congenitally infected, or other moist sources in primary and secondary stages of the disease. Prior to the routine use of gloves, primary infection of the hands of physicians and other healthcare workers was occasionally recognized *(445)*, but such events are now exceedingly rare *(446,447)*. Standard Precautions are sufficient to prevent transmission.

Gonorrhea *Neisseria gonorrhoeae*, the causative agent of gonorrhea, is a gram-negative diplococcus that primarily infects columnar or cuboidal epithelium. Consequently, the major risk of healthcare-associated transmission to healthcare workers involves conjunctivitis, usually due to inoculation of the eye by a contaminated finger. Although pharyngeal infection occurs, subsequent respiratory transmission does not appear to be a concern. The skin lesions of disseminated gonococcal infection rarely contain viable microorganisms *(447)*.

Unwitting transmission to a healthcare worker is most likely in association with unrecognized disease in patients admitted for other reasons. A particular concern is gonococcal ophthalmia neonatorum, which may occur despite prophylaxis and may remain unrecognized for days. Once again, Standard Precautions are sufficient to prevent transmission.

FUNGAL INFECTIONS

With rare exceptions, fungi are not transmitted from person to person, and healthy workers are not at risk of acquiring fungal infection from patients. Of the deep fungal infections, histoplasmosis, blastomycosis, and coccidioidomycosis have caused outbreaks among healthy persons, but workers in healthcare institutions are no more likely to be involved in such outbreaks than workers in other kinds of facilities in the same geographic area.

Symptomatic infection with *Cryptococcus*, *Aspergillus*, or *Mucorales* rarely or never occurs in normal hosts, and in any event, the microorganisms are abundant in nature. However, *Coccidioides* (and perhaps others of the dimorphic fungi) can germinate and grow in the filamentous form if patient drainage is left undisturbed for several days in bandages and casts; once aerial structures have developed, they are capable of releasing infectious spores *(448)*. Otherwise healthy workers can become sensitized to *Aspergillus* antigens and experience allergic bronchopulmonary aspergillosis when exposed to air from, for example, contaminated humidifiers (one possible cause of "sick building syndrome"), but healthcare workers are not at particularly elevated risk of such exposures.

Sporotrichosis, chromomycosis, or mycetoma could be transmitted by means of a contaminated sharps injury, but neither airborne nor contact spread is plausible. *Candida* is a normal human commensal that can cause opportunistic illness (e.g., thrush, vaginal candidiasis) in otherwise healthy persons, but such infections are usually endogenous. Person-to-person transmission occurs on rare occasions (e.g., newborn thrush, balanitis), but the usual circumstances are not applicable to healthcare workers.

The fungal infections most readily transmitted from person to healthy person are the dermatophytoses, as we are repeatedly reminded by the advertisements for athlete's foot tonics. Although rare, healthcare-associated outbreaks of ringworm and other dermatophyte infections have occurred and involved staff members *(449,450)*. Standard Precautions should be sufficient to prevent spread of fungal infections to the healthy worker.

PROTOZOAL AND PARASITIC INFECTIONS

Amebiasis, giardiasis, cryptosporidiosis, isosporosis, microsporidiosis, enterobiasis, hymenolepiasis, strongyloidiasis, and many of the other diseases caused by intestinal protozoa and helminths are transmitted by the fecal–oral route and, thus, could be transmitted by contact between a patient and an unwary worker. Proper attention to Standard Precautions and hand washing will prevent such infections. Certain of the blood and tissue parasites are well known to be transmitted to healthcare workers by needlestick (especially malaria, but leishmania, trypanosomiasis, or babesiosis could be transmitted similarly), through laboratory accidents (especially toxoplasmosis), or through other blood-to-blood exposures *(451)*, but otherwise, person-to-person transmission does not occur *(452)*. Transmission of trichomoniasis from patient to patient by contaminated fomites is possible, but the requisite genital contact should not occur among staff.

Pneumocystis carinii is a protozoan (or perhaps fungus) that appears to be ubiquitous, because 70% to 80% of children have antibodies by age 4 years *(453)*. Transmission appears to be by air, and several healthcare-associated outbreaks have been reported *(454,455)*. Nonetheless, immunocompetent workers are not at risk (nor are most immunocompromised workers, because they already carry the microorganism, but such workers should avoid exposure). Standard Precautions are sufficient for all these infections.

The parasites with demonstrated ability to cause healthcare-associated outbreaks involving staff and patients are the ectoparasites. Healthcare-associated transfer of pediculosis (head, body, or pubic lice) is possible, but unlikely, because sharing of clothing or bedding (or direct pubic contact) is generally required for transmission *(455)*. In contrast, numerous healthcare-associated outbreaks of scabies have occurred *(452,453,455–459)*, and such outbreaks can be widespread and persistent. *Sarcoptes scabiei,* the itch mite, burrows into the skin and lays eggs; sensitization to mite antigens leads to intense pruritus. Disease is transmitted by direct or indirect contact. Infestation in the normal host involves one to two dozen mites; immunocompromised hosts (e.g., those with alcoholism, Down syndrome, leprosy, or acquired immune deficiency syndrome [AIDS]) can develop "Norwegian" or crusted scabies marked by proliferation of thousands of mites, resulting in hyperkeratotic and crusted skin. Such persons are highly contagious. Management of a healthcare-associated outbreak is difficult and stressful *(456–461)*. If infestation is widespread, all potentially involved persons must be treated simultaneously (within 24 to 48 hours) on two occasions 1 week apart, and all routes of indirect contact (laundry, shared lockers, etc.) must be identified and managed. Fortunately, the mite survives only 48 hours outside the body, permitting decontamination of fomites by storage. Prevention largely depends on a high index of suspicion regarding dermatitis, particularly in immunocompromised patients. Those patients known or suspected to have scabies should be managed with Contact Precautions until properly treated.

Several healthcare-associated outbreaks of infestations caused by pigeon mites have been reported. The disease can mimic scabies, but unlike the itch mite, the pigeon mite can survive for months between meals *(455)*. Workers or, more often, patients can become infested, usually through proximity to ducts, air conditioners, or cracks that lead to pigeon roosts.

Myiasis is seen not uncommonly as a presenting condition in inner-city emergency rooms and can occur as a healthcare-associated infestation of wounds or mucus membranes. However, transmission to workers is not possible.

NONINFECTIOUS DISEASES

Some diseases are spread to healthcare workers by air or by contact but are not infectious. These diseases fall into two principal categories: allergic and toxic.

Diseases Caused by Allergic Reactions

Serious allergic reactions to latex are increasingly being recognized among patients and staff *(462–474)*. An estimated 7% of surgeons and 35% of spina bifida patients have immunoglobulin E antibodies to latex. Numerous allergic reactions have been reported, many severe, and several healthcare workers have had to leave practice. For highly sensitized workers, direct contact with latex is not required; anaphylaxis has been induced when someone nearby changed gloves *(466)*. Early signs of sensitization to latex should prompt an immediate switch to vinyl or other gloves before such extreme sensitization occurs. (See also Chapter 93).

Hypersensitivity pneumonitis can occur in response to numerous fungi and likely to bacterial components as well *(475)*; such reactions may be important in certain cases of "sick building syndrome." Numerous outbreaks of infection attributed to airborne or droplet dispersal of bacteria by humidifiers and air handling systems have occurred among patients who are susceptible because of intubation, presence of wounds, indwelling devices, and so on *(442,476–478)*. Infection of healthy staff by such routes is not known to occur, but the potential for hypersensitivity pneumonitis exists. Prevention depends on proper attention to maintenance and sterile precautions.

Finally, workers highly sensitized to certain drugs can be at risk from exposure to those drugs; for example, the simple flushing of a syringe containing penicillin might adversely affect a worker with high-level penicillin allergy. Employees of pharmaceutical manufacturers have had allergic reactions to drug dusts, but fortunately, modern-day hospital pharmacists do not use mortar and pestle nearly as often as their predecessors.

Diseases Caused by Toxic Exposures

Healthcare workers are exposed to a remarkable variety of chemicals that are known to be toxic by the contact or respiratory routes; ethylene oxide, glutaraldehyde, formaldehyde, xylene, chemotherapeutic agents, pentamidine, ribavirin, and anesthetic gases are among the substances with known toxic potential, most of which are subject to regulation by the Occupational Safety and Health Administration. Depending on the substance, workers must be provided with appropriate training and personal protection, material safety data sheets must be provided, warning labels must be displayed, environmental and personal exposure levels must be monitored, and proper disposal must be ensured. Because many of these toxic substances are pertinent to infection control, the infection control worker should be familiar with the staff and operations of the industrial safety program of the institution.

ORGANIZATIONAL ISSUES

Special Populations

Specific policies should be developed to address certain sensitive issues: (a) healthcare workers infected with blood-borne pathogens such as Hepatitis B, Hepatitis C (see Chapter 73), HIV (see Chapter 74); (b) workers with immune compromise, of whatever cause; and (c) pregnant employees. Pregnant employees often object to providing care to patients with selected infections out of fear that doing so will pose a risk to the fetus. This concern is almost never justified, and pregnant employees should not be routinely excluded from care of any particular patients *(117)*. On the other hand, women who are or might become pregnant should be counseled concerning the importance of complying with established precautions, particularly when dealing with patients infected with agents having known potential for complicating pregnancy (*117*,479). The Society for Healthcare Epidemiology of America has developed guidelines for the management of healthcare workers infected with Hepatitis B, Hepatitis C, or HIV (480).

Vaccination Program

Organization of the employee health service is detailed in Chapter 93, and we will not duplicate that material here except to stress the importance of a comprehensive and well-documented vaccination program. The employee health service should maintain a vaccination registry that documents all vaccinations ever received by all employees; the value of these data in the event of an exposure event or outbreak is enormous. In addition, the institution should, in its own self-interest, ensure up-to-date vaccination (or documented immunity) of all employees with respect to diphtheria, tetanus, pertussis, hepatitis B, measles, mumps, rubella, varicella, and influenza. Other vaccines may be indicated for certain employees (e.g., laboratory researchers or those working in special units), and if indicated should be provided at no cost, such as vaccinia, rabies, hepatitis A, polio, and typhoid (see also Chapter 75).

SUGGESTED READINGS

The topics of this chapter have been the subject of several comprehensive reviews or guidelines (24,*110,122,133, 180,219,233,247–250,289,292,293,302,314,323,326, 335,341,349,381,395,425,*480–482), which may provide additional information.

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CHAPTER 77

Prevention of Occupationally-Acquired Healthcare-Associated Infections in Diagnostic Laboratories

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Laboratorians who work in medical diagnostic laboratories or biological research laboratories are at increased risk of infections resulting from occupational exposures to pathogens (*1–4*,5). This group includes an estimated 500,000 individuals in the United States (6). Visits to the laboratory by clinical staff, improper biological waste disposal, person-to-person transmission of laboratory-acquired infections (LAIs) and point-of-care medical testing may lead to additional exposures and allow dissemination of infectious agents outside of the laboratory. Clearly, measures to ensure the safety of laboratory workers are required and must be strictly adhered to by laboratory personnel (7). Changes are likely to occur in the number and/or composition of potential infectious agents to which laboratory workers are exposed, as global climates change, medical and surgical interventions evolve, and bioterrorism attempts occur. Therefore, safety measures must adapt to these new demands, and protocols to prevent LAIs are increasingly important. The most noteworthy recent event that illustrates this point is the challenge many laboratories faced while responding to the new occupational risk that the 2009 H1N1 Influenza A outbreak posed to healthcare workers (*8*,9). This chapter focuses on the microorganisms that are likely to cause LAIs, modes of spread of such agents in a laboratory setting, and methods that are commonly employed to minimize risk to laboratory workers.

EPIDEMIOLOGY OF LABORATORY-ACQUIRED INFECTIONS

LAIs may be defined as all symptomatic or asymptomatic infections resulting from (usually occupational) exposure to an infectious agent in a laboratory setting (5). There is an extensive literature dating back to the end of the 19th century that describes a wide variety of bacteria, viruses, fungi, and parasites that have caused LAIs. Despite this, the true incidence of LAIs is unknown, since LAIs are usually reported as individual case reports or compiled through laboratory surveys. In addition, these reports of LAIs often lack sufficient detail or precision to allow extrapolation of incidence or other epidemiologic factors. Finally, in some instances, it is difficult to determine if an infection was truly laboratory acquired, as opposed to community acquired (e.g., respiratory virus infection), unless an obvious laboratory accident or similar exposure was tightly linked to the onset of infection.

The most extensive LAI surveys in the United States were conducted by Sulkin and Pike between 1949 and 1970 *(10–12)*. More recent surveys reviewed LAIs in Utah, U.S. public health laboratories, and among subscribers to the ClinMicroNet forum (*13, 14*,15). Based on the earlier data sets, Wilson and Reller estimated that the annual incidence of LAIs in the United States was between 1 and 5 per 1,000 employees (16). More recently, Singh estimated the increased relative risks of infection in laboratory workers compared to the general population for *Brucella* spp. (RR = 8,012), *Neisseria meningitidis* (RR = 40.8), and *Escherichia coli* O157:H7 (RR = 8.6) based on ClinMicroNet survey data (15,17). In the same survey, the relative risks for *Shigella* and *Salmonella* infection were not elevated in laboratory workers, despite the fact that a large number of LAIs were caused by these two agents (15,17).

More systematic surveys of LAIs were performed in the United Kingdom between 1970 and 1995 *(18,19)*. The most recent retrospective survey of occupationally acquired infections in 397 laboratories (1994–1995) in the United Kingdom found an overall incidence rate of 16.2 per 100,000 person years, compared with 82.7 infections per 100,000 person years in a similar survey conducted in 1988 to 1989, suggesting that control measures may be reducing the incidence of such infections *(19)*.

Because of the lack of adequate modern data on LAIs, control measures are proposed and implemented based on extrapolation of prior experience with one infectious agent to others, the epidemiology of relevant microorganisms in nonlaboratory settings, and hazard analysis (6,*13*). Although laboratory workers will always be at some risk for infection, adherence to safety measures is expected to significantly reduce the risk. It is important to note that most reports focus on the occupational risk associated with handling patient specimens and performing microbiologic cultures. By contrast, few reports document the spread of laboratory pathogens from the laboratory to other hospital

areas or to the community *(20)*. Thus, it appears that the risks associated with diagnostic laboratories are mainly those of infection of laboratory workers from microorganisms reaching the laboratory from patient specimens, and much less of microorganisms spreading to the community from the laboratory.

IMPORTANT ETIOLOGIES OF LABORATORY ACQUIRED INFECTIONS

The factors that influence occupationally acquired infections in laboratories are related to host susceptibility and behavior, the virulence and availability of the pathogen, and the work environment (5). In the past, *Brucella* species, *Mycobacterium tuberculosis, Coxiella burnetii,* hepatitis B virus (HBV), *Francisella tularensis,* and *Salmonella* species caused most LAIs (6,*11*). During the 1980s, *M. tuberculosis, Salmonella* species, *Shigella* species, HBV, and hepatitis C virus (HCV) were the most frequent microorganisms causing infection in laboratory workers *(13,14,18)*. A list of selected microorganisms that have caused laboratory infections during the past decade is provided in Table 77-1, and discussion of the most frequently encountered microorganisms follows. A more complete compilation can be found in selected publications in the reference list (*2*,6,7,21).

Bacteria

Over 37 bacterial species account for approximately 43% of LAIs, making bacteria the most frequent cause of LAIs in diagnostic laboratories *(10)*. The risk of transmission of *M. tuberculosis* and *Mycobacterium bovis* in healthcare facilities and clinical laboratories has long been recognized *(28)*. Since 1953, the tuberculosis case rate in the United States has declined nearly tenfold, from 53 cases per 100,000 to 5.6 per 100,000 in 2001, and decreased 40% compared with the most recent peak year of 1992 (http://www.cdc.gov/tb/statistics/reports/2008/default.htm). Historical surveys have demonstrated an incidence of tuberculosis among laboratory workers up to nine times greater than in the general population *(29,30)*. The greatest risk of laboratory-acquired mycobacterial infection is associated with exposure to aerosols generated during handling of liquid specimens, preparation of frozen sections, and performing autopsies, although a few LAI mycobacterial infections have been attributed to direct parenteral inoculation (7,*31*). The relatively low inoculum of *M. tuberculosis* required to establish infection in humans *(32)* makes unprotected exposure to this microorganism in the laboratory quite risky. Although respiratory specimens are most frequently implicated as the source of laboratory-acquired mycobacterial infection, the presence of acid-fast bacilli in specimens other than respiratory secretions (e.g., gastric aspirates, cerebrospinal fluid (CSF), urine, exudates, and tissue) may also result in healthcare-associated transmission to healthcare workers (HCWs) and autopsy personnel *(33)*.

Historically, the second most frequent of the bacterial causes of LAI have been *Brucella* spp., which have caused approximately 24% of all reported LAIs and 11% of LAI-associated laboratory worker deaths in the United States (*34,35*,36,37,*38*,39,*40*). *Brucella* spp. are highly infectious and often cause infections in multiple research or clinical laboratory workers following a single laboratory accident (36,37,*40*). While protocols for proper handling of known *Brucella* isolates in clinical microbiology laboratories are typically in place, misidentification of this microorganism frequently occurs, leading to laboratory staff exposures (36,41). *Brucella* spp. are believed to be transmitted in the laboratory primarily via aerosolization or direct contact. Often, however, it has been impossible to determine the mechanism of transmission. Rare cases of person-to-person transmission have been reported, and in some instances, individuals with very low risk exposure (nonlaboratorians that have made short visits to the laboratory) have contracted brucellosis *(20)*. *F. tularensis* is rarely encountered in the clinical laboratory. However, like *Brucella* spp., it is a fastidious, slow-growing gram-negative coccobacillus that may be difficult to identify early enough to prevent accidental exposures (42).

Bacillus anthracis is a gram-positive spore-forming rod that is a rare cause of human infections in the United States. *B. anthracis* represents a unique risk among potential LAI agents, because the spores it produces are extraordinarily hardy and contaminated surfaces (or hands) are difficult to disinfect with routine procedures. Laboratory-acquired

TABLE 77-1

Selected Microorganisms Involved in Laboratory Infection Episodes Reported in Medical Journals During the Period 2000–2010 by Microorganism Group

Microorganism	*Type of Laboratory*	*Year of Publication*	*Reference*
Bacteria			
Brucella spp.	Diagnostic, Research	2008, 2004, 2001, 2000	(15,*22,34*, 37,*38*)
Toxigenic *E. coli*	Diagnostic	2008, 2005	(15,*53*)
N. meningitidis	Diagnostic, Research	2008, 2007, 2004, 2002	(15,*23,24,46*)
Shigella spp.	Diagnostic	2008	(15)
Mycobacterium spp.	Anatomic	2001	*(33)*
Rickettsiae	Research	2001	*(55)*
Viruses			
West Nile Virus	Diagnostic	2009, 2002	*(25,26)*
Vaccinia	Research	2008	*(27)*

anthrax has most recently been documented in a laboratory worker handling specimens from the 2001 bioterrorism-related anthrax outbreak that occurred in the United States *(43,44)*. In this case, the lab worker acquired cutaneous anthrax from exposure to microorganisms present on the surface of contaminated vials.

Burkholderia pseudomallei, the microorganism responsible for melioidosis, is cited as a rare cause of LAIs but has been associated with a fatal outcome *(45)*. Direct contact with microbiologic cultures or specimens, ingestion, autoinoculation, and exposure to infectious aerosols and droplets all have been implicated in transmission of *B. pseudomallei*. *N. meningitidis* is another infrequent cause of LAIs that has been associated with fatal outcomes *(46)*. In a recent survey, 16 worldwide cases of probable laboratory-acquired *N. meningitidis,* with eight fatal outcomes, were identified between 1985 and 2001, including six US cases between 1996 and 2000 *(47)*. All cases (16/16) occurred among clinical microbiologists who, in most cases (15/16), performed isolate manipulation without respiratory protection *(47)*.

The agent of whooping cough, *Bordetella pertussis*, has caused at least 12 LAIs in the past 30 years, with six probable cases in the United States from 1996 to 2001 (2,5). The source isolates for the US cases were recovered from blood or CSF in five of the six cases and middle ear fluid in the sixth case.

The enteric bacterial pathogens, *Salmonella* species and *Shigella* species, are commonly reported causes of LAIs, while many additional cases likely go unreported (*2,13,19*,21,*48*). In older surveys, *Salmonella typhi* has caused more reported fatalities than any other LAI, while in more recent studies *Shigella* sp. was identified as the most frequent bacterial cause of LAIs (*11,13*,15,*19*). Infections generally occur from handling laboratory specimens and microbiologic cultures or occasionally from ingestion of intentionally contaminated food *(49)*. Gastroenteritis resulting from *Vibrio* species, *Campylobacter* species, enterotoxigenic *E. coli* and *Clostridium difficile* are infrequently reported (15,*50–53*).

The agent of Q fever, *C. burnetii,* is rare in the United States, so the risk for diagnostic laboratory-acquired Q-fever infection in this country is minor compared with that in many other parts of the world. The microorganism is present in blood, urine, feces, milk, and tissue specimens and resists drying. Most LAIs from *C. burnetii* arise from aerosols generated in animal research laboratories, although there are a few reports of parenteral and mucous membrane transmissions (*2*,21,54).

Before 1960, psittacosis was "among the most commonly reported laboratory-associated infections," but only sporadic cases have been reported in the past 20 years (*2*,21). Psittacosis case fatality rates are high compared with those of infections resulting from other agents. *Chlamydia psittaci*, the agent of psittacosis, may be present in tissues, feces, nasal secretions, and blood specimens. Few infections occur from exposure to *Chlamydia trachomatis* and generally result from mucous membrane exposure.

Leptospira interrogans, the cause of leptospirosis, can be present in urine, blood, and tissues of infected patients. Ingestion, accidental parenteral inoculation, and contact of skin or mucous membranes with cultures or infected specimens have all led to infection in laboratory workers. Likewise, LAI with syphilis has been documented, and its agent, *Treponema pallidum,* can be present not only in blood but also in cutaneous, mucous membrane, and other lesions. Laboratory spread of this microorganism follows from parenteral inoculation, contact of mucous membranes or broken skin with infectious clinical materials, and possibly infectious aerosols. Accidental parenteral inoculations are likely sources for laboratory-acquired rickettsial infections, but several infections with typhus have been associated with aerosols or infected airborne particles, and cases of Rocky Mountain Spotted Fever probably have occurred by this route as well *(19,48)*. LAIs from *Rickettsia typhi, Rickettsia coronii,* and *Orientia tsutsugamushi* have also been reported *(2,55)*. Because most diagnostic clinical laboratories do not perform cultures for rickettsia, these infections are more likely to be a risk in research laboratories.

Viruses

The blood-borne viruses (HIV, HBV, HCV) pose the infection risk of greatest concern to hospital workers (6,7,*56*,57). As of September 2007, the Centers for Disease Control and Prevention (CDC) had received reports of 57 HCWs in the United States with documented occupationally acquired HIV seroconversion, and 140 additional reports classified as possible occupational transmission (*http://www.cdc.gov/ncidod/dhqp/bp_hcp_w_hiv.html*). These individuals include 19 laboratory workers (16 clinical laboratory workers and 3 nonclinical laboratory technicians). Forty-eight of the fifty seven documented seroconversions were from percutaneous exposures, five were mucocutaneous, two were both, and two had an unknown route of exposure. Forty-nine HCWs were exposed to HIV infected blood, three to concentrated virus, one to visibly bloody fluid, and four to unspecified fluid. Twenty-six of these individuals had developed acquired immunodeficiency syndrome as of the date of the report.

The risk of infection from HIV, HBV, and HCV following occupational exposure to infected blood is related to the concentration of the virus in blood. HBV can be present in concentrations of 10^8 to 10^9 infectious particles/mL, while the concentrations of HIV and HCV are 10^0 to 10^4 and 10^2 to 10^3 particles/mL, respectively (7,57). The risk of infection following a percutaneous exposure is approximately 18% for HBV, 1.8% for HCV, and 0.3% for HIV. Following the mandatory requirement that employers provide HBV vaccination at no cost to their employees, the incidence of HBV infections in HCWs decreased 95% from 1983 to 1995 *(58)*. The 1% to 2% prevalence of HCV infection among HCWs appears no greater than the rate observed in the general population (7,57).

Although the blood-borne viruses are found in many different body fluids and tissues, the transmission of HCV, HIV, and HBV is most often associated with blood or visibly bloody body fluids. Since the 1990s, biosafety measures have emphasized the reduction of infection from blood-borne pathogens in all HCWs. The risk of acquiring a blood-borne infection is influenced by the prevalence of infection in patients, the amount of blood involved, the type of exposure, the concentration of pathogen in the blood or body

fluid, and the availability of postexposure prophylaxis (57). In addition to infections from human immunodeficiency virus (HIV), HBV, and HCV, blood-borne transmission of at least 20 other agents has been reported (7,*59*).

Most viral LAIs, other than infections from the blood-borne viruses, occur in animal research laboratories following exposure to aerosols or contamination of skin and mucous membranes (5). Arenavirus, Sabia virus, West Nile virus, and other viruses causing hemorrhagic disease have caused such research laboratory infections *(60–62)*. Lymphocytic choriomeningitis virus infections in laboratory workers occur in diagnostic facilities when cell cultures become contaminated with the virus, leading to possible aerosolization or skin or mucous membrane contamination. Specimens suspected of harboring the agent of smallpox, variola major, should not be cultured but rather shipped directly to CDC or a state health laboratory (63,*64*).

Respiratory viral infections acquired in the laboratory are probably underreported, because it is difficult to document occupational acquisition. These viruses can be aerosolized by manipulation of specimens or cultures. In contrast, the agents that cause viral gastroenteritis are rarely transmitted to laboratory workers. Infections with the hepatitis viruses that are principally transmitted by the fecal–oral route are also uncommon causes of LAI; it is hypothesized that since the shedding of Hepatitis A, and probably Hepatitis E, is diminished by the time a patient is symptomatic, there is a decreased risk of transmission in the healthcare facility *(1)*.

Fungi

Laboratory-acquired fungal infections have been reported infrequently since 1980. Generally, fungal infections are acquired from the inhalation of the conidia of the thermally dimorphic fungi *Coccidioides immitis, Histoplasma capsulatum,* or *Blastomyces dermatitidis,* and there is one reported case of infection with *Penicillium marneffei* (5,6,54,*65*). Occasionally, cutaneous infections occur following accidental inoculation *(66,67)*. Coccidioidomycosis and histoplasmosis are the most frequently reported laboratory-acquired fungal infections (6). Arthroconidia from laboratory cultures of *C. immitis* easily become airborne, whereas spherules from tissue are much less likely to be aerosolized. Laboratory-acquired histoplasmosis also results primarily from handling laboratory cultures. The infective conidia are small and likely to become airborne, resist drying, and can cause infection after small inocula are inhaled. Less frequently, pulmonary infection resulting from *B. dermatitidis* has followed inhalation of the conidia by laboratory workers.

Parasites

Laboratory-acquired parasitic diseases are exceedingly rare. However, parasitic diseases are receiving increasing attention because of world travel and increased susceptibility in immunocompromised individuals *(68)*. Over 300 cases of parasitic LAIs have been reported, including malaria, leishmaniasis, trypanosomiasis, and toxoplasmosis *(10,68)*. The two most frequently reported infections from accidental exposure are from *Trypanosoma cruzi* and *Toxoplasma gondii*. The rate of occurrence of laboratory accidents during work with *T. gondii* is reported to be one accident per 9,300 hours of exposure resulting in one infection per 24 person years, while the infection rate for working with *T. cruzi* is calculated to be one infection per 46 person years *(68,69)*. The clinical spectrum of these infections has ranged from asymptomatic to fatal (one case for each microorganism). Herwaldt *(56)* also reported on infections caused by *Plasmodium* species (34 cases) and *Leishmania* species (12 cases). Most of the infections associated with blood and tissue protozoa occurred from parenteral exposure, but acquisition via skin and mucous membrane exposure and ingestion have also been reported. Only 21 cases of LAIs with intestinal protozoans have been reported, involving *Cryptosporidium parvum, Isospora belli,* and *Giardia lamblia*. Fewer reports have involved the helminths, including *Schistosoma* species, *Strongyloides* species, and *Ancylostoma* species. The most probable route of infection was ingestion of contaminated material, although a few cases were associated with aerosols or skin penetration.

RESERVOIRS AND MODES OF SPREAD

LAIs may be transmitted via a variety of modes including inhalation, ingestion, inoculation, and contamination of skin and mucous membranes (6,21,54). Perhaps the most likely mode of transmission is accidental inoculation of skin or soft tissue with needles or other sharps such as scalpels and broken glass from specimen containers. Nearly all pathogenic microorganisms can produce infection by this route and, as noted above, this is the most frequent route of transmission for blood-borne pathogens such as HIV or the hepatitis viruses (7). Hopefully, the accidental percutaneous inoculation of infectious material by laboratory personnel will decrease with the increased use of plastic collection tubes, needleless systems, and engineered safety devices. As a rule, needles should not be used in the laboratory unless there is no other alternative.

Although the intact skin is an excellent barrier to penetration by microorganisms, minor cuts and abrasions are common and may serve as portals of entry in the absence of penetrating trauma. Contamination of mucous membranes by splashes and sprays of infectious material can lead to the laboratory transmission of HIV and other pathogenic agents to laboratory workers (5,7). In animal research facilities, bites and scratches from infected animals present a risk for transmission of an agent.

As in patient care areas, transmission by hand to skin and mucous membranes of the mouth, eye, and nose can cause LAIs *(70)*. Ingestion may occur following mouth pipetting, transfer of microorganisms on contaminated fingers or pencils, accidental splashes, or consumption of food and beverages in the laboratory. The laboratory environment is contaminated during the workday from routine specimen processing and other work practices that produce aerosols or splatters, and this results in contamination of the hands (21,71). Indirect contact with microorganisms can occur when work benches and other environmental objects (e.g., specimen containers, test requisitions, instruments) or surfaces become contaminated with microorganisms. Accidents or spills also can lead to contamination of the workbench or other equipment,

which may lead to contamination by hand contact. The importance of avoiding poor personal hygiene practices, such as applying cosmetics and adjusting contact lenses in the laboratory, must thus be stressed. Cases associated with contamination of food, drink, or tobacco products have declined significantly, because attention has been paid to eliminating eating, drinking, and smoking in the laboratory.

Transmission within the laboratory via airborne spread is also of great concern (7,*64,72*). Many laboratory procedures generate aerosols, droplets, or droplet nuclei that can cause infection when inhaled by the laboratory worker. Droplet nuclei are small (<5 μm in diameter) and therefore tend to remain suspended in air and move throughout the room on air currents and reach the alveoli of the lungs when inhaled *(73)*. They therefore may pose a risk to individuals working in other parts of the laboratory at the time the aerosol is generated. Relevant procedures that generate aerosols include use of bacteriology loops for transferring cultures and flaming them afterward; pipetting (especially with fixed automatic pipettes or during mechanical resuspension of material achieved by repeated pipetting); using syringes and needles; opening tubes and bottles; using centrifuges and blenders; performing autopsies; harvesting viral cultures; lyophilizing; and breaking culture plates, bottles, and tubes. These work practices also produce droplets that contaminate counters or floor surfaces, permitting transmission from these surfaces to hands. Microorganisms in blood droplets can survive for several days after drying on work surfaces or instruments (54). Specific bacteria that may be transmitted by airborne droplets or aerosols were discussed above and include *M. tuberculosis*; *Corynebacterium diphtheriae; N. meningitidis; B. pertussis; Streptococcus pyogenes;* and the potential agents of bioterrorism, *B. anthracis, Yersinia pestis, Brucella* species, *F. tularensis,* and *B. pseudomallei* (*2*,7,21,63,*74*).

It is important to note that the potential bacterial agents of bioterrorism may be transmitted by multiple exposure routes, including aerosols, contamination of skin and mucous membranes, ingestion, and percutaneous inoculation. Infections often occur when laboratory workers do not recognize or suspect the pathogen and neglect to take necessary safety precautions (41). The practice of "sniffing" plates for characteristic odors associated with a specific bacterium should therefore be curtailed *(2)*. In addition to aerosol transmission, laboratory-acquired brucellosis has occurred from direct skin contact with cultures or with other infectious material, percutaneous inoculation, and spray onto mucous membranes. These same transmission routes are important for *B. anthracis,* the agent of anthrax; *F. tularensis,* the cause of tularemia; *C. diphtheriae,* the agent of diphtheria; and *Y. pestis,* the agent of plague. All of these bacteria should be handled with biosafety level (BSL) 2 and 3 safety precautions *(64)*.

GUIDELINES FOR PREVENTION

Ensuring laboratory safety is included in the standards of the Occupational Safety and Health Administration (OSHA), which are driven by the premise that the employer must provide a safe workplace (*56*,57,*75–78*). Compliance with current OSHA standards is subject to review by the agency's inspectors; thus, these regulations are perhaps of greatest importance to clinical diagnostic laboratories. Other groups, such as the CDC *(79,80)*, the National Institutes of Health (21), the College of American Pathologists (CAP), and the Clinical and Laboratory Standards Institute (CLSI), all provide guidelines or regulations regarding laboratory safety. OSHA, the National Institute for Occupational Safety and Health (NIOSH), the CAP, and the Joint Commission include safety among their checklists for laboratory inspectors. State and local licensing inspections and federal inspections for participation in Medicare also focus on safety issues (7).

Guidelines for laboratory safety from these groups cover exposures to chemical agents, fire, and other aspects, but the highlight of each is the prevention of LAI. The following discussion is guided by these various regulations and guidelines and centers on the clinical diagnostic laboratory. The prevention of infection in autopsy, surgical pathology, and research and referral laboratories follows the same general plan considered here, but its implementation varies dramatically in each site according to the work done and the microorganisms involved (7).

Each laboratory must assess its specific risk from handling infectious material and design an exposure control plan to minimize these potential risks. Safety practices, usually containment measures, are designed to reduce or eliminate the exposure of laboratory workers to infectious material (7,21). These practices vary with the pathogenicity and infectious dose of the agent, the routes of transmission, the work performed, and the availability of treatment or prophylaxis (21,81,*82*). The CDC/National Institutes of Health guidelines recommend four levels of biosafety, and each successive level suggests increased occupational risk and more stringent containment practices. These classifications are similar to those adopted by the World Health Organization (WHO) based on increasing level of risk to the individual and community and availability of effective treatment and prevention *(83)*. Laboratories that use, receive, or store select agents must address, in addition to BSL 2 to 4 safety practices, security and reporting issues *(84)*. Additional safety practices are necessary for work in research and anatomic laboratories (7,*85–87*).

OSHA regulations for prevention of infection emphasize engineering controls, work practice modification, and personal protection by immunization and protective equipment *(72,88)*. Guidelines based on CDC recommendations for the clinical diagnostic laboratory can be placed in these same general categories and compared for BSLs 2 and 3. Most guidelines are common to both BSLs 2 and 3, whereas some are unique to level 2, and others are specific to level 3 protection (refer to Tables 77-2–77-4 for a comprehensive description of specific practices). Many of these elements are pertinent to other hospital areas and to laboratories; such policies are discussed in detail in other chapters and are reviewed only briefly here. Several elements of infection prevention are more relevant to the laboratory than to other areas, and these are discussed at greater length in the following sections.

Engineering Controls

Airflow handling is an essential element in several clinical care areas of a hospital where microorganisms likely to be spread by airborne transmission are encountered,

TABLE 77-2

Control Measures for Prevention of Laboratory-Acquired Healthcare-Associated Infections that are Common to BSLs 2 and 3

Engineering Controls

1. Only needle-locking syringes or disposable syringe-needle units are used for injection or aspiration of infectious materials
2. Needles and syringes or other sharps are used only when there is no alternative, such as for parenteral injection, phlebotomy, or aspiration of fluid from diaphragm bottles
3. Syringes that resheath the needle, needleless systems, and other safe devices are used when possible
4. Plasticware is substituted for glassware whenever possible
5. Used disposable needles are carefully placed in conveniently located puncture-resistant containers. Nondisposable sharps are placed in a hard-walled container for transport to a processing area for decontamination, preferably by autoclaving
6. Cultures, tissues, and specimens of body fluids are placed in containers that prevent leakage during collection, transport, handling, processing, storage, or shipping
7. Materials with high concentrations or large volumes of infectious agents may be centrifuged in the open laboratory only if sealed rotor heads or centrifuge safety cups are used and if these rotors or safety cups are opened only in a BSC
8. An eyewash facility is readily available
9. Rugs are not used, because proper decontamination following a spill is difficult
10. Bench tops are impervious to water and resistant to acids, alkali, organic solvents, and moderate heat
11. Laboratory furniture is sturdy, and spaces between benches, cabinets, and equipment are accessible for cleaning
12. Open windows are fitted with fly screens
13. A method for decontamination of infectious or regulated laboratory wastes is available (e.g., autoclave, chemical disinfection, incinerator)

Work Practice Modification

1. Hands are washed after handling infectious material, after removing gloves, and before leaving the laboratory
2. Food is stored outside the work area in cabinets or refrigerators designated for this purpose only
3. Mouth pipetting is prohibited; mechanical pipetting devices are used
4. All procedures are performed carefully to minimize splashes or aerosols
5. Work surfaces are decontaminated at least once a day and after any spill of viable material
6. All cultures, stocks, and other regulated wastes are decontaminated before disposal by an approved decontamination method such as autoclaving
7. Materials to be decontaminated outside of the immediate laboratory are placed in a durable, leak-proof container and closed for transport
8. Materials to be decontaminated off-site from the laboratory are packaged in accordance with applicable local, state, and federal regulations before removal from the facility
9. An insect and rodent control program is in effect
10. A biosafety manual is prepared or adopted
11. Personnel are advised of special hazards and are required to read and follow instructions on practices and procedures
12. Personnel receive appropriate training on potential hazards associated with the work involved, the necessary precautions to prevent exposures, and exposure evaluation procedures. Annual updates, or additional training as necessary for procedural or policy changes, are provided
13. A high degree of precaution always is taken with any contaminated sharp items, including needles and syringes, slides, pipettes, capillary tubes, and scalpels
14. Used disposable needles are not bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal; they are placed in appropriate containers (see above)
15. Broken glassware is not handled directly by hand but is removed by mechanical means (e.g., brush, dustpan, tongs, forceps)
16. Containers of contaminated needles, sharps, and broken glass are decontaminated before disposal according to local regulations
17. Laboratory equipment and work surfaces are decontaminated with an appropriate disinfectant routinely, after work with infectious materials is finished, and especially after contamination by infectious material (e.g., spills, splashes)
18. Contaminated equipment is decontaminated before it is sent for repair or maintenance or packaged for transport
19. Spills and accidents resulting in overt exposures to infectious materials are reported immediately to the laboratory director

Personal Protection

1. Personnel receive appropriate immunizations or tests (e.g., tuberculin skin test) for the agents potentially handled or potentially present
2. Medical evaluation, surveillance, and treatment are provided as appropriate, and written records are maintained following any exposure to infectious agents
3. Persons who wear contact lenses in laboratories should also wear goggles or a face shield

(*Continued*)

TABLE 77-2

Control Measures for Prevention of Laboratory-Acquired Healthcare-Associated Infections that are Common to BSLs 2 and 3 (*Continued*)

4. Protective laboratory coats, smocks, gowns, or uniforms designated for laboratory use are worn while in the laboratory
5. Protective clothing is removed and left in the laboratory before leaving for nonlaboratory areas and is either disposed of in the laboratory or laundered by the institution, never taken home by personnel
6. Gloves are worn when hands might contact infectious materials, contaminated surfaces, or equipment. They are disposed of when contaminated, removed when work with infectious materials is complete, and are not worn outside the laboratory
7. Disposable gloves are not washed or reused

[a]As defined by the Centers for Disease Control and Prevention with the National Institutes of Health (21) and the OSHA *(88).*

especially *M. tuberculosis* and dimorphic fungi *(78)*. In the laboratory, however, the potential for encountering BSL 3 microorganisms that can be spread by air is so much greater that certain standards and guidelines beyond those that apply to the rest of the institution are mandatory (*72*,89). Aerosolization can result from the use of blenders, both low- and high-speed centrifuges, and automatic pipettes, as well as improperly flamed loops used for inoculation of microbiologic cultures. Other standard and seemingly innocuous laboratory procedures such as pipetting, accidentally dropping infected liquids on a counter, and inoculating a tube with a syringe all can generate aerosols. If one adds to this the presence in clinical specimens of microorganisms prone to spread by the airborne route (see above), the need for control of aerosols becomes crucial. Thus, building design that ensures inward directional airflow into the laboratory from corridors and hallways ("negative pressure") and similar engineering for direct exhaust of the air without recirculation are crucial for laboratories handling airborne pathogens. For BSL 3 laboratories, airflow is monitored to ensure that the ventilation system does not fail *(72, 90)*. Air ventilation in the autopsy suite is also critical; the room should be under negative pressure, provide 12 air exchanges per hour, and be exhausted directly to the outside (7).

Biologic safety cabinets (BSCs) are designed to contain the highly infectious agents that are transmitted by an airborne route through infectious splashes or aerosols generated by microbiologic procedures (7,*72,91*). There are three types of BSCs (Classes I, II, and III). Class I BSCs draw room air through the cabinet and discharge it outside, through HEPA filters. While this type of cabinet protects the user from harmful materials inside, it is unsuitable for

TABLE 77-3

Requirements for BSL 2 that Differ from those for BSL 3[a]

Engineering Controls

1. Properly maintained BSCs, preferably class II or other appropriate personal protective equipment or physical containment devices are used for procedures that could create infectious aerosols or splashes. These may include centrifuging, grinding, blending, vigorous shaking or mixing, sonic disruption, opening containers of infectious materials whose internal pressures are different from ambient pressure, and harvesting infected tissues
2. Each laboratory contains a sink for hand washing

Work Practice Modification

1. Access to the laboratory is limited or restricted when work with infectious agents is in progress
2. Eating, drinking, smoking, handling contact lenses, and applying cosmetics are not permitted in the "work area" (laboratory for level 3)
3. Only persons who have been advised of the potential hazard(s) and meet specific entry requirements (e.g., immunization) enter the laboratory
4. When the infectious agents in use in the laboratory require special provisions for entry (e.g., immunization), a hazard warning sign incorporating the universal biohazard symbol is posted on the access door to the laboratory work area. The sign identifies the agent, lists names and telephone numbers of responsible persons, and indicates the special requirements for entering the laboratory

Personal Protection

1. Face protection (e.g., masks, goggles, faceshield) is used for anticipated splashes or sprays of infectious materials when the microorganisms must be manipulated outside the BSC
2. When appropriate, considering the agents handled, baseline serum specimens for personnel are collected and stored. Additional serum specimens may be collected periodically, depending on the agents handled or the function of the facility.

[a]As defined by the Centers for Disease Control and Prevention with the National Institutes of Health and the OSHA (21,*88*).

TABLE 77-4

Requirements for BSL 3 that Differ from those for BSL 2[a]

Engineering Controls

1. The laboratory is separated from areas with unrestricted traffic flow. Passage through two sets of self-closing doors is the basic requirement for entry. A clothes change room (shower optional) may be included in the passageway
2. A ducted exhaust air ventilation system is provided. This system creates directional airflow that draws air from clean areas into the laboratory toward contaminated areas. The air is not recirculated to any other area of the building. It is discharged to the outside with filtration and other treatment optional. The outside exhaust must be dispersed away from occupied areas and air intakes
3. The high-efficiency particulate air (HEPA)-filtered exhaust air from class II or class III BSCs is discharged directly to the outside or through the building exhaust system (for class II cabinets, exhaust air can be recirculated if the cabinet is tested and certified at least every 12 months). Discharged air to the building exhaust system is connected in a manner that avoids any interference with air balance of the cabinets or building exhaust system
4. Properly maintained BSCs are used (class II or III, as appropriate)
5. Continuous flow centrifuges or other equipment that may produce aerosols are contained in devices that exhaust air through HEPA filters before discharge into the laboratory
6. Laboratory doors are kept closed when testing or experiments are in progress
7. Each laboratory contains a sink for hand washing. The sink is foot, elbow, or automatically operated and is near the laboratory exit door
8. The interior surfaces of walls, floors, and ceilings are water resistant, so they can be easily cleaned. Penetrations in these surfaces are sealed or capable of being sealed to facilitate decontamination
9. Windows in the laboratory are closed and sealed

Work Practice Modification

1. Eating, drinking, smoking, handling contact lenses, and applying cosmetics are not permitted in the laboratory ("work area" for level 2)
2. Persons who are at increased risk of infection or to whom infection may be unusually hazardous are not allowed in the laboratory. Access is restricted to persons whose presence is required for program or support purposes
3. Only persons who have been advised of the potential hazard(s), meet specific entry requirements (e.g., immunization), and comply with all entry and exit procedures enter the laboratory
4. When infectious materials are in the laboratory, a hazard warning sign incorporating the universal biohazard symbol is posted on all laboratory and animal room access doors. The sign identifies the agent, lists names and telephone numbers of responsible persons, and indicates any specific requirements for entering the laboratory, such as the need for immunizations, respirators, or other personal protective measures
5. The laboratory director ensures that, before working with microorganisms at BSL 3, all personnel demonstrate proficiency in standard microbiologic practices and techniques and in the practices and operations specific to the laboratory facility. This might include prior experience in handling human pathogens or cell cultures or a specific training program
6. All manipulations involving infectious materials are conducted in BSCs or other physical containment devices within the containment module. No work in open vessels is conducted on the open bench
7. All potentially contaminated waste materials (e.g., gloves, laboratory coats) from laboratories are decontaminated before disposal or reuse
8. Spills of infectious materials are decontaminated, contained, and cleaned up by appropriate professional staff members or others properly trained and equipped to work with concentrated infectious material
9. Animals and plants not related to the work being conducted are not permitted in the laboratory

Personal Protection

1. Outside of a BSC, appropriate combinations of personal protective equipment are used (special protective clothing, masks, gloves, face protection, or respirators) in combination with physical containment devices (e.g., centrifuge safety cups, sealed centrifuge rotors) for manipulation of cultures or other materials that may be a source of infectious aerosols
2. Face protection (goggles and mask or face shield) is worn for manipulations of infectious materials outside the BSC
3. Protective laboratory clothing such as solid-front or wrap-around gowns, scrub suits, or coveralls must be worn in, and not worn outside, the laboratory
4. Reusable laboratory clothing is to be decontaminated before being laundered
5. A laboratory policy exists that addresses the collection and storage of baseline serum specimens for personnel WHICH are collected and stored for all laboratory and other at-risk personnel. Additional serum specimens may be collected periodically, depending on the agents handled or the function of the facility

[a]As defined by the Centers for Disease Control and Prevention with the National Institutes of Health and the OSHA (21,*88*).

microbiology laboratories because plates and other media within the cabinet are not protected from room air contaminants. Most routine clinical laboratories use Class II BSCs that provide protection to the user and prevent external contamination of the materials inside the cabinet by recirculating HEPA filtered air into the cabinet. An effective containment system for handling BSL 2 and 3 agents requires that the BSC is properly maintained, that the BSC be certified annually or whenever the cabinet is moved, and that well-trained employees use good microbiologic technique (7). More detailed characteristics of each type of cabinet and procedures for their correct use have been reviewed and extensively described elsewhere (7,*72,78*).

Other engineering controls for decreasing the risk associated with handling infectious material include safety engineered devices and instruments, sharps containers, safety containers for centrifuges, plastic containers and collection devices for specimens, mechanical pipettes and diluters, bench tops impervious to liquids, and personal protection equipment (7,*92*).

Work Practice Modification

Laboratory workers cannot *a priori* identify specimens that contain infectious agents and, therefore, must practice Standard Precautions. Thus, the concept that all patients and all laboratory specimens are potentially infectious and capable of transmitting infection is practiced in all healthcare settings (7,*93,94*). These guidelines represent the first level of protection of the laboratory worker from a wide variety of pathogens. Hand washing is a fundamental procedure to reduce duration of exposure and transmission of an infectious agent within the healthcare facility, including the laboratory. Adequate hand cleansing using traditional soap and water or an alcohol-based gel should occur before leaving the laboratory, after removing gloves, and after obvious hand contamination *(95)*. Some practices that promote the transfer of microorganisms from surfaces to hands to mucous membranes are universally prohibited in the laboratory. These include eating or storing food, drinking, applying cosmetics or contact lens, smoking, chewing gum, and mouth pipetting. Workers with skin lesions or dermatitis on the hands or wrists should not handle potentially infectious materials without adequate protection (96).

Personnel who collect and transport specimens should be adequately trained. Whether transported by hand or pneumatic tube, specimens should be placed in a leak-proof primary container. This primary container is placed in a leak-proof secondary container, usually a sealable plastic bag. Secondary containers and specimen storage areas should be labeled with a biohazard label to alert individuals to the potential infectious hazard. Needles should be removed before transporting a syringe to the laboratory.

Specimen processing in microbiology requires special steps to prevent infection and should be performed in a BSC. For example, when entering a blood culture bottle with a needle and syringe, the vial should never be held in the worker's hand and the bottle should be placed behind a splashguard or in a BSC. Similarly, unfixed slides should always be handled as if they contain infectious materials (7). Special steps are needed for dealing with the potential hazards associated with the use of diagnostic instruments (7).

Prompt decontamination of spills is particularly important in the laboratory. Most laboratory spills involve blood, other body fluids, or microbiologic media that often contain high concentrations of protein. Because many disinfectants are less active in the presence of these proteins, the bulk of the spilled liquid must be adsorbed before disinfection (7,96). For large spills of microbiologic cultures, the spill is flooded with an appropriate disinfectant and left to stand for 20 minutes before cleanup (7). Phenolic disinfectants are not recommended for use on contaminated medical devices that come in contact with laboratory workers but may be used on laboratory instruments, floors, and countertops. Also, instrument parts made in part or wholly of aluminum are corroded by sodium hypochlorite, so other disinfectants are preferred for disinfection of laboratory instruments containing these parts.

Surface cleaning of the laboratory bench or other surfaces must be meticulous, because these surfaces are likely to be contaminated with potential pathogens (71). Many surfaces (countertops, floors, equipment, centrifuges, etc.) become contaminated by microorganisms during routine processing of clinical specimens and cultures. These surfaces should be carefully disinfected at the completion of work and after accidental spills to prevent contamination of laboratory employees and visiting medical personnel who may unknowingly carry the agent to other parts of the facility or the community (71). All unnecessary material should be removed from these surfaces to facilitate proper cleaning and disinfection.

Waste disposal and handling of biologic materials at the end of processing are especially important topics for the laboratory, because of the volume of the materials involved and because the processing of the specimens often involves amplification of the potential pathogen *(97)*. The laboratory is a major generator of potentially hazardous waste, and should have procedures to segregate materials for discard into designated containers such as "routine," "chemical," and "biohazard" waste for proper decontamination and disposal. Fortunately, the same procedures used in other parts of the facility apply to laboratory waste.

Surveillance of accidents and exposures is a key feature of infection control in all hospital areas but is especially important in the laboratory. The essential components of postexposure management include incident reporting, wound management, evaluation of the transmission risk, and consideration of postexposure prophylaxis (7,*56*,57). Every incident, no matter how trivial the injury or exposure, must be reported to the supervisor, including the date and time of exposure, the details of the accident, information on the source person, and medical evaluation of the injured employee. The immediate reporting of the incident establishes a time relationship, in the event that an infection develops, and permits preventive measures to be implemented. OSHA regulations require that the facility's exposure control plan include hepatitis B vaccination at no cost to the employee, postexposure evaluation and follow-up, communication of potential hazards to employees, and appropriate records and reporting (7,56,57,*98*).

Follow-up for the individual is vital. Procedures for medical follow-up of exposure to blood-borne pathogens are dealt with in separate chapters (see Chapters 73 and 74). Equally important is the periodic and regular analysis of the incidents that occur in a given laboratory. Laboratory, Occupational Health, and Infection Prevention

personnel should cooperate in the compilation and analysis of incident report data to search for common patterns, to eliminate identified risk factors, and to modify laboratory procedures to minimize occurrence of these incidents *(99)*.

The shipment of infectious material is regulated by national and international rules and regulations promulgated by the U.S. Department of Transportation, International Airline Transport Association, and the WHO *(83)* and are beyond the scope of this chapter.

Personal Protection

Immunization Laboratory workers must be encouraged to participate in the same immunization program that is offered throughout the institution (7,*100*). This includes, at a minimum, provision of HBV immunization at no cost to the employee. The laboratory worker may be at greater risk of exposure to body fluids containing one of the hepatitis viruses, so it might be worth the special effort to emphasize immunization to laboratory employees. Immunizing trainees against HBV is particularly important, because the risk of infection often is high during training.

Bacillus Calmette–Guérin (BCG) vaccine is made from an attenuated strain of *M. bovis*. It is not routinely offered to hospital workers in the United States, because a positive tuberculin skin test when the vaccine is effective is thought to be a hindrance to surveillance for natural tuberculosis and because adverse effects are associated with immunization (e.g., abscess at the injection site). However, it may be considered for laboratory employees who process large volumes of specimens containing *M. tuberculosis*. Other possible vaccines for laboratory workers include meningococcal polysaccharide vaccine, rabies vaccine, polio vaccine, and typhoid vaccine. Vaccines for anthrax and/or smallpox may be considered for workers in research or BioThreat response laboratories. Primary prevention in the laboratory should focus on biosafety practices, but these vaccines are a consideration for personnel who work with these agents on a frequent and regular basis (see also Chapter 75).

Personal Protective Equipment Gloves, masks, and gowns are used throughout a hospital to protect workers from contact with blood and other potentially infectious materials. The laboratory is no exception to this practice, because all specimens handled in the laboratory are considered potentially infectious. Laboratory workers must be trained in the appropriate use, limitations, and disposal of personal protective equipment. In general, only powder-free latex or other nonlatex gloves should be used in the laboratory as part of the Standard Precaution guidelines. Puncture-resistant gloves should be available in the autopsy suite or when handling scalpels and other sharps. In addition to protective clothing, laboratory workers should wear face shields or work behind splashguards when removing stoppers or withdrawing samples from specimen tubes (7). When extensive soaking by potentially infectious material is a possibility, waterproof coats, gowns, or aprons should be worn. Respiratory protection in the form of NIOSH-approved masks (e.g., N95 particulate respirator, with prior formal testing to confirm mask fit) is recommended when working with *M. tuberculosis* or other similar BSL 3 microorganisms (7,21). Shoes should cover the feet to protect the skin from spills or dropped sharps. All personal protective equipment, including laboratory coats, gowns, or other protective covers, should not be worn outside the laboratory area.

ACKNOWLEDGMENT

This chapter contains information presented in Chapter 82 of the third edition of this book by David E. Sewell.

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CHAPTER 78

Prevention of Occupationally Acquired Infections in Prehospital Healthcare Workers

James M. Melius

Prehospital healthcare workers now number over 200,000 workers employed to provide this type of healthcare *(1)*. This estimate does not include the large number of volunteer prehospital healthcare workers or the police and fire fighters who also may be required to provide emergency medical assistance as part of their jobs. Many of these prehospital healthcare personnel work for modern well-equipped emergency medical systems in major metropolitan areas. Others volunteer their time for local rescue companies with very limited resources, often in rural areas. Some are full-time professional healthcare workers dedicated to a career in emergency medical services, whereas others may only provide voluntary services for a few hours per month or may only occasionally have to provide emergency medical care as part of their full-time jobs as firefighters or police officers.

Working in the prehospital environment is in many ways similar to providing care in hospitals and other healthcare facilities. Prehospital healthcare workers encounter a variety of seriously ill patients with many types of illness, and, like other healthcare workers, emergency medical workers face an increased risk of acquiring a number of different infectious diseases as a result of their work. The potential risk of a bioterrorism incident expands the number of conditions that must be considered.

Prehospital healthcare workers usually spend only a short time with each patient. This limited contact undoubtedly lowers their risk of acquiring a patient-related infection. However, a number of other factors may increase this risk.

In responding to traffic accidents or entering the homes of their patients, these workers provide medical care in many different settings over which they have little control. In most situations, they do not have complete information on the patient's medical condition. This lack of control of their work environment and the incomplete diagnostic information have significant implications in preventing the transmission of infectious diseases from the patients to these workers.

Another important difference from many other healthcare workers is the variety of types of organizations that employ these workers and the lack of programs within those organizations for providing infection control services. In some cases, the organizations may lack the resources or the commitment for the operation of good infection control programs. Although infection control programs for prehospital workers have improved in recent years, there are still large disparities among different organizations.

This chapter provides an overview of the infectious diseases risks faced by prehospital healthcare workers and of the methods useful for their prevention. These preventive steps are quite similar to those used in other healthcare settings. Therefore, this chapter emphasizes preventive approaches especially important to prehospital healthcare workers rather than reiterating infection control procedures described elsewhere in this book. Finally, the chapter briefly discusses approaches for organizing better preventive programs for these workers.

PREHOSPITAL HEALTHCARE

Prehospital healthcare workers include many thousands of healthcare workers in many organizational settings. Some work full time as emergency medical care workers for private or public providers. Others spend most of their time conducting other tasks (e.g., fire fighting) but must occasionally provide emergency medical care. Others volunteer their services, spending a few to many hours every week with volunteer rescue squads (usually in rural areas).

These workers also differ in their medical training. Some have years of specialized training for their careers and frequent updating of their medical training. Others have only very limited emergency care training and little continued training because of their other job requirements.

The common tasks performed by these workers include the provision of emergency medical care outside the hospital (or healthcare facility) setting and the transport of these patients to healthcare facilities. The types of patient being cared for obviously vary among different prehospital care providers. Some mainly transport patients who are not critically ill, whereas others mainly respond to trauma incidents. Geographic location and many other factors obviously affect the potential exposure of these workers to people with communicable diseases.

The workplace for prehospital healthcare providers can be viewed as including four settings: (a) the accident scene or other place where initial care for the patient is provided, (b) the transport vehicle, (c) the healthcare facility receiving area (usually emergency room), and (d) the facility in which the responder is stationed (e.g., hospital,

fire house). From the perspective of infection control, the third setting is not discussed in this chapter. However, it should be noted that emergency medical providers may be at some risk for acquiring infections even after arrival at the healthcare facility.

The site of the initial care (e.g., patient's residence, accident scene) is probably the most problematic of the four locations. In contrast to most other healthcare workers, the emergency medical responder usually has little information about the patient's condition when initially providing medical care at the scene. Thus, the responder is usually not aware of whether the patient has a communicable disease. Collection of some diagnostic information is obviously a critical aspect of providing initial emergency care, but information about a specific infectious disease often will not be obtained. Often, a specific infectious disease will not be diagnosed until after the patient has been hospitalized.

In providing care, the responder usually must rely on verbal information from the patient or the family that may not fully reflect the patient's medical condition. In some cases, the patient may be unconscious and otherwise unable to provide any information, and knowledgeable family members may not be present. In the absence of specific diagnostic information, the responder must depend on his or her initial physical assessment of the patient, perhaps with additional knowledge such as the likelihood of the patient having an infectious disease because of the geographic location (i.e., how common is the disease in that area).

The responder not only lacks diagnostic information but must also provide emergency medical care at the site. In many cases, this care must be provided at the patient's residence. The responders may have a very limited work area and poor lighting, making certain procedures, such as starting intravenous lines, difficult. In addition, the patient may be combative or otherwise difficult to manage, further increasing the risk of this type of procedure. For airborne communicable diseases, there may be increased risk of exposure, because the responder must work in a residential environment in which the patient has been staying. This area may lack adequate ventilation and may have contaminated surfaces.

An accident or trauma scene may pose additional dangers. In addition to the limited space, poor lighting, and other problems, the trauma scene may have broken glass and other sharp objects that could contribute to the spread of blood-borne pathogens. In some cases, the responder may have to spend a long period stabilizing the patient until the patient can be extricated from a motor vehicle. Taking proper infection control precautions in a confined space with a seriously injured patient may be quite difficult.

Another aspect of providing emergency care at the scene that is obvious but is especially important is that all protective equipment that is needed at the scene must be carried by the responders. If they do not bring the necessary equipment with them, the equipment must either be retrieved from their transport vehicle or from their station or not used at all. Anticipating what will be needed and then providing ready access to that equipment can be quite challenging. The availability of equipment may be particularly problematic for responders who most often fulfill other duties (e.g., law enforcement or fire fighting) but are also expected to provide emergency medical care.

The situation in transport vehicles is somewhat better. The patient is usually stable enough to be transported. Better medical and monitoring equipment is also available. However, this setting also has a number of problems. First, patients often must be rapidly transported to the hospital and may often be in very critical condition. Medical care and procedures such as starting intravenous lines must be conducted very quickly. Most transport vehicles have very little room, further compounding this problem. Transport also may cause problems because of the movement of the vehicle during transport. This is obviously a problem while trying to perform procedures during transport (e.g., insertion of intravenous lines). Another potential problem is that most emergency transport vehicles are poorly ventilated. Most ventilation either comes from opening windows or from the vehicle's heating or cooling systems, which often simply recirculate most of the air in the vehicle *(2)*. Recent studies have also demonstrated the potential for surfaces in the transport vehicles to be contaminated with methicillin-resistant *Staphylcoccus aureus* and other bacterial pathogens that may be a source of risk for both the patients and the prehospital healthcare workers (3,4).

Another site where emergency medical responders work is their station. In some cases, this may be a hospital. In others, it may be a fire house or a similar structure. Some responders may even work from their homes (e.g., rural volunteer units). This location is most important in terms of infection control in that responders must often return to that site to clean their equipment. Proper equipment and practices for this setting are obviously important.

OCCUPATIONALLY ACQUIRED INFECTIONS

Prehospital healthcare workers share many of the risks of occupationally acquired infections with healthcare workers in other settings. Although most of their contacts with infectious patients are relatively brief, the lack of information about the patient's conditions and difficult environmental conditions may increase their risk relative to the more controlled hospital environment.

There is relatively little documentation of the actual risk of occupationally acquired infections among emergency medical providers. Hepatitis B has probably received the most attention *(5)*. However, other infections have occasionally been reported. For example, there is a case report of toxic shock syndrome in a firefighter from a *Streptococcus pyogenes* infection acquired from cardiopulmonary resuscitation of an infected child *(6)*.

Although somewhat dated, the most complete documentation of the infectious diseases risk for prehospital healthcare workers comes from a survey of the emergency medical service in Portland, Oregon *(7)*. Using verbal and written exposure reports and other sources, the author documented 256 reported infectious disease exposure incidents over a 2-year period (1988–1989). The incidence of reported exposures was 4.4 per 1,000 emergency medical service

calls. Of these, approximately 24% involved respiratory exposure and 47% involved exposure of intact skin. Approximately 29% involved the exposure of nonintact skin or mucous membranes to blood or other body fluids or needlesticks. Fourteen incidents involving either needlesticks or exposure of nonintact skin or mucous membranes to blood or other body fluids were reported over the 2-year period. Although difficult to generalize to other emergency medical settings, these data do provide some sense of the scope of infectious diseases exposures for prehospital healthcare workers.

A survey of emergency medical service workers serving three inner-city emergency departments focused only on occupational blood contact *(8)*. Based on 62 self-reported blood contact incidents while transporting 2,472 patients, the study estimated that each worker had 12.3 blood contacts per year, including 0.2 annual percutaneous exposures. Bleeding patients were the main source of the exposures. A more recent study in Rhode Island used first-responder visits to Emergency Departments for blood or body fluid exposures found an average incidence rate of 23.29 visits per 100,000 ambulance runs (9).

Some older surveys of prehospital healthcare workers for hepatitis B markers provide some indication of these worker's risk for that disease. A study of 59 Seattle, Washington, paramedics found that 25% had evidence of antibody to hepatitis B surface or core antigen *(10)*. A similar survey of 338 Houston, Texas, paramedics found the prevalence of hepatitis antibodies to be approximately 26%, whereas a survey of Boston, Massachusetts, paramedics and emergency medical technicians found the prevalence to be approximately 28% *(11,12)*. A recent review article summarizes much of the available literature on hepatitis B and C risks for public safety workers including the marked decrease in Hepatitis B infection (13).

There is little documentation of the prevalence or the incidence of other occupationally acquired infections in prehospital healthcare workers. Based on the type of work, one would expect them to be potentially at risk for the same types of infections as other healthcare workers (especially emergency room workers) (see Chapters 73, 74, and 76). However, the incidence of particular infections is difficult to estimate.

ATTITUDES

Studies of emergency medical workers in the late 1980s and early 1990s showed significant concerns about the risk for acquiring blood-borne infections such as HIV, and many preferred not to treat HIV-infected patients *(14)*. More recent studies have found similar concerns among prehospital healthcare workers about pandemic influenza (15,16). An Australian study reported that 43% of prehospital healthcare workers would refuse to work during a pandemic (15). A similar study in the United States found that 12% would not report to work voluntarily during an influenza pandemic, and this would increase to 52% if risk of disease transmission to their family existed (16). To what extent these attitudes may have changed based on these workers' knowledge about and experiences during the recent H1N1 pandemic is not known.

Legal Requirements

Requirements for qualifications and training for prehospital healthcare workers vary from state to state. Most states do not have specific regulations regarding infection control practices and training, although many receive some training in this area and may be held to some general standard of practice. However, in the last few years, the federal government has gotten more involved in regulating infection control practices through occupational safety and health regulation, initially in the area of blood borne infections and more recently with airborne infections. Although the scope of this regulation (see Chapters 74 and 97) clearly covers prehospital healthcare workers, legal coverage of the standard varies. Many states do not provide occupational safety and health regulation or enforcement for public employees. The federal Occupational Safety and Health Administration (OSHA) does not cover public employees if the state does not provide such coverage. Coverage for volunteer rescue squads or fire departments also varies from state to state. More recently, OSHA has issued enforcement guidelines for protecting healthcare workers from the risk of tuberculosis. A more comprehensive infection control standard has been proposed and is currently under review.

One very troublesome issue for prehospital healthcare providers has been the issue of notification of providers after they have transported and cared for patients with infectious diseases. Although confidentiality protection for HIV-infected patients has contributed to this difficulty, other factors are also important. The infected patient may not be diagnosed for some time after admission. Most often, the prehospital care provider is not employed by the healthcare facility in which the patient is diagnosed, and infection control staff members in that facility may not be aware of the potential exposure of the prehospital care provider. Difficulties in communication and patient confidentiality further complicate this situation.

The Ryan White Act passed by Congress in 1990 mandated the development of a notification system for all prehospital care providers. For potentially fatal infections spread by airborne routes, healthcare facilities were required to notify the prehospital care provider if a patient whom he or she had transported was diagnosed with such an infection. For blood-borne infections, prehospital healthcare providers were allowed to inquire about a patient's diagnosis through a designated liaison if the prehospital healthcare provider was significantly exposed (e.g., needlestick) while transporting the patient. The law included a mechanism for review of the significance of the exposure and for protecting the confidentiality of the patient. The Department of Health and Human Services has now implemented this portion of the legislation. This requirement has helped to improve communication between prehospital care providers and hospitals regarding these issues.

PROGRAMS

Although infection control activities for prehospital healthcare workers are essentially the same as for other healthcare workers, some issues should be emphasized.

First, emergency medical providers are often unaware of the patient's diagnosis when arriving at the site of care or during transport to a healthcare facility. Therefore, standard protocols for the application of infection control procedures are especially important. Standard adherence to Universal Precautions (now Standard Precautions in healthcare facilities—see Chapters 73, 74, and 90) for all patient care activities is an obvious example. Another approach would be to initiate certain precautions for specific types of patients triggered by their symptoms or by knowledge of the presence of specific infectious diseases in their service area (17). Assuming that all infectious patients can be individually identified at the scene is not good practice. Any selective protocols need to be simple and easy to apply.

Second, proper protective equipment must be available for use at the scene. This includes equipment such as masks and gloves needed during patient care and equipment for disposal. Requiring used needles to be brought back to the station for disposal increases the risk for these providers *(8)*. Use of self-capping intravenous catheters for prehospital emergency care workers has been shown to result in a marked decrease in reported needlestick injuries *(18)*. The responsible parties need to ensure that necessary equipment is available. Proper equipment for cleaning used equipment in the station is also important. Cleaning such equipment in an area used for food preparation (e.g., responder's home or in a fire house) is not good practice. Proper procedures for medical waste disposal also need to be followed.

Third, proper infection control practices need to be adapted to the situation when the responder may have other job duties such as law enforcement or fire fighting. If the responder may arrive at the scene equipped for one type of duty but then must act as an emergency medical responder, proper equipment needed for infection control must still be provided.

Adequate training is extremely important (19). The application of standard practices throughout the provider organization is critical, because the providers usually will not base their use of precautions on prior knowledge of whether the patient has an infection. All staff members need to be appropriately trained and familiar with the infection control practices for the organization.

The threat of a bioterrorism attack will pose additional challenges to the development and delivery of infection control programs for prehospital workers. The bioterrorism threat will require additional training and other resources. Meeting this challenge will also place more emphasis on the need for improved administration of the infection control programs for these organizations and on the necessity for better and more rapid communication with public health authorities.

ORGANIZATION OF SERVICES

Perhaps the most difficult issue with the implementation of infection control programs for prehospital care providers is the organization of these services given the different types of organizations in which these responders work (20). Other than hospital-based responders, the organization and provision of the necessary training and medical services needed for a good infection control program must be implemented by the provider organization. The following suggestions apply mainly to other types of organizations (e.g., fire departments, rescue squads).

First, given the growing importance and complexity of good infection control programs for these workers, one person in each organization must be made fully responsible for this program. Implementation of program elements can be delegated to others in the organization, but there needs to be a single position responsible for the overall program. This responsibility includes training, procurement and placement of proper equipment, and medical follow-up. This person must seek input from all parts of the organization to ensure that the infection control program is being properly implemented. Joint labor–management health and safety committees are one means for obtaining this input.

Second, there needs to be some liaison with a medical provider capable of providing the medical care and advice needed for the infection control program. This could be the infection control staff at the major hospital serviced by the responder. It could also be the emergency medical department providing emergency medical training or consultation for the responder organization. This medical liaison is critical for two functions. First, they can assist with infection control training and provide consultation on specific issues. Second, they can provide the medical consultation needed for issues related to immunization, surveillance programs, and incident follow-up. Although both are important, the latter best illustrates the need for such a medical liaison. Prompt follow-up medical care is critical after an incident such as a needlestick injury. Attempting to arrange such follow-up without any planning or preparation puts a great burden on the person at risk. It is far better to have developed a comprehensive medical program as part of the overall infection control program.

Many prehospital care providers have limited finances and are already strained by the requirements of providing good medical service. Additional training and immunizations may add to the financial strains, but such assistance is critical to the development and operation of a good infection control program.

CONCLUSIONS

Although there are few data on the extent of occupationally acquired infections among prehospital healthcare workers, their risk appears to be similar to that of other emergency care workers. The development of good infection control programs for these workers is hampered by the nature of the work and the diversity of organizations providing such care. However, sound infection control programs for these workers have been developed and should be beneficial.

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CHAPTER 79

Prevention of Occupationally-Acquired Infections in Posthospital Healthcare Workers

Charles W. Stratton IV

Infectious diseases can be transmitted from one human to another by a number of different mechanisms. Some of these mechanisms such as aerosolized respiratory droplets pose a direct threat to persons nearby, whereas others involve direct contact or exposure to biologic specimens from infected patients. Consequently, healthcare workers are recognized as being at risk for contracting an infection from patients or patient specimens (*1*,2,*3–6*). Such risks for occupationally acquired infections in healthcare workers have long been appreciated, as is evident by the protective clothing once worn during the plague epidemic of the 14th century (Fig. 79-1). The 2009 H1N1 influenza A pandemic *(7)*, the severe acute respiratory syndrome (SARS) outbreak *(8)*, the threat of bioterrorism *(9)*, and the ongoing acquired immunodeficiency syndrome (AIDS) epidemic *(10)* have all focused considerable attention on occupationally acquired infections. Such attention has resulted in Centers for Disease Control and Prevention (CDC) infection control guidelines for H1N1 influenza *(11)*, SARS *(12)*, Public Health Service (PHS) regulations for select agents and toxins *(13)*, and Occupational Safety and Health Administration (OSHA) regulations for blood-borne pathogens *(14)*. The reemergence of tuberculosis *(15,16)* similarly has resulted in CDC guidelines *(17)* and federally mandated regulations *(18)*.

Several important references related to reducing the risk of occupationally acquired infections in healthcare workers are readily available. The Clinical and Laboratory Standards Institute (CLSI) offers Document M29-A3, "Protection of Laboratory Workers from Occupationally Acquired Infections" (19). The CDC also offers guidelines for infection control in hospital personnel (20). These guidelines include recommendations for nonpatient healthcare personnel, management of exposures, prevention of transmission of infections in microbiology and biomedical laboratories, and prevention of latex barrier hypersensitivity reactions.

More persons in the United States today are employed in the healthcare sector than in any other industry *(21)*. Historically, most of these workers have been employed in the hospital setting. Thus, occupationally acquired infections in healthcare workers have received the greatest attention for workers in the hospital setting. Hospitals have developed comprehensive infection control programs and occupational health services that address the prevention of occupationally acquired infections. However, the horizons of infection control continue to expand in the 21st century *(21,22)* due to the recognition that the risk of infections transmitted from patients to healthcare workers is not limited to hospital workers but extends to out-of-hospital healthcare workers *(22)*. Today, healthcare is delivered in outpatient, transitional care, long-term care, rehabilitative care, home care, and private office settings *(21,23)*. The out-of-hospital setting is receiving increasing attention, and infection control requirements and activities have been established (*24*,25). This chapter covers the prevention of occupationally acquired infections in posthospital healthcare workers.

EXAMPLES OF POSTHOSPITAL HEALTHCARE WORKERS AND THEIR RISK FOR OCCUPATIONALLY ACQUIRED INFECTIONS

The definition of posthospital healthcare workers continues to expand and evolve *(21,23)*. Outpatient healthcare workers and medical personnel at reference laboratories, for example, can be either prehospital or posthospital healthcare workers. Following are examples of common categories of posthospital healthcare workers and their risk for occupationally acquired infections.

Pathologists and Medical Technologists

Although pathologists and medical technologists generally work in the hospital setting, they may be involved in either hospital care or posthospital care. For example, pathologists and medical technologists who are involved in surgical pathology, cytology, and clinical laboratories are usually involved in hospital care, whereas pathologists and morgue personnel involved in autopsies could be considered posthospital healthcare workers. Moreover, some pathologists and medical technologists work in reference

FIGURE 79-1 Protective garb worn by healthcare workers in the Middle Ages to protect themselves against plague.

laboratories that are not associated with a hospital. As nonhospital-associated freestanding operations, these reference laboratories most often do not have the assistance of hospital infection preventionists (IPs) and, hence, may fall short in providing protective measures appropriate to the infectious risks. The use of such freestanding reference laboratories for testing of specimens from hospitalized patients and for testing of specimens from patients in the prehospital and posthospital setting is increasing. This, in turn, has resulted in potential infectious risks for personnel involved in the packaging, handling, and transport of medical specimens. Accordingly, the PHS and CLSI have developed regulations and guidelines for proper procedures for the handling and transport of diagnostic specimens and etiologic agents (*13*,*26*). Moreover, the CLSI, the CDC, and the National Institutes of Health (NIH) address biosafety issues in microbiology and biomedical laboratories (19,*27*). All pathologists and medical technologists have unique risks for occupationally acquired infections because of contact with patient specimens. The risk for pathologists and medical technologists involved in clinical laboratories is covered in Chapter 77. The risks for pathologists who perform autopsies (19,*28,29*) are addressed in this chapter. Biosafety considerations for autopsies are important topics that often are not addressed by hospital infection control committees.

Home Healthcare Workers

Cost containment has shifted a great deal of medical care from the hospital setting to the outpatient setting. Accordingly, infection control issues in the home care and hospice setting are now being addressed (30). Although the home setting is considered to have fewer infection risks, studies have not confirmed this (31). Clearly, some patients receiving home healthcare have infections and, thus, pose a risk for home healthcare workers (30,*31*). Home healthcare patients are often elderly and may have unrecognized tuberculosis *(32)*. AIDS patients are another group of patients commonly cared for in a domiciliary setting *(33)*. Such infection risks in the home healthcare setting are only beginning to be studied. Research is needed to delineate such risks and to identify ways to minimize or prevent these infections from being transmitted to home healthcare workers. The topic of infection control in the home healthcare setting is discussed in Chapter 99.

Residential Long-Term Healthcare Workers

The number of persons entering assisted-living facilities and nursing homes for residential long-term care is substantial and is increasing. Many of these nursing home, residential care, and assisted-living patients enter such facilities directly from the hospital. The need for residential long-term care facilities to provide comprehensive infection control programs is well recognized (*34*,35). A number of infectious diseases problems are common to long-term care facilities and often are unappreciated *(36)*. A typical presentation of infections is generally acknowledged and may lead to delays in diagnosis and treatment of infections such as tuberculosis. The physical plant of many long-term care facilities is often a factor; many residents live in confined settings with few private rooms, and rooms appropriate for isolation often are not available. Finally, many long-term care facilities experience rapid turnover of personnel, and residential long-term care workers frequently have less training than those in the hospital setting. Long-term care facilities need a well-developed infection control program that in part identifies and minimizes the risk of occupationally acquired infections. Such programs can be developed best with the assistance of the hospital-based IP (37) (see Chapter 98).

Outpatient Healthcare Workers

The delivery of healthcare continues to shift from the hospital setting to the outpatient setting *(23)*. For example, an increasing number of surgical procedures are done on an outpatient basis, and postoperative complications are now seen by emergency departments (35). Thus, many outpatient healthcare workers can be considered posthospital workers and share the risks of posthospital healthcare workers *(36)*. The Joint Commission (TJC) is actively reviewing infection control programs for outpatient services that are affiliated with hospitals and has published standards for ambulatory surgery centers (37).

Rehabilitation Facility Workers

Another shift in providing healthcare has been the establishment of rehabilitation facilities. Follow-up care of many illnesses is now carried out in these facilities, and healthcare-associated infections are common *(38)*. Healthcare workers in these facilities have similar risks to hospital workers, yet these rehabilitation facilities may not be associated with a hospital and have access to IPs and policies. Surveillance and infection control measures, nonetheless, are needed (35).

Dialysis Facility Workers

Freestanding dialysis facilities have become very common. Clearly, the risk for many blood-borne pathogens in such facilities is high *(39)*. These centers may not have access to IPs and policies; however, surveillance and infection control measures clearly are needed. Accordingly, the CDC has published guidelines and recommendations for the prevention and control of dialysis-associated infection (40).

Healthcare Laundry Workers

Freestanding healthcare laundries serving multiple hospitals have been established in many cities. The risk for these workers is high for certain infections, including blood-borne pathogens because of the presence of sharp objects such as needles *(41)*. Workers in these laundries also are at risk for scabies. Laundries may not have access to IPs and policies. Guidelines and recommendations for the prevention and control of infections in the laundry setting are included in the CDC guidelines for infection control in healthcare settings (42).

Funeral Home Workers

The risk for exposure to infectious agents during autopsies is becoming better known and has resulted in guidelines for performing autopsies to minimize this risk *(17,28,29,43)*. In particular, guidelines designed to minimize the risk of human immunodeficiency virus (HIV) infection *(44,45)* and tuberculosis *(46)* have been published. Funeral home workers can be considered posthospital healthcare workers and share some of the same risks as a pathologist performing an autopsy *(47)*. A study of funeral practitioners has noted a low rate of occupational exposures and a high rate of hepatitis B vaccination in comparison with prior studies, which suggests both improved education for and compliance with the recommendations for preventing transmission of blood-borne pathogens in the workplace *(48)*. Such efforts should be continued.

Trash Haulers and Landfill Operators

The potential for exposure to infectious diseases in trash haulers and landfill operators is a very important issue *(49,50)*. Although minimal *(51,52)*, the risk is real and should be controlled. The proper disposal of medical waste is a key factor in controlling this risk; CLSI Document GP5-A "Clinical Laboratory Waste Management: Approved Guideline—Second Edition" addresses this topic (53), and federal law now requires compliance *(54)*.

EPIDEMIOLOGY OF OCCUPATIONALLY ACQUIRED INFECTIONS

Although quite a few pathogens can be transmitted to a worker in the healthcare setting, there are relatively few mechanisms by which such transmission can occur. The most common and important mechanisms of transmission are exposure to aerosols, exposure to blood or body fluids via direct contact or inoculation, and hand-to-mouth transmission. These are reviewed in some detail.

Exposure to Aerosols

The transmission of *Mycobacterium tuberculosis* occurs mainly by inhalation of droplet nuclei *(55)*. The influenza A virus may be spread by droplet nuclei *(7)*. Finally, there is also evidence that in some cases the coronavirus responsible for SARS has been spread by droplet nuclei *(8)*. These droplets are airborne particles and must be <5 μm in size to reach the alveolar spaces. Droplet nuclei can be produced when persons with upper and lower respiratory tract infections or with laryngeal infections speak, sneeze, cough, or sing. If these persons are in a healthcare setting such as a nursing home, and the diagnosis of tuberculosis, influenza A, or SARS is unknown, they become a risk to healthcare workers. Multidrug-resistant tuberculosis, SARS, and the 2009 H1N1 influenza A pandemic have refocused infection control efforts on airborne transmission of infection *(56–58)*. Consider, for example, the findings of a study investigating the potential for airborne distribution of influenza virus in an urgent care medical clinic *(59)*. This study collected airborne particles from an Urgent Care Clinic using stationary National Institute for Occupational Safety and Health (NIOSH) 2-stage cyclone aerosol sampler. The presence of airborne influenza A, influenza B, and respiratory syncytial virus (RSV) was determined using real-time quantitative polymerase chain reaction (PCR). The results of this study demonstrated that airborne particles containing influenza and RSV RNA were detected throughout this healthcare facility. Moreover, these airborne particles were small enough to remain airborne for an extended period of time and to be inhaled deeply into the respiratory tract *(59)*.

Clearly, airborne transmission of infection is important. Healthcare workers in laboratories are also at risk for airborne pathogens, because there are certain manipulations with patient samples that may produce an aerosol. An important example of such a manipulation is dropping of fluids containing microbial suspensions (e.g., urine containing *M. tuberculosis* microorganisms because of renal tuberculosis) onto a hard surface, producing an aerosol. Working with *Neiserria meningitidis* cultures is also considered a risk, and microbiology technologists should be immunized against this pathogen.

The risk of aerosolized *M. tuberculosis* from patients with unsuspected tuberculosis to posthospital healthcare workers such as home healthcare, nursing home, and clinic healthcare workers has become quite clear with the resurgence of tuberculosis in the United States. This risk increases in settings such as outpatient clinics where many sick people congregate in waiting and treatment rooms or halls and is also increased in communities where the incidence of HIV and/or tuberculosis is high. Outbreaks of tuberculosis among healthcare workers have occurred *(60–62)*; some have involved multidrug-resistant *M. tuberculosis (61,62)*. This risk can best be appreciated by considering the tuberculosis skin test conversion rates among healthcare workers that have ranged from 0.11% to 10% *(63,64)*. This risk increases considerably in healthcare workers who are exposed to persons from countries where tuberculosis is endemic, to HIV patients, and to patients known to have tuberculosis; the skin test conversion rates in such settings have ranged from 18% to 55% *(65,66)*. Transmission of tuberculosis to healthcare workers can be a major problem requiring prevention and control *(66)*. This problem is covered in great detail in Chapter 38.

A less well-appreciated, but equally important, risk for posthospital healthcare workers such as pathologists and funeral home workers is the risk for aerosolized transmission of infectious agents when working with deceased patients *(67)*. In addition to the risk of dropping body fluids containing microbial suspensions, a number of other procedures associated with autopsies produce an aerosol. For example, the Rokitansky method, in which the abdominal and thoracic organs are eviscerated as a unit, continues to be commonly used at autopsy. However, this method involves blunt blind dissection in both cavities, which is cumbersome and creates unnecessary aerosols. The CLSI now recommends removing organs singly (the Virchow technique) to avoid the more hazardous aerosolization risk associated with complete evisceration by the Rokitansky method (19). The CLSI also recommends that organs not be photographed until they have been fixed in formalin to decrease the risk of aerosolized microorganisms. Unfortunately, this does not provide complete protection against aerosolized *M. tuberculosis* because this pathogen survives fixation in formalin, although the fixation does decrease the number of mycobacteria and thus lessens the degree of infectivity *(68)*. The need to saw the calvarium is perhaps the most problematic autopsy procedure, because it unavoidably creates an aerosol. Aerosolization can be minimized by doing this procedure inside a plastic bag or plastic head frame, using a hand saw (difficult to do), or having a vacuum attached to the oscillating saw.

Another important risk factor for aerosolization during an autopsy is the use of side-arm faucet water aspirators to remove pleural or peritoneal fluids from these body cavities, because these aspirating devices produce an infectious aerosol. Side-arm faucet water suction devices should not be used in autopsy suites or in funeral homes. Instead, they should be replaced by surgical-type vacuum reservoirs that are attached to the hospital vacuum lines that have appropriate traps, filters, and regulators *(69)*.

Air flow in the autopsy suites (but not funeral homes) has been addressed by the American Society of Heating, Refrigerating, and Air Conditioning Engineers and by the CDC *(17)*. Adequate air flow is an important means of minimizing the risk of aerosolized pathogens. Both groups recommend that autopsy suites have at least 12 total air exchanges per hour and that autopsy room air be exhausted directly to the outside. In addition, the College of American Pathologists recommends that autopsies on high-risk patients be done only in rooms with good ventilation *(69,70)*.

It is important to have a clear understanding of what constitutes good ventilation. There are three important engineering factors that allow good ventilation/control of air within a room. First, negative pressure in the room should be maintained with respect to surrounding areas. This means that air should move from an area of low infectivity (i.e., outside the room) to an area of higher infectivity (i.e., inside the room). Second, the number of air changes in the room should be increased, which can substantially decrease the risk of the transmission of aerosolized pathogens by dilution and removal of these pathogens. Good ventilation also dictates that within-room mixing of air (i.e., ventilation efficiency) is adequate. This is usually accomplished by placing air supply outlets in the ceiling and exhaust inlets near the floor. This provides a downward movement of clean air, which travels through the breathing zone to the floor area for exhaust. Third, there should be adequate exhaust to the outside. Because the air in a high-risk room such as the autopsy suite is likely to be contaminated with infectious droplet nuclei, it should not be recirculated within the room or within the building. Instead, this potentially contaminated air should be exhausted to the outside, away from intake vents, people, and animals. An episode in a medical examiner's office in Syracuse, New York, *(62)* illustrates this point. Two workers in the Onondaga County medical examiner's office were infected by *M. tuberculosis* after they were exposed during autopsies on cadavers of prison inmates who had been infected with *M. tuberculosis* before death. In addition to the two workers who contracted clinical manifestations of tuberculosis, the tuberculin skin tests of 30% of the staff in the medical examiner's office converted to positive; this included a secretary whose desk was right under the ventilation system that circulated air from the morgue. The examiner's office responded to this episode by installing a new ventilation system, adding ultraviolet treatment of the air in the morgue, and initiating a respiratory protection program for personnel who worked in the morgue. Chapter 84 provides additional information on the design and maintenance of ventilation systems and prevention of airborne infections.

If adequate ventilation is not possible, healthcare workers who have any possibility of being exposed to aerosolized infectious particles should participate in a respiratory protection program. This is accomplished by wearing particulate respirators. A standard surgical mask is not a particulate respirator because lack of a tight face seal allows particles between 1 and 3 μm to be inhaled. Disposable particulate respirators are available. There are two types: the dust/mist filter, which excludes particles of 2 μm, and the fume filter, which excludes particles 0.6 to 1.0 μm. The CDC has published guidelines for the use of particulate respirators that include training, fit testing, care, and maintenance *(17)*; OSHA requires that a fume filter be used in particulate respirators *(18)*.

Exposure to Blood or Body Fluids via Direct Contact or Inoculation

It is well appreciated today that exposure to blood or body fluids via direct contact or inoculation can result in the transmission of a number of pathogens, of which the best known examples are hepatitis B virus (HBV) and HIV. The risk of HIV has increased the awareness of this problem. Numerous incidents of exposure of healthcare workers to HIV-infected blood have been evaluated in multiple prospective studies. These studies have identified HIV infections, usually involving individuals who had been punctured with needles; seroconversions are rare in staff members with intact skin. The rate of infection with HIV in healthcare workers after exposure to HIV-infected blood is approximately 0.3% *(71)*. It is instructive to review these seroconversions in healthcare workers analyzed by the CDC *(71)*, including six from prospective studies. Of the 34 individuals with

seroconversion, 12 were nurses, 11 were laboratory workers, 4 were physicians, and the other 7 were from other occupational groups. All underwent HIV seroconversion within 1 year of exposure, which had been mucocutaneous contact or percutaneous inoculation with blood or fluids containing HIV. Of the 28 percutaneous inoculations, 14 occurred while drawing venous blood and 2 occurred while drawing arterial blood; 5 of these were associated with carrying out intravenous infusions. Of the remaining injuries, two had occurred while injecting laboratory specimens, one while holding a specimen vial and two while manipulating a transvenous pacemaker. The remaining injuries were a result of other or unknown causes. Most of these percutaneous inoculations occurred after unexpected movement by a patient, a coworker, or equipment (seven exposures); inadequate needle disposal (nine exposures); and recapping of needles (seven exposures). Thirteen of these twenty-eight occurred through the workers' gloved hands. Of the five mucocutaneous exposures that resulted in seroconversion, one involved pressure hemostasis with an ungloved hand, three occurred during accidents involving blood spillage, and one involved an individual who was sprayed with concentrated virus. The CDC has concluded that the most frequent cause of occupational transmission of HIV or HBV is injury by a needle contaminated with the virus *(71)*. However, other mechanisms such as virus-contaminated body fluids being splashed on mucosal membranes and, to a lesser degree, skin clearly are important. Finally, but most importantly, postexposure prophylaxis with antiretroviral therapy with zidovudine (ZDV) has been found to be associated with a >80% reduction in the risk of occupational infection *(72)*. Prophylaxis clearly is important (73,*74*). For this reason, the PHS recommends that ZDV, lamivudine, and sometimes a protease inhibitor such as indinavir should be given prophylactically within 1 to 2 hours of a high-risk exposure to HIV *(74)* (see also Chapter 74).

PREVENTION

Prevention of Exposure to Blood and Body Fluids

Strategies are needed to reduce the occupational exposure to infectious agents by inoculation and/or direct contact. These are summarized in Table 79-1. Chapters 73, 74, and 76 cover healthcare-associated infections in healthcare workers caused by infectious agents acquired by exposure to blood and body fluids or by direct contact with other infectious substances. Specific risks associated with autopsies and appropriate preventive measures are discussed further in this chapter.

Autopsy protocols (19,*28,29,43–46,62,67–70,75*) should include measures to prevent or minimize exposure of the prosector and his or her assistant to potentially contaminated tissues and body fluids by direct contact or via inoculation. These measures should also prevent other areas of the autopsy suite from becoming contaminated so that bystanders, housekeeping personnel, and others will not be exposed to contaminated tissue and fluids. In short, autopsy precautions should be directed at the prevention of needlesticks, accidental cuts, and splash or direct contamination of mucous membranes or skin in any person who for any reason enters the autopsy suite. A rational approach to the safe conduct of autopsies includes (19,*28,29,43–45*) performance of autopsies by experienced and well-trained personnel, use of appropriate safety-oriented devices, a safe work environment, appropriate work practices, appropriate vaccination against vaccine-preventable diseases such as hepatitis B, and Standard Precautions (formerly Universal Precautions). These are discussed in greater detail.

Experienced and Well-Trained Personnel It is logical to assume that the risk of accidental injury is greatest among the inexperienced. This has been confirmed by a study wherein a laceration injury occurred in 1 of every

TABLE 79-1

Strategies for Risk Reduction from Occupational Exposure to Infectious Agents by Inoculation or Direct Contact

Strategy	*Comment*
Improved education/training on the safe handling and disposal of needles	This is an approach that will most rapidly reduce risks
Modifications of work-practice habits involving the way devices are used	The proper education/training should lead to such changes in habit
Improvements in personal protective equipment to include design, comfort, and availability and use and aimed at providing a better barrier between the blood/body fluids of a patient and the healthcare worker	Although this is a slower process than education, it can be done in a short period; education and training on the use of personal protective equipment obviously is needed to ensure its proper use
Engineering controls that are designed to eliminate the problem	Examples are needle-free devices for intravenous access and devices that cover a needle after use; these are the least rapid strategies to implement
Administrative controls and policies to ensure the implementation of such controls	Examples are postexposure management procedures and vaccination against HBV; these, like education and training, can be implemented quite rapidly

11 autopsies conducted by pathology residents. In contrast, one such injury occurred for every 53 autopsies performed by staff pathologists *(76)*. In addition, there should not be time constraints (self-imposed or otherwise) that could lead to hurried carelessness. For this reason, many pathology departments do not routinely conduct autopsies after 4 p.m.

There must be a sufficient number of experienced and well-trained personnel. Most autopsies are done with two persons, the prosector and his or her assistant. A logical recommendation is to have a third person (19,*29*). This third person functions as a circulator and does not directly participate in the autopsy procedure. Thus, the prosector and his or her assistant are "dirty," whereas the circulator remains clean, avoiding direct contact with contaminated tissues and body fluids. The circulator's tasks include the following:

1. Preparation of the 0.5% sodium hypochlorite solution from commercial bleach solution by diluting the latter 1:10. This solution is used to swab surfaces and/or to soak instruments.
2. Preparation of plastic biohazard bags for bagging soiled linens from the stretcher and for the gowns and scrub suits, which are deposited in plastic bags after the autopsy has been finished. Other plastic bags are prepared for waste such as gloves, masks, and foot covers, which will be incinerated. All bags must be labeled with a biohazard tag as per OSHA regulations *(14)* and with the disposition (incineration or laundering). Many medical centers now have colored bags to indicate the disposition (e.g., red for incineration, orange for laundering).
3. Assistance in the collection of all specimens by bringing clean containers to the table in which specimens may be placed. Also, the propane gas cylinder can be lit for the searing spatula. The circulator should do all paperwork such as laboratory requisitions. The circulator also ensures that specimen containers are washed clean and wiped with 0.5% sodium hypochlorite solution, the caps and covers are tightly fastened, the containers are labeled with biohazard tags and the deceased's name and hospital number, and the containers are placed in waterproof bags for transportation to the various laboratories for further processing and studies. Finally, the circulator attaches the accompanying laboratory requisitions to the proper specimens.
4. Assistance in providing any instruments or other supplies to the prosector.
5. Recording the organ weights and other descriptive notes, often using dictating equipment.
6. Adjusting the lamp and microphone over the autopsy table.
7. Communication with physicians, nursing supervisors, funeral directors, and other relevant personnel so that the telephone receiver does not get contaminated by the prosector.
8. Handling of containers in which tissues for fixation are to be placed to avoid contamination of the outer surface of the container.
9. Wiping up any drops of blood or body fluids that may fall on the floor around the autopsy table. Gloves should be worn. Paper towels and 0.5% sodium hypochlorite solution are used. This minimizes any soiling of the autopsy floor.

Use of Appropriate Safety Devices Safety devices for the routine autopsy have become an important aspect of Standard Precautions and are well documented and described (*14*,19). Particularly important in the autopsy suite are personal protective items. Eyes should be protected by goggles or face shields. Eye glasses are often worn instead of goggles or face shields but provide only minimal protection for the eyes. Goggles under which eye glasses can be worn are available. Surgical caps and masks should be worn for the performance of the autopsy. The mask is particularly important for the prevention of tuberculosis. These masks should not be the standard surgical mask but instead a disposable particulate respirator. OSHA, of course, requires a fume filter that excludes particles 0.6 to 1.0 μm in size. A number of pathologists use and are very pleased with powered respirators. Scrub suits should be worn. These should have long sleeves with either attached or separately provided water-repellent sleeves. The scrub suit must not be worn outside of the autopsy suite. Surgical gowns have been recommended (19). These should be waterproof disposable gowns with disposable forearm guards. A waterproof apron must be worn. Protective shoes should be worn. These are not to leave the autopsy suite. Waterproof shoe coverings should be worn over these shoes; these should be disposable. Two pairs of gloves are recommended because latex loses its integrity after a period of use *(77)*. Frequent changing of the outer pair is recommended. Many prosectors now use a fine-mesh metallic glove or a Kevlar "fish" glove. The latter was developed for workers cleaning fish and is very flexible and not clumsy. These Kevlar gloves can be purchased more cheaply from a sporting goods store than from a laboratory safety catalog. If such gloves are not worn routinely, they should be worn for high-risk procedures such as removing the pelvic organs or cutting the ribs. Ribs should not be cut through the bony portion but instead should be incised medial to the costochondral junction. Uncalcified cartilage, unlike bone cuts with spicules, will not scratch or puncture the skin if there is unexpected contact. A safe yet practical approach to gloving is a pair of tight-fitting latex surgical gloves underneath Kevlar gloves, with a larger pair worn on top of the Kevlar gloves. The outer pair should be changed frequently.

Other safety devices concern the use of instruments and their design. There should be only one blade in the dissection field at any given time. Blades with rounded ends are available. Changing blades should not be attempted with forceps and clamps, because these contribute to flying blades. When an oscillating (Stryker) saw is used, a vacuum device can be attached to minimize aerosols. Alternatively, a damp towel can be held over the saw by a second person or a clear plastic bag can be used to contain the entire procedure. Many prosectors now recommend that the cranium be opened with a hand saw, although this is exceedingly difficult. Blunt needles are available for aspirating body fluids.

Safe Work Environment It is the responsibility of each medical center to provide an adequately equipped and safe morgue facility. Of utmost importance is proper ventilation. Good lighting is important. A shower should be available in both the men's and women's locker rooms. All surfaces

should be of a material that is easy to clean (e.g., stainless steel); contaminated surfaces should be promptly cleansed and treated with an appropriate disinfectant. Floors and walls are best painted with enough coats of epoxy paint to seal such materials as cinder blocks, bricks, tile, and concrete. The floors should have drains connected with appropriate traps and filters to the hospital drainage system. High-pressure hose sprays should be avoided during the autopsy cleanup procedure. Similarly, side-arm faucet water aspirators that use the Bernoulli principle to create an inexpensive suction device should be avoided, because these may create an infectious aerosol. Instead, surgical-type vacuum reservoirs that are properly connected to the hospital system should be available.

Appropriate Work Practices Work practices and attitudes regarding the transmission of infectious diseases during the autopsy are evolving and are being shaped by new scientific evidence. For example, Bankowski et al. *(78)* described the postmortem recovery of human immunodeficiency virus type 1 (HIV-1) from the plasma and mononuclear cells of patients with AIDS. Recovery of infectious HIV-1 from 51% of blood samples of deceased AIDS victims should prompt pathologists and morticians to reevaluate policies regarding Standard Precautions and the handling of known HIV-1–infected cadavers. Of particular interest in this comprehensive evaluation is the authors noting that time from death until specimen acquisition was the only factor significantly associated with recovery of HIV-1. No HIV-1 was recovered from cadavers sampled more than 21 to 25 hours after death. Thus, delaying an autopsy for 24 hours may markedly decrease the potential HIV-1 infectivity. However, it is clear that the risks are not entirely eliminated by postponement of the autopsy. Infectious HIV has been recovered from tissue, bone, and blood after a postmortem interval of 6 days and from an unfixed spleen specimen stored at 20°C for 14 days after death *(79)*. Unfortunately, a 24-hour delay in the autopsy would not be well received by funeral directors and embalmers who already have identified significant delays in obtaining autopsied cases from hospitals *(80)*.

Hepatitis B Vaccination Healthcare workers with occupationally acquired HBV infection have died from this infection *(81)*. Despite all the concern about autopsies in the AIDS era, among the greatest risks to pathologists continues to be viral hepatitis *(82)*, both hepatitis B and hepatitis C. The prevalence of anti–hepatitis B antibody in pathologists is 27%, exceeded only by surgeons at 28% *(83)*. Accordingly, there are now available guidelines for prevention and strategies for surveillance for these and other blood-borne viruses *(84–86)*. The risk of acquiring HBV infection from occupational exposure depends on the nature and frequency of exposure to blood or to body fluids containing blood *(87)*. The risk of infection is at least 30% after a percutaneous exposure to blood from a hepatitis B e antigen-seropositive source *(88)*. Unlike HIV-1, hepatitis B vaccination is readily available, and all pathologists who are seronegative for hepatitis B should be vaccinated. Vaccination for hepatitis B has been shown to effectively prevent healthcare-associated hepatitis B *(89)*, and the CDC now recommends such vaccination *(90)* (see Chapter 73).

Standard Precautions The concept of Standard Precautions is quite simple. This concept recognizes that medical history and examination cannot reliably identify all patients with blood-borne pathogens; therefore, blood and body fluid precautions should be used *consistently* for *all* patient specimens. This approach is recommended by the CDC and is referred to as "universal blood and body fluid precautions" (now contained within Standard Precautions). All patient tissues, blood, and body fluids should be considered potentially infectious. This concept is further discussed in Chapters 73 and 74.

The concept of Standard Precautions is extremely important to undertakers and mortuary workers *(48,62)*. Although all deceased patients known to have a contagious disease should have the body bag marked with a biohazard or blood precautions tag to warn funeral directors and other mortuary personnel, not all cases of transmissible infectious diseases are identified at the time of death. The greatest risk for mortuary workers is the injection and distribution of embalming fluid, which displaces the natural body fluids. This procedure carries the risk of needlestick injuries, direct contact with displaced body fluids, and aerosolization of displaced body fluids. Therefore, mortuary workers should follow the same precautions as outlined for the autopsy.

After the introduction of Universal Precautions in 1986, with reaffirmation by the CDC in subsequent publications *(91,92)*, a modified approach *(93)* was published in 1988. The difference between these two proposals is that, initially, all body fluids were treated as if they were equally infectious; the modified approach excluded certain body fluids unless they were contaminated with blood. This topic has been further updated on a CDC/NIOSH web site (94). Experience has revealed that compliance with Standard Precautions is not ideal, with perceived risk and appropriate education as important factors in compliance *(95–99)*. Nonetheless, these guidelines remain prudent today and are summarized in Table 79-2.

It is important to realize that these guidelines are only for blood-borne infections and do not address transmission of aerosolized infectious pathogens. It was initially estimated that the cost of Universal Precautions would be between $1 and $10 per patient admitted to hospitals in the United States *(100)*. Subsequent data *(101)* found that the cost of implementing the CDC Universal Precautions in a university hospital was closer to the $10 per patient estimate. Finally, it should also be realized that no data confirm the efficacy of these guidelines. Nonetheless, they are sensible if they are followed correctly.

Prevention of Diseases Transmitted by Hand-to-Mouth Contact

Although airborne transmission and direct contact and inoculation of infectious pathogens are the most common risks for occupationally acquired infections in posthospital healthcare workers, hand-to-mouth transmission is nevertheless an important mechanism in the pathogenesis of these infections. Basically, the mechanism consists of a healthcare worker contaminating his or her hand(s) with an infectious agent from a patient and then transferring this pathogen to his or her mouth. As might be anticipated, most of these infections involve pathogens that cause diarrheal illnesses, although

TABLE 79-2

Modified Recommendations for Standard Precautions

Following the precautions with:
- Amniotic fluid
- Blood and other body fluids containing visible blood
- CSF
- Pericardial fluid
- Peritoneal fluid
- Pleural fluid
- Semen
- Synovial fluid
- Tissues
- Vaginal secretions

It is not necessary to follow the precautions with the following body fluids unless they are contaminated with blood:
- Feces
- Nasal secretions
- Sputum
- Sweat
- Tears
- Urine
- Vomitus

It is not necessary to follow the precautions with the following body fluids unless they are contaminated with blood:
- Feces
- Nasal secretions
- Sputum
- Sweat
- Tears
- Urine
- Vomitus

viral hepatitis is another infection that can be transmitted by hand-to-mouth contact (i.e., fecal–oral contamination).

Fecal–oral contamination occurs, because many patients have poor personal hygiene and soil the environment, after which poor hand-washing practices by healthcare workers result in transmission of the diarrheal illness to themselves.

Outbreaks of diarrhea in long-term care facilities appear to be a common problem *(36,102,103)*. The risk for nursing home workers and posthospital healthcare workers can be appreciated by reviewing the medical literature on this topic. Norovirus, for example, is a common cause of gastroenteritis in long-term care facilities *(104,105)*. During an average outbreak, almost one-third of residents and one-fifth of staff members are infected *(106)*. Noroviruses also are a common cause of outbreaks of acute gastroenteritis on cruise ships; poor cleaning practices in the restrooms have been a factor in such outbreaks *(107)*. Restroom and hand hygiene practices are likely to be important in long-term facilities as well. One nursing home report *(108)* described an outbreak of *Giardia lamblia* that originated with an infected meal and then progressed by fecal–oral contamination and eventually affected 35 residents and 38 employees of the facility. Other bacterial pathogens have caused serious gastroenteritis outbreaks in the nursing home setting. For example, *Escherichia coli* 0157:H7 caused a period of enteritis exceeding 18 days in 33% of nursing home residents and 13% of staff members *(109)*. HIV-infected patients are recognized as commonly having diarrhea caused by enteric viruses *(110)*. Finally, *Clostridium difficile* is now recognized as one of the most common causes of healthcare-associated infections in long-term care facilities *(111,112)*. This, in part, is due to the emergence of a new, more virulent strain of *C. difficile (113)*. Clearly, the problem of fecal–oral transmission in posthospital healthcare workers is important.

Healthcare workers who are at risk for outbreaks spread by fecal–oral contamination must practice good hand-washing techniques themselves and reinforce the importance of hand washing for everyone within the facility, including healthcare workers, competent patients and residents, and visiting friends and family members *(114)*. In addition, supplies of soap, towels, and gloves must be adequate throughout the facility. If hand washing is difficult to do, the substitution of a waterless alcohol hand rub containing emollients is recommended *(115,116)* except for situations in which *C. difficile* is the suspected pathogen *(117)*. Soap and water is superior to alcohol hand rub and antiseptic wipes for removal of *C. difficile (117)*. The use of gloves must include changing gloves before going from one patient to another and washing hands each time a pair of gloves is removed. This is because many pathogens can stick to the latex gloves after contamination, and adherence persists despite washing the gloves with soap, chlorhexidine, or isopropyl alcohol *(118)*.

Finally, although the concept of interrupting or preventing outbreaks of infections with hand washing began with Semmelweis in 1847 *(119)* and is still considered necessary, the role of hand washing remains problematic even today *(120)*. Moreover, compliance with hand-washing recommendations has been poor *(121–123)*, leading to the use of alcoholic preparations that require no water *(115,116,124)*. The subject of hand washing and hand disinfection is extensively covered in Chapter 91. Hand washing is vital to interrupt the fecal–oral route of transmission of infection *(125,126)*.

KEY INFECTIOUS PATHOGENS OF CONCERN FOR POSTHOSPITAL HEALTHCARE WORKERS

A diverse group of specific pathogens are involved in healthcare-associated infections. These are discussed in detail in Section V of this book. Management, evaluation, and training for healthcare workers exposed to healthcare-associated pathogens and to other highly infectious pathogens are important topics, and guidelines for this have been published *(127–129)*. Some infectious pathogens are of minimal risk for occupationally acquired infections in posthospital healthcare workers (e.g., coagulase-negative staphylococci). On the other hand, a number of infectious pathogens may or may not be associated with healthcare-associated infections *per se* but are of particular concern to posthospital healthcare workers such as prosectors and morticians. Examples of these pathogens include HIV-1, rabies virus, and human prion agents. These and other

agents of particular concern to posthospital healthcare workers are briefly discussed in this section.

Human Immunodeficiency Virus

HIV-1, as already mentioned, is responsible for altering the approach to prevention of occupational exposure to infectious agents in the healthcare workplace *(130)*. Mechanisms for transmission of HIV-1 to posthospital healthcare workers include direct contact (e.g., splashing mucosal surfaces) and inoculation. To date, there is no evidence for airborne transmission or fecal–oral transmission. Obviously, the posthospital healthcare workers at risk include all those involved with blood and body fluids of premortem or postmortem AIDS victims and the trash haulers and landfill operators who may be exposed to improperly disposed needles. The key to prevention of HIV-1 infections in these persons is to prevent exposure. A number of these preventive measures were discussed previously in this chapter.

Additional measures include decontaminating any spills of blood or body fluids in the work area with 5% sodium hypochlorite. All instruments used for AIDS patient care should be soaked in disinfectant for 30 minutes before routine washing. HIV-1 is inactivated by a wide range of disinfectants *(131,132)*, including 50% ethanol, 3% hydrogen peroxide, phenolic compounds (e.g., Lysol), iodophor compounds (e.g., Betadine), and sodium hypochlorite (household bleach) in a freshly prepared 1:10 dilution in water (final concentration: 0.5%). Because of their corrosive action, soaking instruments in bleach solutions should be limited to 30 minutes. Instruments using electronic devices that are an integral part of the equipment are more difficult to disinfect *(133)*. Fortunately, studies have shown that HIV-1 is reliably eliminated by routine disinfection for such electronic instruments *(134)*. In addition, there are now guidelines for disinfection practices for semicritical items *(135)* (see Chapter 80).

Disposable needles must be used and disposed of properly. These needles should not be purposely bent, clipped, recapped, or otherwise manipulated by hand. A puncture-resistant container for sharp instruments should be within easy reach and must be used. Needles and syringes should be dropped into this container after use.

The risk for acquiring HIV-1 infection from an occupational exposure has been studied extensively in numerous prospective studies. These studies consistently have documented a comparatively low rate of infection per percutaneous exposure. When results of these studies are combined, the magnitude of risk for HIV-1 infection appears to be 0.32% per exposure (136). This means that, in general, one might expect between three and four occupational infections for every 1,000 parenteral exposures to blood from HIV-1–infected patients. The risk may be higher or lower, depending on the severity of injury. For example, if a large volume of blood is injected via a needlestick injury, the risk is considered higher than with a low volume. The risk for HIV-1 infection after a mucous membrane exposure is believed to be lower but is not zero.

A retrospective case control study *(71)* to identify risk factors for HIV seroconversion among healthcare workers after a percutaneous exposure to HIV-infected blood found that workers were more likely to become infected if they were exposed to a larger amount of blood (i.e., presence of visible blood on the device before injury, needle had been placed directly into the patient's vein or artery, or deep injury). Increased rates of transmission were also noted from terminally ill patients with AIDS that has been attributed to an increased titer of HIV in the blood of these patients.

If a posthospital healthcare worker is exposed to HIV-1, a number of issues must be addressed (136,*137,138*). The first is immediate and aggressive first aid. This may not eliminate the risk for HIV-1 infection after exposure but is probably of some help in reducing the healthcare worker's postinjury emotional and psychologic stress. Current recommendations for first-aid measures after exposure to HIV-1 include vigorous scrubbing of parenteral injury sites for 10 minutes with 10% povidone-iodine solution. Milking the wound site to promote bleeding is encouraged. Exposure of mucous membranes to HIV-1 should be followed by irrigation of these membranes with normal saline for 15 minutes. Immediately after completion of these first-aid measures, the employee should report the occupational exposure formally to appropriate persons. These include the responsible supervisor and medical personnel (e.g., occupational medical service, if available; emergency room if not). The safety officer and quality assurance personnel, if applicable, may be informed as well. The healthcare worker should be advised, however, that discussing the exposure widely with coworkers may prove to be a problem if the exposure does result in infection.

When appropriate medical personnel are notified, they should evaluate the injury, review and repeat first-aid measures, and initiate medical and psychologic therapy. The postinjury evaluation should include the route of exposure, the source (i.e., specific blood or body fluid involved), the likely volume of inoculum, the condition of the source patient (i.e., the stage of HIV-1 infection and history of any antiretroviral therapy), the amount of time (if any) between the removal of a needle (or other sharp instrument) and the penetration of the exposed worker, the extent of injury, the type and promptness of first-aid measures, and the health status and anxiety level of the injured healthcare worker. The worker's hepatitis B and hepatitis C infection status should be determined, because occupational hepatitis is also a potential problem *(139,140)*. Postexposure management for occupational exposure to hepatitis B and C virus is discussed in each respective section.

All parenteral injuries should be treated equally with identical initial postinjury triage and management for all reported injuries. Such identical triage and initial management tactics allow for the potential lack of a precise occupational exposure history from an anxious healthcare worker, serve to reassure the injured worker, and place the institution in a clear position of healthcare worker advocacy.

Because of the common and often extreme emotional reaction of exposed healthcare workers, initial guidance about relative risk may not be comprehended at the initial encounter and should be reviewed again at later counseling sessions. It is important that several such counseling sessions are scheduled soon after the exposure. Counseling should include relevant estimates of the risk for infection associated with the type of exposure experienced by the healthcare worker. Most exposed workers

find the relatively low 1/360 to 1/500 risk associated with parenteral exposure to HIV-1 to be somewhat reassuring. However, the counselor must explain that these figures represent an average risk and that the worker's specific injury may be associated with a higher or lower risk for infection. Counseling initially should address the rationale for considering antiretroviral prophylaxis. This must be done quickly, because prophylaxis should be initiated as soon as possible after the exposure. Counseling must include a plan for follow-up to include such measures as serologic testing and additional counseling. In addition, counseling should include the possibility that the exposure may result in infection, and precautions that may avoid transmission to others should be discussed. Finally, counseling should provide emotional support for the worker and should address all questions related to the exposure. This support may need to include other members of the worker's family. It is useful to provide a standard written summary for the counseling and advice provided so that lack of retention of the information because of the emotional state of the worker does not cause a problem.

A major issue with occupational exposure to HIV-1 has been whether or not to offer chemoprophylaxis. Part of the reason for this problem was that initially it was unknown whether ZVD could prevent HIV infection if it was administered before and/or during exposure. An animal study used infant rhesus macaques to investigate the efficacy of ZVD prophylaxis in preventing simian immunodeficiency virus (SIV) infection after a low dose of SIV *(141)*. In this study, ZVD prophylaxis given 2 hours before the SIV dose effectively prevented infection. Clinical experience with ZVD prophylaxis *(71)* has revealed that such prophylaxis is useful. Currently, postexposure prophylaxis with multiple antiretroviral agents is recommended (*72*,73,*74*,135). This postexposure prophylaxis should be initiated within the first 2 hours but could be instituted as late as 1 to 2 weeks after HIV exposure in high-risk exposures. ZVD should be considered for all regimens because of sufficient data to support its use in this setting. In addition, lamivudine should be added to ZDV therapy for increased antiretroviral activity and activity against ZVD-resistant strains. Finally, a protease inhibitor such as indinavir should be added for high-risk exposure or if ZVD-resistant strains are likely. The latest CDC guidelines for prophylaxis *(74)* should be obtained and reviewed; these are constantly being updated.

Most medical centers offer antiretroviral postexposure chemoprophylaxis to healthcare workers who sustain parenteral or mucous membrane occupational exposures to HIV-1, provided these institutions are able to provide emergency evaluation, treatment, and consultation 24 hours a day, 7 days a week (see Chapter 74). Clearly, it is much more difficult to offer such therapy to many posthospital healthcare workers. Such workers may want to participate, if possible, in an ongoing program at a local medical center.

Counseling is an extremely important aspect of postexposure care of the employee yet can be extremely difficult to provide to most posthospital healthcare workers. Such counseling can be complex, labor intensive, and time consuming. Because guidelines for counseling have been established *(138)* and are used at many medical centers, such centers may be able to provide this kind of counseling to posthospital healthcare workers on a contractual basis. Appropriate follow-up is needed and can also be supplied by the counseling service. (For a more thorough review of this topic, see Chapter 74.)

Hepatitis B Virus

HBV is the etiologic agent causing a form of acute hepatitis that characteristically has a long incubation period (40–120 days) after the initial contact with the infectious virion *(142)*. This form of hepatitis was first recognized in 1833 after administration of smallpox vaccine that contained human lymphatic fluids. It was not until the 1940s and 1950s that the percutaneous transfer of material containing human serum was appreciated as an important route of transmission *(143)*. Unfortunately, the appreciation of this route resulted in the name "serum jaundice" or "serum hepatitis" as opposed to the shorter incubation variety (i.e., that caused by hepatitis A virus [HAV]), which was called "infectious hepatitis." Although the name serum jaundice accurately describes the first recognized route, it implies that this is the only route. That is not the case with HBV, because it has become clear in recent years that HBV is most commonly spread by routes that do not involve direct percutaneous transfer *(144)*. Examples of these routes include sexual contact, transmission from mothers to their newborn infants, and contact with saliva *(145,146)*.

HBV is a well-recognized occupational hazard in the healthcare worker *(81–87,146)*. As with HIV, the major routes involving healthcare workers are percutaneous transfer and exposure of mucosal tissues and open sores to blood or body fluids containing the virus. As already mentioned, the prevalence of HBV antibody in physicians such as pathologists and surgeons approaches 30% *(83)*. Overall, healthcare workers who frequently encounter blood or blood products have an intermediate risk for HBV infections; approximately 1% to 2% of these workers are hepatitis B surface antigen (HBsAg)-positive, whereas 15% to 30% of workers have other markers, such as anti-HBs and antibody to hepatitis B core antigen (anti-HBc).

For healthcare workers, the most effective way to deal with the threat of hepatitis B is by preexposure immunization with hepatitis B vaccine *(89,90,147)*. There are several types of vaccines available *(89)*: the first, a plasma-derived vaccine (Heptavax-B), was licensed in 1981; the second, a recombinant vaccine (Recombivax-HB), was licensed in 1986. Subsequently, a second recombinant vaccine (Engerix-B, SmithKline Beecham) was licensed. Prospective, double-blind, placebo-controlled trials have shown >90% protection *(89,148)*. Those few individuals who later became infected with HBV have been among the vaccine recipients who failed to convert. The presence of anti-HBs antibody in the serum of healthcare workers after a course of three vaccinations with hepatitis B vaccine can be detected by serologic testing, and the occasional failure of vaccination can be identified. Healthcare workers who do not respond to or do not complete the primary vaccination series should be revaccinated with a second three-dose vaccine series or evaluated to determine whether they are HBsAg seropositive *(90)*. Revaccinated healthcare workers should be tested for anti-HBs at the completion of the second series. Vaccine-induced antibodies decline gradually with time, and as many as

60% of those who initially respond to vaccination will lose detectable anti-HBs by 8 years *(89)*.

Healthcare workers should be vaccinated against hepatitis B not only to protect their own health but also to prevent spread of hepatitis B infection to patients *(149)* or their families if healthcare workers become infected. Despite the availability of vaccines for over a decade, with vaccination available for free in many cases, and the cogent reasons for such vaccination, there are still healthcare workers involved in posthospital care who have not been vaccinated. The worry of possible transmission of AIDS in the plasma-derived vaccine has been shown to be groundless *(150)*. The ability of the HBV vaccine to protect healthcare workers is clearly documented *(89)*. There is no reason whatsoever for healthcare workers not to receive vaccination against HBV, and all should do so *(90)*.

For those workers who are not vaccinated and who are potentially exposed by accidental needlestick injury, mucosal splash with body fluids, or other such incident, a plan similar to that outlined for HIV is useful. In addition, postexposure prophylaxis of hepatitis B with hepatitis B vaccine and hepatitis B immune globulin is useful and should be undertaken (151). (For additional details, see Chapters 73 and 75.)

Other Types of Viral Hepatitis

The ability to serologically diagnose acute viral hepatitis caused by infection with HAV or HBV has led to the recognition of other viral hepatitis agents that are predominantly transmitted either by the percutaneous (blood) or the fecal–oral routes. These agents are grouped as non-A, non-B hepatitis agents. The first of these described was the hepatitis delta virus (HDV), which is made up of a single-stranded RNA (1,700 nucleotides) surrounded by a protein coat *(152)*. This protein coat is encoded by the delta virus genome and has an outer membranous protein envelope consisting of HBsAg encoded by the HBV. This HBsAg-containing envelope allows the delta virus to attach to hepatic cells. The delta virus is then infectious, provided that the new host has an active hepatitis B infection, because the delta virus coinfects with and requires the function of active HBV for its replication. The delta virus can infect a person simultaneously along with hepatitis B or superinfect a person who is already infected with hepatitis B. The duration of infection caused by the HDV, of course, is determined by the duration of and cannot outlast the hepatitis B infection. HDV thus also should be screened for in any situations involving potential transmission of hepatitis B infection.

The molecular cloning of a parenterally transmitted virus, referred to as hepatitis C virus (HCV), has been described *(153)* and is the recognized cause of most non-A, non-B hepatitis in the developed world. Because of its blood-borne route of transmission and its prevalence, this type of hepatitis is of concern to healthcare workers and is discussed separately.

A second form of non-A, non-B hepatitis is epidemiologically distinct, is transmitted by the fecal–oral route, and causes large epidemics in third-world countries. Additional work *(154)* suggests that a single virus is responsible for most of this form of hepatitis seen worldwide. This virus is hepatitis E virus *(155)* and, like HAV, is of somewhat less concern to the healthcare worker, because this virus is transmitted mainly by the fecal–oral route *(155,156)*.

Hepatitis C

HCV is of particular concern to healthcare workers, because its routes of transmission are similar to those of hepatitis B and because of the potential long-term untoward effects. In fact, one of the most disturbing features of HCV to healthcare workers exposed to this agent is the fact that this viral infection of the liver has a propensity to progress to chronic hepatitis with biochemical evidence of chronic hepatitis *(157)*. In addition, long-term follow-up studies have shown that 20% to 25% of patients ultimately develop cirrhosis of the liver *(158)*. HCV is currently considered one of the major causes of cirrhosis in the United States and ranks as one of the most common reasons for liver transplantation in adults. Multiple reports have shown that healthcare workers are at risk for HCV infection *(159–162)*.

Although HCV was not cultured until 2005 *(163,164)*, the previous development of an assay to detect antibody against a recombinant polypeptide of HCV had allowed investigators to pursue the epidemiologic study of this infection *(158,165)*. Confirmatory HCV testing has become commercially available and includes the Abbott MATRIX-HCV immunoblot assay and the Ortho-Chiron recombinant immunoblot assay. However, the interpretation of these anti-HCV assay results is limited by several factors, including lack of detection in approximately 5% of infected patients; inability to distinguish between acute, chronic, and past infections; prolonged interval between the onset of acute illness with HCV and seroconversion; and false-positive rates as high as 50% in areas with low prevalence of HCV infection *(165)*.

Despite these remarkable advances, the epidemiology of this infection in healthcare workers is not yet totally clear. What is now known is that transmission of HCV by blood products has been unequivocally demonstrated. Hepatitis C is, in fact, the most common cause of post-transfusion hepatitis *(158)*. Transmission of HCV by organ transplantation has also been documented *(166)*. In addition, this form of hepatitis has been shown to have sexual, vertical, and intrafamilial spread *(158)*.

Several case reports have demonstrated transmission of HCV infection from anti-HCV–seropositive patients to healthcare workers as a result of accidental needlestick injury or lacerations with sharp instruments *(152,165)*. The rate of anti-HCV seroconversion averaged 1.8%, whereas studies using HCV detection by PCR assay revealed a 10% rate of transmission *(154,157,162)*.

High-risk source patients for HCV infection clearly would include parenteral drug abusers, hemophilia patients, dialysis patients, multiply transfused patients, and patients with unexplained acute or chronic liver disease or enzyme elevation. Recommendations for follow-up of healthcare workers after occupational exposure to HCV now exist *(167,168)*, and regulations for the prevention of occupationally acquired HCV have been established *(13)*. Unfortunately, effective postexposure prophylaxis for HCV has not yet been determined (151). However, combination therapy of chronic hepatitis C with peginterferon-alpha-2a and oral ribavirin now appears to be a valuable first-line treatment option *(169,170)*. This combination may in time

prove useful for postexposure prophylaxis for HCV. In the meantime, medical centers should use the same general approach for HCV as that used for HIV and HBV. This approach should also be applied to posthospital healthcare workers. Readers wishing more information are referred to Chapter 73.

Mycobacterium Tuberculosis After a steady decline in the incidence of tuberculosis from the mid-1950s to the mid-1980s, tuberculosis again become a major health problem in the United States in the 1990s because of an increasing incidence and a similar increase in the numbers of multidrug-resistant and extensively drug-resistant strains *(15,16,171–175)*. The reasons for this resurgence are complex and include the AIDS epidemic, increasing numbers of homeless persons, increased migration from countries with a high prevalence of tuberculosis, increased crowding in housing among the poor, increased numbers of residents in long-term care facilities, decreased compliance in tuberculosis therapeutic regimens, atypical tuberculosis in AIDS patients, delayed recognition of tuberculosis, delayed recognition of multidrug-resistant and extensively drug-resistant isolates, and inadequate hospital facilities for treating patients with tuberculosis *(55–57,175–179)*. Fortunately, the response to this resurgence of tuberculosis after a sluggish start has become vigorous in the first decade of the 21st century *(15,180–182)*. Factors that have reversed this resurgence are new diagnostic methods for the detection of *M. tuberculosis (183)*, the use of directly observed therapy *(184,185)*, a four-drug/2-month "intensive phase" for treatment of active tuberculosis *(185)*, increased duration (at least 18 months) for treatment of multidrug-resistant tuberculosis *(186)*, interferon-gamma release assays for detection of active and latent tuberculosis *(187,188)*, increased collaboration and convergence between programs to control HIV and tuberculosis *(189)*, and development of new treatment regimens for the therapy of tuberculosis *(190)*.

The risk of acquiring tuberculosis by healthcare workers has increased *(60–67,179,191–197)*. The healthcare-associated transmission of tuberculosis has even been reported from patients with draining lesions *(198,199)*. Posthospital healthcare workers, like all others, are at greater risk for tuberculosis, as shown by outbreaks in nursing homes *(36)* and autopsy suites *(62,67)*.

Measures to prevent the spread of tuberculosis in posthospital healthcare workers are identical to those used to prevent the spread in hospitals and include infection control measures for source control and engineering controls (*17,18*,19,20,*27–29,46,55–57,66,175,179,191–197,200–202*,203,*204*). Infection control measures should be standardized based on guidelines from the CDC *(17)* and documented in an appropriate procedure manual. Such control measures include rapidly identifying and isolating patients with presumptive tuberculosis, having patients cover their mouths when coughing, using masks, and initiating antituberculosis therapy as soon as the diagnosis is established. Engineering controls include rapid air exchange, negative pressure ventilation with air exhausted to the outside, high-efficiency particulate air (HEPA) filters, and ultraviolet lighting.

Many healthcare-associated outbreaks of tuberculosis have been related to lack of adherence to proper infection control measures for tuberculosis and/or to inadequate functioning of isolation rooms *(60–62,67,179,191–197,200,205–207*). If hospitals have such problems, facilities in which posthospital healthcare workers are employed, such as nursing homes or patient homes, can hardly be expected to have adequate isolation rooms.

Although establishing and maintaining effective isolation rooms is necessary for preventing transmission of tuberculosis, such rooms alone do not offer sufficient protection for healthcare workers who take care of patients. This is because such persons who are physically close to patients with active tuberculosis will be exposed to infectious aerosols before ventilation can reduce the aerosol concentration significantly. Thus, healthcare workers who care for patients should wear appropriate respirators. The definition of an appropriate respirator currently is debated. The CDC *(17)* defines an appropriate respirator as a "particulate respirator," which is the same as what the NIOSH calls a "disposable dust/mist-filter respirator." This type of respirator excludes particles 2 μm in diameter. NIOSH instead recommends a fume filter that uses HEPA-filter media and excludes particles 0.6 to 1 μm in size (*18*,203). Finally, all types of air-purifying respirators allow some inward leakage of droplet nuclei around the face seal. Particulate respirators permit 10% to 20% leakage, whereas a powered air-purifying respirator with qualitative or quantitative fit testing as recommended by NIOSH (203) for high-risk medical procedures such as bronchoscopy permit far less leakage (2%).

The CDC has released guidelines for preventing tuberculosis transmission in healthcare facilities *(17)*, and these should help clarify many of these issues. In addition, OSHA has issued guidelines *(18)* for enforcement of tuberculosis protection requirements as delineated in 29 CFR 1910. Key elements of these tuberculosis protection requirements include the following:

1. Healthcare workers who enter rooms occupied by patients with suspected or known infectious tuberculosis or who perform high -risk procedures (e.g., bronchoscopy) on such individuals must use NIOSH-approved fume (HEPA) respirators. In addition, a complete respiratory protection program, including qualitative (irritant fume) or quantitative fit testing of respirators, must be in place.
2. Records of employee exposure to tuberculosis, of tuberculosis skin testing, and of medical evaluations and treatment for tuberculosis are subject to OSHA record-keeping rules. Any positive tuberculosis skin test in an employee (other than preemployment) would be presumed to be occupational and should be recorded on the OSHA 200 log as would any clinical infection with tuberculosis.
3. Medical management of any clinical manifestations of tuberculosis, including positive skin tests, is the responsibility of the employer. In addition, employers are expected to establish tuberculin skin testing programs for the early identification of personnel with tuberculosis infection. Finally, like the blood-borne pathogen standard, employers will be expected to have yearly training/educational programs for tuberculosis.

This clarification of OSHA regulations (*18*,203) is an important step. Employers of healthcare workers, including

posthospital healthcare workers, have access to additional information on control of tuberculosis *(204–207)*, including the use of screening methods *(208)* and vaccination *(209)*. Readers wishing additional information on tuberculosis should read Chapter 38, whereas Chapter 84 addresses the design and maintenance of hospital ventilation systems.

Methicillin-Resistant *Staphylococcus aureus*

Infections caused by *Staphylococcus aureus* continue to be an important clinical problem *(210)*. The emergence of antimicrobial resistance has been a consistent characteristic of this pathogen, with resistance generally following the widespread use of a particular antimicrobial agent *(211)*. This was seen for penicillin in the 1940s, erythromycin in the 1950s, methicillin in the 1960s, ciprofloxacin in the 1980s, and vancomycin in the 21st century. Methicillin-resistant *S. aureus* (MRSA) was first seen in the 1960s *(212)*, although the term *methicillin resistance* is somewhat misleading, because these isolates are resistant to many other antimicrobial agents such as aminoglycosides, clindamycin, and ciprofloxacin *(211)*. This multidrug resistance makes therapy and/or eradication very difficult. Moreover, resistance has raised the level of concern in healthcare workers who frequently deal with healthcare-associated staphylococcal infections and worry that they may become colonized and subsequently become infected themselves or transmit this pathogen to their patients or family *(213)*. Since the 1960s, MRSA has spread worldwide *(214)* and today is commonly found in hospitals, in long-term care facilities, and in the community *(215–217)*. The isolation of community-acquired MRSA (CA-MRSA) in children with no identified predisposing risk *(217)* has turned out to represent a genetic variant of MRSA that has a different epidemiology as well as additional virulence factors *(218–220)*. Infections caused by these strains are more invasive and serious *(220–222)*. Moreover, these CA-MRSA isolates are now recognized as causes of healthcare-associated infections as well as community-acquired infections (*223*,224). Finally, a report of vancomycin-resistant *S. aureus* containing the *vanA* resistance gene *(225)* is also very worrisome, because vancomycin resistance in MRSA strains will make therapy of staphylococcal infections more difficult.

Colonization of healthcare workers by MRSA is common *(226,227)*. Although the carriage on the hands may only be transient, *S. aureus* (susceptible strains, MRSA, as well as CA-MRSA) adheres well to human nasal epithelial cells *(228)*. Thus, healthcare workers may develop nasal colonization with MRSA, which may then be a significant risk factor for infection by spread of the colonizing strain *(229–232)*. Because of Standard Precautions, many healthcare workers now routinely wear gloves when taking care of patients. Unfortunately, some wear one pair of gloves while taking care of several patients. Hand washing sometimes is done between patients without removing the gloves. Staphylococci adhere well to gloves, and washing while wearing gloves facilitates transfer of *S. aureus* through the glove to the hand *(118)*. Obviously, hands should be washed between patients with an antimicrobial soap *(233)* after gloves are removed. Finally, the transfer of MRSA from inanimate objects to the hands of healthcare workers may be a real problem, as suggested by a number of reports *(233,234)*.

Although this possible mechanism remains controversial *(235)*, there are clearly instances wherein inanimate objects can harbor staphylococci or perhaps other pathogens. Perhaps wearing gloves facilitates the transfer of the staphylococci from the inanimate object to the hands of a healthcare worker and, if improper hand-washing techniques are used, from the hands of a healthcare worker to a patient. Bedrails are now thought to be an important factor in such transmission and may deposit microorganisms on the clothing of healthcare workers as they lean on these rails while caring for a patient. The use of gowns and gloves for routine care of patients with known colonization by multidrug-resistant microorganisms has been recommended.

Healthcare workers have noted the increase in healthcare-associated infections caused by MRSA and CA-MRSA and are concerned that they may become colonized or infected. Such concern about infection is valid because a number of reports have documented these kinds of infections in healthcare personnel *(236–239)*. The frequency of nasal carriage among healthcare workers ranges from 20% to 90%, but fewer than 10% of healthy nasal carriers disperse the microorganisms into the air *(240)*. However, nasal carriers with upper respiratory symptoms can disseminate the microorganisms into the air more effectively. It should be somewhat comforting for healthcare workers to understand that they alone can prevent such colonization and infection with MRSA and CA-MRSA by proper hand-washing techniques. These techniques are covered in detail in Chapter 91. Additional information on *S. aureus* and on MRSA is found in Chapters 28 and 29.

Group A Streptococcus

Group A streptococcus (*Streptococcus pyogenes*) is one of the most common and ubiquitous of human pathogens and causes an impressive variety of infections. These include acute pharyngitis, impetigo, sinusitis, otitis, peritonsillar and retropharyngeal abscess, pneumonia, scarlet fever, toxic shock syndrome, erysipelas, cellulitis, lymphangitis, puerperal sepsis, vaginitis, myositis, gangrene, necrotizing fasciitis, septic arthritis, suppurative thrombophlebitis, bacteremia, endocarditis, and osteomyelitis. This pathogen is also known for its association with two nonsuppurative sequelae, acute rheumatic fever and acute glomerulonephritis, which are related to specific immune responses by the host. It is no wonder that healthcare workers are concerned about this microorganism.

Although *S. pyogenes* is not generally viewed as a healthcare-associated pathogen, outbreaks have long been recognized in hospitals and nursing homes *(241–245)*. There has been a marked increase in the incidence of such invasive group A streptococcus outbreaks in long-term care facilities in the past decade *(246–249)*, which has resulted in guidelines for infection control measures for these outbreaks *(250)*. Clearly, healthcare workers are at risk for this infection. Because *S. pyogenes* is such a ubiquitous pathogen, it is sometimes difficult to determine if a healthcare worker has a group A streptococcal infection resulting from work-related acquisition. However, a number of streptococcal infections in healthcare workers have been determined as having been caused by work-related acquisition (*251–253*,254). One report describes

the healthcare-associated transmission of *S. pyogenes* from a single source patient to 24 healthcare workers *(251)*. Another report describes food-borne streptococcal pharyngitis, which has been reported in a hospital pediatric clinic after a potluck luncheon *(255)*. Healthcare workers with pharyngitis or other types of suspected streptococcal infections are at risk for spreading this pathogen *(256)*. It is for this reason that restriction from patient care activities and food handling is indicated for healthcare workers with group A streptococcal infections until 24 hours after they have received appropriate antimicrobial therapy. Unfortunately, asymptomatic carriage of *S. pyogenes* by healthcare workers also can result in healthcare-associated outbreaks *(257,258)*.

S. pyogenes is spread by respiratory secretions. This mechanism of transmission is facilitated by the ability of these streptococci to adhere to human epithelial cells *(259)* via lipoteichoic acid *(260)*, which is present at the streptococcal cell wall and adheres to surface fibronectin on the surface of oral epithelial-cell membranes *(261)*. Heavily encapsulated strains of *S. pyogenes* seem to be more readily transmitted from person to person than those with minimal hyaluronate capsules *(262)*. This may be due to initial attachment of the capsule to mucus. Once attached to human oral mucosal tissue, the group A streptococci may simply become colonizers of this tissue or may cause invasive streptococcal infections. Throat cultures of approximately 20% of persons with pharyngitis are positive for *S. pyogenes*. Unfortunately, if a control group without pharyngitis is also cultured for *S. pyogenes*, the cultures of 20% of this group are also positive *(263)*. It can be very difficult to differentiate active streptococcal pharyngitis from the carrier state in a symptomatic person *(264)*. The antistreptolysin O titer and other similar antibody titers such as antihyaluronidase and antideoxyribonuclease (DNase) B are useful, because these antibody titers become elevated with active infection. These are obtained as a single serologic test referred to as the "streptozyme test."

In addition to causing acute pharyngitis, group A streptococci are also recognized for their propensity to cause skin infections. This is not unexpected when the pathogenesis of these skin infections is understood *(265–267)*. Fibronectin, the attachment site on mucosal epithelial cells, is also found in other tissues such as blood vessels, in which it stabilizes cell-to-cell and cell-to-substrate attachments to endothelial cells *(268)*. Damage to blood vessels and their endothelial lining such as caused by an abrasion or any other such skin surface wound will expose the fibronectin in the endothelial lining and offer an attachment site for *S. pyogenes*. With 20% of the population carrying group A streptococci in their nasopharynx, it is no wonder that occasional injuries to the skin become infected by this pathogen.

S. pyogenes remains susceptible to β-lactam agents and is relatively easy to treat. If it were not for the sequelae of acute rheumatic fever, acute glomerulonephritis, and the superantigen-mediated toxic shock-like syndrome *(269)*, these infections would not cause as much concern. Concern by healthcare workers has increased, because acute rheumatic fever, after declining for many years *(270)*, has reemerged and remains a problem *(271–273)*. This reemergence has been associated with a concomitant increase in the rate of isolation of very mucoid well-recognized rheumatogenic serotypes (e.g., types 1, 3, 5, 6, and 18). Healthcare workers are also concerned because of the risk for toxic shock–like syndrome *(269)* as well as necrotizing fasciitis *(274)*.

The sequelae of acute rheumatic fever and acute glomerulonephritis are now thought to be related to a host immune response to M protein. This protein is a filamentous molecule consisting of two protein chains in a coiled configuration extending about 60 nm above the surface of the streptococcus *(275)*. The M protein is antigenic and can be studied using serologic methodology. The M serotype appears to be one marker of rheumatogenicity, and those M serotypes most strongly associated with acute rheumatic fever and postpharyngeal and postpyodermal acute glomerulonephritis appear to be distinct *(276)*. Indeed, purification of M protein combined with genetic analysis demonstrated distinct structural differences between the M proteins of streptococci associated with acute rheumatic fever and those known to cause acute glomerulonephritis *(277)*. Of clinical interest is the fact that the acute rheumatogenic sequelae can be prevented by timely treatment of the streptococcal infection, whereas the glomerulonephritic sequelae are not influenced by antimicrobial therapy.

From the viewpoint of prevention of streptococcal infection and sequelae in posthospital healthcare workers, it does not make sense to be overly concerned about a pathogen that can be isolated from 20% of the population in general. However, it would seem prudent to exercise some precautions when taking care of a patient with known group A streptococcal infection. Precautions taken for wound infections with a multiresistant pathogen such as MRSA (to include gloves and gown) would appear appropriate. This is because group A streptococci have been transmitted from infected patients to healthcare workers who have had contact with infectious secretions *(253,278)*, and these infected workers have subsequently acquired a variety of group A streptococcal illnesses. Equally important is the fact that healthcare workers who have become carriers of group A streptococcus have been linked to sporadic outbreaks of streptococcal infections *(257,279–281,281a)*. Finally, the therapy of group A streptococcal infection has not progressed as rapidly as has the understanding of the molecular pathogenesis *(282)*. However, intravenous immunoglobulin promises to be useful for superantigen-mediated aspects (toxic shock and necrotizing fasciitis) of these infections *(269,283)*. (See Chapter 32 for additional information on group A streptococci.)

Rabies Virus

The name rabies comes from Latin and means "rage" or "madness." Rabies has been the object of human fear ever since the disease was first recognized in antiquity *(283–286)*. Cases of human rabies have increased in the United States in the past decade; many of these are bat-associated cryptic cases *(287)*. In addition, rabies virus was inadvertently transmitted to a lung transplant recipient through donor lungs *(288)*. Needless to say, concerns about the possible transmission of rabies to healthcare workers are not at all surprising. This concern most often involves hospitalized patients with suspected or proven

rabies *(288,289)* and hospital healthcare workers. When patients with rabies die, similar concerns are voiced by prosectors and funeral home employees. Moreover, these posthospital healthcare workers may deal with a death by unknown causes in which the etiologic role of rabies is not recognized until long after the autopsy has been completed *(287,290,291)*.

These concerns, although not supported by actual case reports in which healthcare workers have become infected by rabies after direct exposure to an infected patient, are based on some data that clearly allow for the possibility of such transmission. Indeed, rabies virus has been detected in human tracheal secretions, saliva, nasal swabs, and human tissue *(292)*, and airborne transmission in a laboratory worker has been described *(293)*. The virus has never been detected in blood, urine, or feces.

As with any potentially transmissible infection, it is useful for the healthcare worker to understand the pathogenesis of rabies *(294,295)*. The rabies virus is present in high titers in infected animal's saliva and is introduced during a bite to the muscle tissue of another animal. The virus may attach to and enter peripheral nerve cells immediately if a large inoculum is introduced by the bite such that the virus comes into direct contact with these nerves. Otherwise, the inoculated rabies virus attaches to the plasma membrane of human cells via a glycoprotein present in spikelike projections in the outer layer *(296)*. The binding sites on human cells include the nicotinic acetylcholine receptor *(295,297,298)*. The rabies virus is thought to be amplified by replication in skeletal-muscle cells near the site of inoculation until the concentration of virus is high enough to reach and attach to unmyelinated sensory and motor terminals *(299)*. Once attached to the nerve cells, rabies virus readily enters the cell and then is able to travel through nerve cells, from one to the next via the endplates, until it reaches the central nervous system *(295)*. Once the virus has entered the nerve cells, it is sequestered from the immune system, and immunization from then on will be ineffective. Once the rabies virus reaches the spinal cord via retrograde axoplasmic flow at 8 to 20 μm/day, the first symptoms of the infection—pain or paresthesia at the wound site—may occur *(300)*. This is followed by rapidly progressive encephalitis as the virus first disseminates through the central nervous system. The virus next spreads throughout the body along the peripheral nerves. On arrival via peripheral nerves to the salivary glands, the rabies virus is shed in the saliva.

It is also useful to review the epidemiology of rabies *(284,285,301)*. Human rabies is uncommon in the United States, primarily because of canine rabies–control programs *(302)*; dogs account for <5% of the cases in animals. Moreover, ready access to improved human rabies biologicals (human rabies immune globulin and rabies vaccine) has been responsible, in part, for preventing rabies in those persons who come in contact with potentially rabid animals such as bats (bat rabies is enzootic in the United States, with cases reported from all of the 48 contiguous states), raccoons (predominant in the southeast and the northeast), foxes (predominant in upper New York State and upper Vermont and in parts of Arizona and Texas), skunks (predominant in California and the south-central and north-central states), and coyotes (predominant in the Texas panhandle) *(302)*.

Of particular interest to IPs are the reports of postexposure prophylaxis in healthcare workers and other patient contacts exposed to rabies virus–infected patients. In one report of postexposure prophylaxis in healthcare workers and other patient contacts exposed to a rabies virus–infected lung transplant recipient *(288)*, 131 individuals received postexposure prophylaxis. In another more extensive review of 14 patients with rabies treated in US hospitals, 576 contacts of the patients received postexposure prophylaxis *(303)*. Seventy percent of those who received postexposure prophylaxis were medical personnel, most of whom were nurses and respiratory therapists, who would have the greatest contact with saliva. Another example is that of an 11-year-old girl in New York State who died of unknown meningoencephalitis and was later found to have died of rabies when routine histopathologic slides of brain tissue were reviewed approximately 2 to 3 weeks after death. When the diagnosis was made, rabies postexposure prophylaxis was administered to 55 persons, including 8 family members, 3 friends, 35 healthcare workers, 5 members of the autopsy team, 3 transport personnel, and 1 mortician *(304)*. Thus, 9 of 55 were posthospital healthcare workers.

It becomes clear that a rapid antemortem diagnosis of rabies is important. The importance of early suspicion of rabies is not that the course or prognosis of rabies can be altered but that measures to reduce the number of persons potentially exposed to the rabies virus during patient care can be reduced, and those persons who are candidates for postexposure prophylaxis can be more easily identified. Rabies should be considered in the differential diagnosis of any acute progressive encephalitis of unknown etiology. Other clinical manifestations suggestive of rabies include paresthesia at an injury site, hydrophobia (patients withdraw when offered a drink and have difficulty swallowing oral secretions; strep throat is often blamed for these symptoms), and copious salivation. Once rabies is considered in the differential diagnosis, it is possible to make an antemortem diagnosis of human rabies by sending cerebrospinal fluid (CSF), serum, saliva, and a biopsy of nuchal skin or of brain tissue to the state laboratory or CDC. Tests for antibodies in the CSF and serum, PCR and/or cultures for rabies virus in the CSF and saliva, and fluorescent antibody tests for tissue inclusion bodies can be diagnostic.

Appropriate infection control measures are also indicated whenever a patient is suspected of being infected with rabies *(305)*. Wearing gloves, gowns, masks, and goggles is indicated for healthcare workers caring for possible rabies patients or for posthospital healthcare workers participating in an autopsy, involved in transportation of the patient, or involved as a mortician. In addition, respiratory precautions (as done with active pulmonary tuberculosis) should be followed, because transmission of rabies through inhalation of virus has been reported *(293)*. Finally, inoculation of some body fluids (such as saliva or tracheal secretions but not blood) could transmit rabies and should be avoided, whenever possible, with preventive measures such as those used for AIDS patients.

Preexposure and postexposure rabies prophylaxis for healthcare workers has not been satisfactorily delineated to date, and decisions regarding postexposure prophylaxis

should be made on a case-by-case basis after discussion with public health authorities (*90*,306). The lack of such guidelines for who should or should not receive prophylaxis most often results in overuse of this preventive measure because of the high level of anxiety associated with rabies *(303)*. Fortunately, guidelines for preexposure and postexposure rabies prophylaxis have been published (*90*,306).

When rabies prophylaxis has been decided on as a preventive measure, there are clear guidelines as to how to do this (*90*,306). The initial step in prevention of rabies in healthcare workers is to provide local wound treatment if the exposure involved a wound (e.g., a leak of respiratory or salivary fluid through a latex glove to an open wound). This treatment is similar to that used for HIV exposure via an open cut or wound and consists of immediate and thorough washing with soap and water or other antiseptic preparation for hand washing. Human rabies immune globulin and rabies vaccine should be used for exposures that do not involve bites and bites and cuts if the risk is high (e.g., a confirmed case and a respiratory therapist who cared for this patient). Ideally, treatment with both should be initiated for high-risk healthcare personnel. For low-risk persons, treatment can be delayed for up to 48 hours, pending the results of laboratory tests. The usual interval between exposure and prophylactic treatment for rabies in the United States is 5 days *(303)*, which suggests that delays do not seriously compromise successful prophylaxis. Remember, however, that the pathogenesis involves a race between the immunoglobulins and attachment and penetration of the rabies virus to nerve cells. Thus, it would be predicted that longer delays and/or higher inoculum would occasionally result in prophylaxis failures, which have been reported *(307,308)*.

Prophylaxis consists of both the human rabies immune globulin and the vaccine. The human rabies immune globulin should be given in a dose of 20 IU/kg, with one-half of this dose injected into the wound area and one-half given intramuscularly in the gluteal area (*90*,306). Two rabies vaccines are currently available: human diploid-cell rabies vaccine (HDCV: Imovax Rabies) and rabies vaccine absorbed (RVA), which are considered equivalent in terms of safety and efficacy. There are two approved schedules for rabies prophylaxis in the United States. The first is a postexposure schedule in which 1.0 mL of HDCV or RVA is given intramuscularly in the deltoid area on days 0, 3, 7, 14, and 28. The preexposure schedule is most often given to persons such as veterinarians and other animal handlers and consists of 1.0 mL of HDCV or RVA intramuscularly in the deltoid area on days 0, 7, and 21 or 28 or 0.1 mL of HDCV intradermally in the skin over the deltoid area on days 0, 7, and 21 or 28. Boosters may be needed if there is continuing risk. Although vaccination is quite effective, it is not 100% effective *(307,308)* (see also Chapter 47).

Transmissible Spongiform Encephalopathies Agent

The transmissible spongiform encephalopathies are fatal degenerative diseases of the central nervous system in humans and animals and are caused by prions *(309,310)*. They may be sporadic, infectious, or inherited in origin and are caused by abnormally configured (i.e., misfolded) host-encoded cell-surface glycoproteins (i.e., prion proteins) that accumulate in the central nervous system. Human prion diseases include Creutzfeldt–Jakob disease (CJD), variant Creutzfeldt–Jakob disease (vCJD), Gerstmann–Straussler–Scheinker (GSS) Syndrome, Fatal Familial Insomnia (FFI), and Kuru *(310,311)*. Although quite rare, CJD and other prion diseases are considered risks for healthcare workers (*312,313*,314,*315–317*). Because this progressive and relentless neurologic disease has a 100% mortality rate, it is not surprising that healthcare workers are aware of this rare disease and are concerned about the risk for transmission.

As mentioned, CJD is one of four recognized forms of spongiform encephalopathies in humans. The other three are kuru, GSS syndrome, and FFI syndrome. There are also animal forms of spongiform encephalopathies; these include scrapie in sheep and goats, bovine spongiform encephalopathy in cattle and dairy cows, chronic wasting disease in deer and elk, and transmissible mink encephalopathy. The bovine spongiform encephalopathy has been termed "mad cow disease" by the lay press. These spongiform encephalopathies are caused by novel infectious pathogens called prions, which means *pro*teinaceous *in*fectious particles. In brain tissue, prions produce a characteristic neuropathic spongiform change. Infected brains demonstrate an amyloid protein that can transmit an identical spongiform disease to experimentally inoculated animals *(310)*. Because prions resist inactivation by procedures and agents that modify nucleic acids and appear to consist only of an amyloid protein *(318)*, they are now considered an abnormal derivative of normal protein that results in infectious amyloidosis. Thus, it appears that an abnormal protein seed molecule is able to serve as a template for the alteration of other normal precursor protein molecules that are being produced in the cell. The precursor protein of these various spongiform encephalopathies is a membrane-anchored glycoprotein that is found in most organs and cell types, including neurons. The exact biologic role of the protein is unknown. Mutation of the coding gene for this precursor protein has been associated with inherited spongiform encephalopathies. This precursor protein coded by the mutated gene then acts as a template to normal precursor protein and alters these proteins such that they aggregate as insoluble amyloid fibrils. The mutation of this gene can be transmitted to offspring, and about 10% of cases of CJD have been recognized as familial. Familial prion disease causing CJD appears to be an autosomal dominant disorder, like Huntington's disease. When the mutated gene is introduced in genetic material of transgenic mice, spontaneous central nervous system degeneration occurs and is characterized by clinical signs indistinguishable from experimental murine scrapie. Moreover, neuropathy consisting of spongiform morphology and astrocytic gliosis is identical in both. The genetic disease caused by this mutation can become contagious if the altered protein itself is transmitted from an infected host to a normal host. This has been seen in experimental animal inoculation and with iatrogenic inoculation of humans by contaminated neurosurgical instruments, corneal and dura mater grafts, and pituitary hormone extracts. This abnormal protein then acts as a seed molecule to produce template-induced polymerization of normal proteins in the newly infected host.

From an infection control standpoint, the risk of transmission of CJD in healthcare personnel is limited to inoculation with infected central nervous system material (314,*319,320*). Clearly, patients known or suspected of having CJD become a potential problem in this regard if neurosurgical or autopsy procedures are performed. The precautions taken to prevent the transmission of HIV would be similar, the goal being to reduce the chance of inoculation injury. The World Health Organization has developed infection control guidelines for transmissible spongiform encephalopathies *(312)*. Moreover, a detailed description of precautions has been developed by the American Neurological Association and is available for those who wish more details *(313)*. The Centers for Disease Control (CDC) has also addressed infection control issues involving prions (314). Finally, comprehensive recommendations for disinfection and sterilization of medical devices contaminated by the Creutzfeldt–Jakob agent have been published (321) (see also Chapters 47 and 80).

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SECTION XI
Disinfection and Sterilization

CHAPTER 80

Selection and Use of Disinfectants in Healthcare

William A. Rutala and David J. Weber

Each year in the United States there are 46 million procedures performed on hospital inpatients and an estimated 53.3 million surgical and nonsurgical procedures performed during ambulatory surgery visits *(1,2)*. For example, there are at least 10 million gastrointestinal endoscopies per year *(3)*. Each of these procedures involves contact by a medical device or a surgical instrument with a patient's sterile tissue or mucous membranes. A major risk of all such procedures is the introduction of infection. Failure to properly disinfect or sterilize equipment carries not only the risk associated with breach of the host barriers but also the additional risk of person-to-person transmission (e.g., hepatitis B virus) and transmission of environmental pathogens (e.g., *Pseudomonas aeruginosa*).

Achieving disinfection and sterilization through the use of disinfectants and sterilization practices is essential for ensuring that medical and surgical instruments do not transmit infectious pathogens to patients. Because it is unnecessary to sterilize all patient-care items, healthcare policies must identify whether cleaning, disinfection, or sterilization is indicated based primarily on the items' intended use.

Multiple studies in many countries have documented lack of compliance with established guidelines for disinfection and sterilization *(4,5)*. Failure to comply with scientifically based guidelines has led to numerous outbreaks *(5–9)*. In this chapter, which is an update of previous chapters (10,11,*12*,13–16), a pragmatic approach to the judicious selection and proper use of disinfection processes is presented. This is based on well-designed studies assessing the efficacy (via laboratory investigations) and effectiveness (via clinical studies) of disinfection and sterilization procedures.

DEFINITION OF TERMS

Sterilization is the complete elimination or destruction of all forms of microbial life and is accomplished in healthcare facilities by either physical or chemical processes. Steam under pressure, dry heat, ethylene oxide (ETO) gas, hydrogen peroxide gas plasma, ozone, hydrogen peroxide vapor, and liquid chemicals are the principal sterilizing agents used in healthcare facilities. Sterilization is intended to convey an absolute meaning, not a relative one.

Unfortunately, some health professionals as well as the technical and commercial literature refer to "disinfection" as "sterilization" and items as "partially sterile." When chemicals are used for the purpose of destroying all forms of microbiological life, including fungal and bacterial spores, they may be called *chemical sterilants*. These same germicides used for shorter exposure periods may also be part of the disinfection process (i.e., high-level disinfection).

Disinfection describes a process that eliminates many or all pathogenic microorganisms on inanimate objects, with the exception of bacterial spores. Disinfection is usually accomplished by the use of liquid chemicals or wet pasteurization in healthcare settings. The efficacy of disinfection is affected by a number of factors, each of which may nullify or limit the efficacy of the process. Some of the factors that affect both disinfection and sterilization efficacy are the prior cleaning of the object; the organic and inorganic load present; the type and level of microbial contamination; the concentration of and exposure time to the germicide; the nature of the object (e.g., crevices, hinges,

and lumens); the presence of biofilms; the temperature and pH of the disinfection process; and, in some cases, the relative humidity of the sterilization process (e.g., with ETO).

By definition then, disinfection differs from sterilization by its lack of sporicidal property, but this is an oversimplification. A few disinfectants will kill spores with prolonged exposure times (e.g., 3–12 hours) and are called *chemical sterilants*. At similar concentrations but with shorter exposure periods (e.g., 20 minutes for 2% glutaraldehyde), these same disinfectants will kill all microorganisms with the exception of large numbers of bacterial spores and are called *high-level disinfectants*. *Low-level disinfectants* may kill most vegetative bacteria, some fungi, and some viruses in a practical period of time (≤10 minutes), whereas *intermediate-level disinfectants* may be cidal for mycobacteria, vegetative bacteria, most viruses, and most fungi but do not necessarily kill bacterial spores. The germicides differ markedly among themselves primarily in their antimicrobial spectrum and rapidity of action. Table 80-1 is discussed later and consulted in this context.

Cleaning, on the other hand, is the removal of visible soil (e.g., organic and inorganic material) from objects and surfaces, and it normally is accomplished by manual or mechanical means using water with detergents or enzymatic products *(17)*. Thorough cleaning is essential before high-level disinfection and sterilization since inorganic and organic materials that remain on the surfaces of instruments interfere with the effectiveness of these processes. Also, if the soiled materials become dried or baked onto the instruments, the removal process becomes more difficult and the disinfection or sterilization process less effective or ineffective. Surgical instruments should be presoaked or rinsed to prevent drying of blood and to soften or remove blood from the instruments. *Decontamination* is a procedure that removes pathogenic microorganisms from objects so they are safe to handle, use, or discard.

TABLE 80-1

Methods of Sterilization and Disinfection

	Sterilization		*Disinfection*		
	Critical Items (Will Enter Tissue or Vascular System or Blood Will Flow Through Them)		*High-Level (Semicritical Items; [Except Dental] Will Come in Contact with Mucous Membrane or Nonintack Skin)*	*Intermediate-Level (Some Semicritical Items[a] and Noncritical Items)*	*Low-Level (Noncritical Items; Will Come in Contact with Intact Skin)*
Object	*Procedure*	*Exposure Time*	*Procedure (Exposure Time 12–30 min at ≥20°C)[b,c]*	*Procedure (Exposure Time ≥1 m)[d]*	*Procedure (Exposure Time ≥ 1 m)[d]*
Smooth, hard Surface[a,e]	A	MR	D	K	K
	B	MR	E	L[f]	L
	C	MR	F	M	M
	D	10 h at 20–25°C	H	N	N
	F	6 h	I[g]		O
	G	12 m at 50–56°C	J		P
	H	3–8 h			
Rubber tubing and catheters[c,e]	A	MR	D		
	B	MR	E		
	C	MR	F		
	D	10 h at 20–25°C	H		
	F	6 h	I[g]		
	G	12 m at 50–56°C	J		
	H	3–8 h			
Polyethylene tubing and catheters[c,e,h]	A	MR	D		
	B	MR	E		
	C	MR	F		
	D	10 h at 20–25°C	H		
	F	6 h	I[g]		
	G	12 m at 50–56°C	J		
	H	3–8 h			
Lensed instruments[e]	A	MR	D		
	B	MR	E		
	C	MR	F		
	D	10 h at 20–25°C	H		
	F	6 h	I[g]		
	G	12 m at 50–56°C	J		
	H	3–8 h			

(*Continued*)

TABLE 80-1

Methods of Sterilization and Disinfection (*Continued*)

	Sterilization		*Disinfection*		
	Critical Items (Will Enter Tissue or Vascular System or Blood Will Flow Through Them)		*High-Level (Semicritical Items; [Except Dental] Will Come in Contact with Mucous Membrane or Nonintack Skin)*	*Intermediate-Level (Some Semicritical Items[a] and Noncritical Items)*	*Low-Level (Noncritical Items; Will Come in Contact with Intact Skin)*
Object	*Procedure*	*Exposure Time*	*Procedure (Exposure Time 12–30 min at ≥20°C)[b,c]*	*Procedure (Exposure Time ≥1 m)[d]*	*Procedure (Exposure Time ≥ 1 m)[d]*
Thermometers (oral and rectal)[i]				K[h]	
Hinged instruments[e]	A	MR	D		
	B	MR	E		
	C	MR	F		
	D	10 h at 20–25°C	H		
	F	6 h	I[g]		
	G	12 m at 50–56°C	J		
	H	3–8 h			

[a]See text for discussion of hydrotherapy.
[b]The longer the exposure to a disinfectant, the more likely it is that all microorganisms will be eliminated. Ten-minute exposure is not adequate to disinfect many objects, especially those that are difficult to clean because they have narrow channels or other areas that can harbor organic material and bacteria. Twenty-minute exposure at 20°C is the minimum time needed to reliably kill *M. tuberculosis* and nontuberculous mycobacteria with a 2% glutaraldehyde. With the exception of >2% glutaraldehydes, follow the FDA-cleared high-level disinfection claim. Some high-level disinfectants have a reduced exposure time (e.g., ortho-phthalaldehyde at 12 min at 20°C) because of their rapid activity against mycobacteria or reduced exposure time due to increased mycobactericidal activity at elevated temperature (e.g., 2.5% glutaraldehyde at 5 min at 35°C, 0.55% OPA at 5 min at 25°C in automated endoscope reprocessor).
[c]Tubing must be completely filled for high-level disinfection and liquid chemical sterilization; care must be taken to avoid entrapment of air bubbles during immersion.
[d]By law, all applicable label instructions on EPA-registered products must be followed. If the user selects exposure conditions that differ from those on the EPA-registered products label, the user assumes liability from any injuries resulting from off-label use and is potentially subject to enforcement action under FIFRA.
[e]Material compatibility should be investigated when appropriate.
[f]A concentration of 1,000 ppm available chlorine should be considered where cultures or concentrated preparations of microorganisms have spilled (5.25% to 6.15% household bleach diluted 1:50 provides >1,000 ppm available chlorine). This solution may corrode some surfaces.
[g]Pasteurization (washer-disinfector) of respiratory therapy or anesthesia equipment is a recognized alternative to high-level disinfection. Some data challenge the efficacy of some pasteurization units.
[h]Thermostability should be investigated when appropriate.
[i]Do not mix rectal and oral thermometers at any stage of handling or processing.
The selection and use of disinfectants in the health-care field is dynamics, and products may become available that are not in existence when this chapter was written. As newer disinfectants become available, persons or committees responsible for selecting disinfectants and sterilization processes should be guided by products cleared by the FDA and the EPA as well as information in the scientific literature.
A, Heat sterilization, including steam or hot air (see manufacturer's recommendations, steam sterilization processing time from 3 to 30 min).
B, Ethylene oxide gas (see manufacturer's recommendations, generally 1–6 h processing time plus aeration time of 8–12 h at 50–60°C).
C, Hydrogen peroxide gas plasma (see manufacturer's recommendations for internal diameter and length restrictions, processing time between 28 and 72 min), ozone, and hydrogen peroxide vapor (see manufacturer's recommendations for internal diameter and length restrictions).
D, Glutaraldehyde-based formulations (≥2% glutaraldehyde, caution should be exercised with all glutaraldehyde formulations when further in-use dilution is anticipated); glutaraldehyde (1.12%) with 1.93% phenol/phenate; glutaraldehyde (3.4%) with 26% isopropanol. One glutaraldehyde-based product has a high-level disinfection claim of 5 min at 35°C.
E, Ortho-phthalaldehyde (OPA) ≥0.55%
F, Hydrogen peroxide 7.5% (will corrode copper, zinc, and brass) and 2.0% accelerated hydrogen peroxide.
G, Peracetic acid, concentration variable but 0.2% or greater is sporicidal. Peracetic acid immersion system operates at 50–56°C. This liquid chemical sterilant processing system should be used only for processing heat-sensitive semicritical and critical devices that are compatible with the sterilant and processing system and cannot be sterilized by other fully validated terminal sterilization methods for the device.
H, Hydrogen peroxide (7.35%) plus 0.23% peracetic acid; hydrogen peroxide 8.3% plus peracetic acid 7.0%; hydrogen peroxide 1% plus peracetic acid 0.08% (will corrode metal instruments).
I, Wet pasteurization at 70°C for 30 min with detergent cleaning.
J, Hypochlorite, single use chlorine generated on-site by electrolyzing saline containing >650–675 active free chlorine; (will corrode metal instruments).
K, Ethyl or isopropyl alcohol (70–90%).
L, Sodium hypochlorite (5.25–6.15% household bleach diluted 1:500 provides >100 ppm available chlorine).
M, Phenolic germicidal detergent solution (follow product label for use-dilution).
N, Lodophor germicidal detergent solution (follow product label for use-dilution).
O, Quaternary ammonium germicidal detergent solution (follow product label for use-dilution).
P, Accelerated hydrogen peroxide 0.5% (follow product label).
MR, Manufacturer's recommendations.
NA, Not applicable.

Terms with a suffix "cide" or "cidal" for killing action also are commonly used. For example, a germicide is an agent that can kill microorganisms, particularly pathogenic microorganisms ("germs"). The term *germicide* includes both antiseptics and disinfectants. *Antiseptics* are germicides applied to living tissue and skin, whereas *disinfectants* are antimicrobials applied only to inanimate objects. In general, antiseptics are only used on the skin and not for surface disinfection, and disinfectants are rarely used for skin antisepsis, because they may cause injury to skin and other tissues. Other words with the suffix "cide" (e.g., virucide, fungicide, bactericide, sporicide, and tuberculocide) can kill the type of microorganism identified by the prefix. For example, a bactericide is an agent that kills bacteria *(18–23)*.

A RATIONAL APPROACH TO DISINFECTION AND STERILIZATION

Over 40 years ago, Earle H. Spaulding *(19)* devised a rational approach to disinfection and sterilization of patient-care items or equipment. This classification scheme is so clear and logical that it has been retained, refined, and successfully used by infection preventionists and others when planning methods for disinfection or sterilization (10,11,*18,20,22,24,25*). Spaulding believed that the nature of disinfection could be understood more readily if instruments and items for patient care were divided into three categories based on the degree of risk of infection involved in the use of the items. The three categories he described were critical, semicritical, and noncritical.

Critical Items

Critical items are so called because of the high risk of infection if such an item is contaminated with any microorganism, including bacterial spores. Thus, it is critical that objects that enter sterile tissue or the vascular system be sterile, because any microbial contamination could result in disease transmission. This category includes surgical instruments, cardiac and urinary catheters, implants, and ultrasound probes used in sterile body cavities. Most of the items in this category should be purchased as sterile or be sterilized by steam sterilization if possible. If heat-sensitive, the object may be treated with ETO, hydrogen peroxide gas plasma, ozone, hydrogen peroxide vapor, or by liquid chemical sterilants if other methods are unsuitable. Table 80-1 lists several germicides categorized as chemical sterilants. These include ≥2.4% glutaraldehyde-based formulations; hypochlorous acid/hypochlorite 650 to 675 ppm free chlorine (or 400–450 ppm free chlorine at 30°C); 1.12% glutaraldehyde with 1.93% phenol/phenate; 3.4% glutaraldehyde with 26% isopropanol *(26)*; 7.5% hydrogen peroxide; 7.35% hydrogen peroxide with 0.23% peracetic acid; 8.3% hydrogen peroxide with 7.0% peracetic acid; 0.2% peracetic acid; ≥0.55% ortho-phthalaldehyde; 2.0% accelerated hydrogen peroxide; and 1.0% hydrogen peroxide with 0.08% peracetic acid *(27)*. Liquid chemical sterilants can be relied upon to produce sterility only if cleaning, to eliminate organic and inorganic material, precedes treatment and if proper guidelines as to concentration, contact time, temperature, and pH are met.

Semicritical Items

Semicritical items are those that come in contact with mucous membranes or nonintact skin. Respiratory therapy and anesthesia equipment, gastrointestinal endoscopes, bronchoscopes, laryngoscope blades, esophageal manometry probes, endocavitary probes, anorectal manometry catheters, infrared coagulation probes, cystoscopes *(28)*, and diaphragm fitting rings are included in this category. These medical devices should be free of all microorganisms, although small numbers of bacterial spores may be present. Intact mucous membranes, such as those of the lungs or the gastrointestinal tract, generally are resistant to infection by common bacterial spores but susceptible to other microorganisms such as bacteria, mycobacteria, and viruses. Semicritical items minimally require high-level disinfection using chemical disinfectants. Glutaraldehyde, hydrogen peroxide, ortho-phthalaldehyde, and peracetic acid with or without hydrogen peroxide are cleared by the Food and Drug Administration (FDA) and are dependable high-level disinfectants provided the factors influencing germicidal procedures are met (Table 80-1) *(27)*. When a disinfectant is selected for use with certain patient-care items, the chemical compatibility after extended use with the items to be disinfected also must be considered.

The complete elimination of all microorganisms in or on an instrument with the exception of small numbers of bacterial spores is the traditional definition of high-level disinfection. FDA's definition of high-level disinfection is a sterilant used for a shorter contact time to achieve a 6-$\log_{10}$ kill of an appropriate mycobacterium species. Cleaning followed by high-level disinfection should eliminate sufficient pathogens to prevent transmission of infection *(29,30)*.

Laparoscopes and arthroscopes entering sterile tissue should be sterilized between patients. As with flexible endoscopes, these devices may be difficult to clean and sterilize due to intricate device design (e.g., long narrow lumens, hinges). Meticulous cleaning must precede any sterilization process. Newer models of these instruments can withstand steam sterilization.

Semicritical items should be rinsed with sterile water after high-level disinfection to prevent their contamination with microorganisms that may be present in tapwater, such as nontuberculous mycobacteria *(9,31)*, *Legionella (32,33)*, or gram-negative bacilli such as *Pseudomonas (22,24,34–36)*. In circumstances where rinsing with sterile water rinse is not feasible, a tapwater or filtered water (0.2-μm filter) rinse should be followed by an alcohol rinse and forced air drying (11,36–39). Forced air drying markedly reduces bacterial contamination of stored endoscopes, most likely by removing the wet environment favorable for bacterial growth *(37)*. After rinsing, items should be dried and stored (e.g., packaged) in a manner that protects them from recontamination.

Some items that may come in contact with nonintact skin for a brief period of time (i.e., hydrotherapy tanks, bed side rails) are usually considered noncritical surfaces and are disinfected with low- or intermediate-level disinfectants (i.e., phenolic, iodophor, alcohol, chlorine) *(40)*. Since hydrotherapy tanks have been associated with spread of infection, some facilities have chosen to disinfect them with recommended levels of chlorine *(40)*.

Noncritical Items

Noncritical items are those that come in contact with intact skin but not mucous membranes. Intact skin acts as an effective barrier to most microorganisms; therefore, the sterility of items coming in contact with intact skin is "not critical." Examples of noncritical items are bedpans, blood pressure cuffs, crutches, bed rails, bedside tables, patient furniture, and floors. The five most commonly touched items in the patient environment have been quantitatively shown to be bed rails, bed surface, supply cart, overbed table, and IV pump *(41)*. In contrast to critical and some semicritical items, most noncritical reusable items may be decontaminated where they are used and do not need to be transported to a central processing area. There is virtually no documented risk of transmitting infectious agents to patients via noncritical items *(35)* when they are used as noncritical items and do not contact nonintact skin and/or mucous membranes. However, these items (e.g., bedside tables, bed rails) could potentially contribute to secondary transmission by contaminating hands of healthcare workers or by contact with medical equipment that will subsequently come in contact with patients *(18,42–45)*. Table 80-1 lists several low-level disinfectants that may be used for noncritical items. The exposure time listed in Table 80-1 is equal to or >1 minute. Most Environmental Protection Agency (EPA)–registered disinfectants have a 10-minute label claim. However, multiple investigators have demonstrated the effectiveness of these disinfectants against vegetative bacteria (e.g., *Listeria*, *Escherichia coli*, *Salmonella*, vancomycin-resistant enterococci [VRE], methicillin-resistant *Staphylococcus aureus* [MRSA]), yeasts (e.g., *Candida*), mycobacteria (e.g., *Mycobacterium tuberculosis*), and viruses (e.g. poliovirus) at exposure times of <60 seconds *(42–57)*. Thus, it is acceptable to disinfect noncritical medical equipment (e.g., blood pressure cuff) and noncritical surfaces (e.g., bedside table) with an EPA-registered disinfectant or disinfectant/detergent at the proper use dilution and a contact time of at least 1 minute *(58)*. Since the typical drying time for a germicide on a surface is 1 to 3 minutes (unless the product contains alcohol [e.g., a 60–70% alcohol will dry in about 30 seconds])(N. Omidbakhsh, written communication), one application of the germicide on all surfaces to be disinfected is recommended.

Mops (microfiber and cotton-string), reusable cleaning cloths, and disposable wipes are regularly used to achieve low-level disinfection *(59,60)*. Microfiber mops have demonstrated superior microbial removal compared with cotton string mops when used with detergent cleaner (95% vs. 68%, respectively). Use of a disinfectant did significantly improve microbial removal when a cotton string mop was used (95% vs. 95%, respectively) *(60)*. Mops (especially cotton-string mops) are commonly not kept adequately cleaned and disinfected, and if the water-disinfectant mixture is not changed regularly (e.g., after every three to four rooms, no longer than 60-minute intervals), the mopping procedure may actually spread heavy microbial contamination throughout the healthcare facility *(61)*. In one study, standard laundering provided acceptable decontamination of heavily contaminated mopheads, but chemical disinfection with a phenolic was less effective *(61)*. The frequent laundering of cotton-string mops (e.g., daily) is, therefore, recommended.

Hospital cleanliness continues to attract patient attention and in the United States it is still primarily assessed via visual appearance, which is not a reliable indicator of surface cleanliness *(62)*. Three other methods have been offered for monitoring patient room hygiene and they include adenosine triphosphate (ATP) bioluminescence *(63,64)*; fluorescent markers (65,*66*); and microbiologic sampling *(64)*. Studies have demonstrated suboptimal cleaning was documented by aerobic colony counts as well as the use of the ATP bioluminescence and fluorescent markers.

FACTORS AFFECTING THE EFFICACY OF DISINFECTION AND STERILIZATION

The activity of germicides against microorganisms depends on a number of factors, some of which are intrinsic qualities of the microorganism, while others depend on the chemical and external physical environment. An awareness of these factors should lead to a better utilization of disinfection and sterilization processes; thus, they will be briefly reviewed. More extensive consideration of these and other factors may be found in the references for this section *(18,19,21,67–69)*.

Number and Location of Microorganisms

All other conditions remaining constant, the larger the number of microbes present, the longer it takes for a germicide to destroy all of them. This relationship was illustrated by Spaulding when he employed identical test conditions and demonstrated that it took 30 minutes to kill 10 *Bacillus atrophaeus* (formerly *B. subtilis*) spores but 3 hours to kill 100,000 *B. atrophaeus* spores. This reinforces the need for scrupulous cleaning of medical instruments before disinfection and sterilization. Reducing the number of microorganisms that must be inactivated through meticulous cleaning increases the margin of safety when the germicide is used according to the labeling and shortens the exposure time required to kill the entire microbial load. Researchers have also shown that aggregated or clumped cells are more difficult to inactivate than monodispersed cells *(70)*.

The location of microorganisms also must be considered when assessing factors affecting the efficacy of germicides. Medical instruments with multiple pieces must be disassembled and equipment such as endoscopes that have crevices, joints, and channels are more difficult to disinfect than flat-surface equipment because it is more difficult to penetrate all parts of the equipment with a disinfectant. Only surfaces in direct contact with the germicide will be disinfected, so there must be no air pockets and the equipment must be completely immersed for the entire exposure period. Manufacturers should be encouraged to produce equipment that is engineered, so cleaning and disinfection may be accomplished with ease.

Innate Resistance of Microorganisms

Microorganisms vary greatly in their resistance to chemical germicides and sterilization processes (Fig. 80-1) *(71)*. Intrinsic resistance mechanisms in microorganisms to disinfectants vary. For example, spores are resistant to disinfectants because the spore coat and cortex act as a barrier,

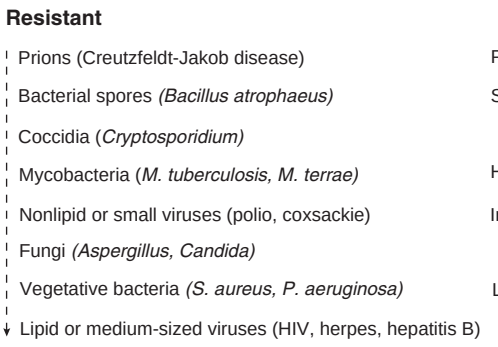

FIGURE 80-1 Decreasing order of resistance of microorganisms to disinfection and sterilization and the level of disinfection or sterilization. (Data from Favero MS, Bond WW. Chemical disinfection of medical and surgical materials. In: Block SS, ed. *Disinfection, sterilization, and preservation*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001:881–917; Russell AD. Bacterial resistance to disinfectants: present knowledge and future problems. *J Hosp Infect* 1998;43:S57–S68.)

mycobacteria have a waxy cell wall that prevents disinfectant entry, and gram-negative bacteria possess an outer membrane that acts as a barrier to the uptake of disinfectants *(71–74)*. Implicit in all disinfection strategies is the consideration that the most resistant microbial subpopulation controls the sterilization or disinfection time. That is, in order to destroy the most resistant types of microorganisms-bacterial spores, the user needs to employ exposure times and a concentration of germicide needed to achieve complete destruction. With the exception of prions, bacterial spores possess the highest innate resistance to chemical germicides, followed by coccidia (e.g., *Cryptosporidium*), mycobacteria (e.g., *M. tuberculosis*), nonlipid or small viruses (e.g., poliovirus and coxsackievirus), fungi (e.g., *Aspergillus* and *Candida*), vegetative bacteria (e.g., *Staphylococcus* and *Pseudomonas*), and lipid or medium-size viruses (e.g., herpes, and HIV). The germicidal resistance exhibited by the gram-positive and gram-negative bacteria is similar with some exceptions (e.g., *Pseudomonas aeruginosa*, which shows greater resistance to some disinfectants) *(75–77)*. *P. aeruginosa* have also been shown to be significantly more resistant to a variety of disinfectants in their "naturally occurring" state as compared to cells subcultured on laboratory media *(75,78)*. *Rickettsiae*, *Chlamydiae*, and mycoplasma cannot be placed in this scale of relative resistance because information on the efficacy of germicides against these agents is limited *(79)*. Since these microorganisms contain lipid and are similar in structure and composition to other bacteria, it might be predicted that they would be inactivated by the same germicides that destroy lipid viruses and vegetative bacteria. A known exception to this supposition is *Coxiella burnetii*, which has demonstrated resistance to disinfectants *(80)*.

Concentration and Potency of Disinfectants

With other variables constant, and with one exception (i.e., iodophors), the more concentrated the disinfectant, the greater its efficacy and the shorter the time necessary to achieve microbial kill. Generally not recognized, however, is that all disinfectants are not similarly affected by concentration adjustments. For example, quaternary ammonium compounds and phenol have a concentration exponent of 1 and 6, respectively; thus, halving the concentration of a quaternary ammonium compound requires a doubling of its disinfecting time, but halving the concentration of a phenol solution requires a 64-fold (i.e., 2^6) increase in its disinfecting time *(69,81,82)*.

Quality control is indispensable for automated disinfectant dilution systems. While these systems are economical, efficient and promote a safer workplace, compared to manual dilution methods, failure to provide the required concentration of the disinfectant has been reported. Disinfectants must be used in the dilution specified by the manufacturer for optimal decontamination and attention must be given to quality control and preventive maintenance of automated disinfectant dilution systems as they regularly fail *(83)*.

It is also important to consider the length of the disinfection time, which is dependent upon the potency of the germicide. This was illustrated by Spaulding who demonstrated using the mucin-loop test that 70% isopropyl alcohol destroyed 10^4 *M. tuberculosis* in 5 minutes, whereas a simultaneous test with 3% phenolic required 2 to 3 hours to achieve the same level of microbial kill *(19)*.

Physical and Chemical Factors

Several physical and chemical factors also influence disinfectant procedures: temperature, pH, relative humidity, and water hardness. For example, the activity of most disinfectants increases as the temperature increases, but there are exceptions. Further, too great an increase in temperature will cause the disinfectant to degrade, weaken its germicidal activity, and may produce a potential health hazard.

An increase in pH improves the antimicrobial activity of some disinfectants (e.g., glutaraldehyde, quaternary ammonium compounds) but decreases the antimicrobial activity of others (e.g., phenols, hypochlorites, and iodine). The pH influences the antimicrobial activity by altering the disinfectant molecule or the cell surface *(69)*.

Relative humidity is the single most important factor influencing the activity of gaseous disinfectants/sterilants such as ETO, chlorine dioxide, and formaldehyde.

Water hardness (i.e., high concentration of divalent cations) reduces the rate of kill of certain disinfectants. This occurs because divalent cations (e.g., magnesium, calcium) in the hard water interact with the disinfectant to form insoluble precipitates *(18,84)*.

Organic and Inorganic Matter

Organic matter in the form of serum, blood, pus, fecal, or lubricant material may interfere with the antimicrobial activity of disinfectants in at least two ways. Most commonly, the interference occurs by a chemical reaction between the germicide and the organic matter resulting in a complex that is less germicidal or nongermicidal, leaving less of the active germicide available for attacking microorganisms. Chlorine and iodine disinfectants, in particular, are prone to such interaction. Alternatively, organic material may protect microorganisms from attack by acting as a physical barrier *(85)*.

The effects of inorganic contaminants on the sterilization process were studied in the 1950s and 1960s *(86,87)*. These studies and other studies show the protection of microorganisms to all sterilization processes is due to

occlusion in salt crystals *(88,89)*. This further emphasizes the importance of meticulous cleaning of medical devices before any sterilization or disinfection procedure since both organic and inorganic soils are easily removed by washing *(88)*.

Duration of Exposure

Items must be exposed to the germicide for the appropriate minimum contact time. Multiple investigators have demonstrated the effectiveness of low-level disinfectants against vegetative bacteria (e.g., *Listeria*, *Escherichia coli*, *Salmonella*, vancomycin-resistant Enterococci [VRE], methicillin-resistant *Staphylococcus aureus* [MRSA]), yeasts (e.g., *Candida*), mycobacteria (e.g., *M. tuberculosis*), and viruses (e.g. poliovirus) at exposure times of 30 to 60 seconds *(42–57,90–95)*. By law, all applicable label instructions on EPA-registered products must be followed. If the user selects exposure conditions that differ from those on the EPA-registered products label, the user assumes liability for any injuries resulting from off-label use and is potentially subject to enforcement action under FIFRA. While we are unaware of an EPA enforcement action against healthcare facilities for "off label" use of a surface disinfectant, there have been citations reported from The Joint Commission and the Center for Medicare and Medicaid Services (CMS).

All lumens and channels of endoscopic instruments must come in contact with the disinfectant. Air pockets will interfere with the disinfection process and items that float on the disinfectant will not be disinfected. The disinfectant must be introduced reliably into the internal channels of the device. The exact times for disinfecting medical items are somewhat elusive because of the effect of the aforementioned factors on disinfection efficacy. Contact times that have proved reliable are presented in Table 80-1, but, in general, the longer contact times are more effective than shorter ones.

Biofilms

Microorganisms may be protected from disinfectants due to the production of thick masses of cells *(96)* and extracellular materials or biofilms *(97–104)*. Biofilms are microbial masses attached to surfaces that are immersed in liquids. Once these masses are formed, microbes may be resistant to the disinfectants by multiple mechanisms including higher resistance of older biofilms, genotypic variation of the bacteria, microbial production of neutralizing enzymes, and physiologic gradients within the biofilm (e.g., pH). Bacteria within biofilms are up to 1,000 times more resistant to antimicrobials than the same bacteria in suspension *(105)*. Although new decontamination methods *(106)* are being investigated for removal of biofilms, chlorine and monochloramines are effective for inactivation of biofilm bacteria *(99,107)*. Investigators have hypothesized that the glycocalyx-like cellular masses on the interior walls of polyvinyl chloride pipe would protect embedded microorganisms from some disinfectants and serve as a reservoir for continuous contamination *(97,98,108)*. Biofilms have been found in whirlpools *(109)*, dental unit waterlines *(110)*, and numerous medical devices (e.g., contact lenses, pacemakers, hemodialysis systems, urinary catheters, central venous catheters, endoscopes) *(102,105,107,111)*. Their presence may have serious implications for immunocompromised patients and patients with indwelling medical devices. Some enzymes *(105,112,113)* and detergents *(105,114)* can be used for the degradation of biofilms or reduction in viable bacterial numbers, but no products are registered by the EPA or cleared by the FDA for this purpose. One study evaluating the clearance effect of enzymatic and nonenzymatic detergents against *E. coli* biofilms on the inner surface of gastroscopes found that both nonenzymatic detergents and high-speed lavage (250 mL/min) are important in temporal formed biofilm elimination *(115)*.

In general, the available data suggest that reusable medical devices (e.g., flexible endoscopes) that are properly cleaned, disinfected, rinsed, and dried pose little risk for biofilm development. However, biofilms can develop inside channels if established protocols are not met, and these biofilms can be difficult to remove *(104)*.

CLEANING

Cleaning is the removal of foreign material (e.g., soil and organic material) from objects, and it is normally accomplished using water with detergents or enzymatic products. Thorough cleaning is required before high-level disinfection and sterilization since inorganic and organic materials that remain on the surfaces of instruments interfere with the effectiveness of these processes. Also, if the soiled materials become dried or baked onto the instruments, the removal process becomes more difficult and the disinfection or sterilization process less effective or ineffective. Surgical instruments should be presoaked or rinsed to prevent drying of blood and to soften or remove blood from the instruments.

Cleaning is done manually when the use area does not have a mechanical unit (e.g., ultrasonic cleaner, or washer-disinfector), or for fragile or difficult-to-clean instruments. If cleaning is done manually, the two essential components are friction and fluidics. Using friction (e.g., rubbing/scrubbing the soiled area with a brush) is an old and dependable method. Fluidics (i.e., fluids under pressure) is used to remove soil and debris from internal channels after brushing and when the design does not allow the passage of a brush through a channel *(116)*. When using a washer-disinfector, care should be taken as to the method of loading instruments. Hinged instruments should be opened fully to allow adequate contact with the detergent solution. The stacking of instruments in washers should be avoided. Instruments should be disassembled as much as possible.

The most common types of mechanical or automatic cleaners include ultrasonic cleaners, washer-decontaminators, washer-disinfectors, and washer-sterilizers. Ultrasonic cleaning removes soil by a process called *cavitation and implosion* in which waves of acoustic energy are propagated in aqueous solutions to disrupt the bonds that hold particulate matter to surfaces. Bacterial contamination may be present in used ultrasonic cleaning solutions (and other used detergent solutions) as these solutions generally do not make antibacterial label claims *(117)*. While ultrasound alone does not cause significant inactivation of bacteria, sonication can act synergistically to increase the cidal efficacy of a disinfectant *(118)*. Users of ultrasonic cleaners should be aware that the cleaning fluid could

result in endotoxin contamination of surgical instruments that could cause severe inflammatory reactions *(119)*. Washer-sterilizers are modified steam sterilizers that clean by filling the chamber with water and detergent through which steam is passed to provide agitation. Instruments are subsequently rinsed and subjected to a short steam sterilization cycle. Another washer-sterilizer employs rotating spray arms for a wash cycle followed by a steam sterilization cycle at 285°F *(120,121)*. Washer-decontaminators/disinfectors act like a dishwasher that uses a combination of water circulation and detergents to remove soil. These units sometimes have a cycle that subjects the instruments to a heat process (e.g., 93°C for 10 minutes) *(122)*. Washer-disinfectors are generally computer-controlled units for cleaning, disinfecting, and drying solid and hollow surgical and medical equipment. In one study, cleaning (measured as 5- to 6-$\log_{10}$ reduction) was achieved on surfaces that were adequately in contact with the water flow in the machine *(123)*. Detailed information on cleaning and preparation of supplies for terminal sterilization is provided by professional organizations *(124,125)* and books *(126)*. Studies have shown that manual and mechanical cleaning of endoscopes achieves approximately a 4-$\log_{10}$ reduction of contaminating microorganisms *(127–130)*. Thus, cleaning alone is very effective in reducing the number of microorganisms present on contaminated equipment. Quantitative analysis of residual protein contamination of reprocessed surgical instruments has been done, and median levels of residual protein contamination per instrument for five trays were 267, 260, 163, 456, and 756 μg *(131)*. In another study, the median amount of protein from reprocessed surgical instruments from different hospitals ranged from 8 to 91 μg *(132)*. When manual methods are compared to automated methods for cleaning reusable accessory devices used for minimally invasive surgical procedures, the automated method was more efficient for cleaning biopsy forceps and ported and nonported laparoscopic devices and achieved a >99% reduction in soil parameters (i.e., protein, carbohydrate, hemoglobin) in the ported and nonported laparoscopic devices *(133,134)*.

The best choice for instrument cleaning is neutral or near-neutral pH detergent solutions, as these solutions generally provide the best material compatibility profile and good soil removal. Enzymes, usually proteases, are sometimes added to neutral pH solutions to assist in the removal of organic material. Enzymes in these formulations attack proteins that make up a large portion of common soil (e.g., blood, pus). Cleaning solution also can contain lipases (enzymes active on fats) and amylases (enzymes active on starches). Enzymatic cleaners are not disinfectants and proteinaceous enzymes may be inactivated by germicides. Like all chemicals, enzymes must be rinsed from the equipment or adverse reactions (e.g., fever, residual amounts of high-level disinfectants, proteinaceous residue) could result *(135,136)*. Enzyme solutions should be used in accordance with manufacturer's instructions, which includes proper dilution of the enzymatic detergent for the amount of time specified on the label *(136)*. Detergent enzymes may be associated with asthma or other allergic effects in users. Neutral pH detergent solutions that contain enzymes are compatible with metals and other materials used in medical instruments and are the best choice for cleaning delicate medical instruments, especially flexible endoscopes *(129)*. Alkaline-based cleaning agents are used for processing medical devices as they dissolve protein and fat residues efficiently; *(137)* however, they may be corrosive *(129)*. Some data demonstrate that enzymatic cleaners are more effective cleaners than neutral detergents *(138,139)* in removing microorganisms from surfaces, but two more recent studies found no difference in cleaning efficiency between enzymatic- and alkaline-based cleaners *(112,137)*. A new nonenzyme, hydrogen peroxide–based formulation (not FDA-cleared), was as effective as enzymatic cleaners in removing protein, blood, carbohydrate, and endotoxin from surface test carriers *(140)*. In addition, this product was able to effect a 5-$\log_{10}$ reduction in microbial loads with a 3-minute exposure at room temperature *(140)*. Although the effectiveness of high-level disinfection and sterilization mandates effective cleaning, there are no "real-time" tests that can be employed in a clinical setting to verify cleaning. If such tests were commercially available, they could be used to ensure that an adequate level of cleaning has been done *(141–144)*. The only way to ensure adequate cleaning is to conduct a reprocessing verification test (e.g., microbiologic sampling), but this is not routinely recommended *(145)*. Validation of the cleaning processes in a laboratory-testing program is possible by microorganism detection, chemical detection for organic contaminants, radionuclide tagging, and chemical detection for specific ions *(88,143)*. In the past few years, data have been published describing the use of an artificial soil, protein, endotoxin, X-ray contrast medium, or blood to verify the manual or automated cleaning process *(123,146–151)* and adenosine triphosphate bioluminescence and microbiologic sampling to evaluate the effectiveness of cleaning *(152)*. Minimally, all instruments should be individually inspected and be visibly clean.

DISINFECTANTS USED IN HEALTHCARE

A great number of disinfectants are used alone or in combinations (e.g., hydrogen peroxide and peracetic acid) in the healthcare setting. These include alcohols, chlorine and chlorine compounds, formaldehyde, glutaraldehyde, orthophthalaldehyde, hydrogen peroxide, iodophors, peracetic acid, phenolics, and quaternary ammonium compounds. The properties of an ideal disinfectant are described in Table 80-2. With some exceptions (e.g., ethanol or bleach), commercial formulations based on these chemicals are considered unique products and must be registered with the EPA or cleared by the FDA. In most instances, a given product is designed for a specific purpose and is to be used in a certain manner. Therefore, the label should be read carefully to ensure that the right product is selected for the intended use and applied in an efficient manner. Additionally, caution must be exercised to avoid hazards with using cleaners and disinfectants on electronic medical equipment. Problems associated with inappropriate use of liquids on electronic medical equipment have included equipment fires, equipment malfunctions, and healthcare worker burns *(153)*.

Disinfectants are not interchangeable and an overview of the performance characteristics of each is provided below, so the user has sufficient information to select an

TABLE 80-2

Properties of an Ideal Disinfectant

Broad spectrum: should have a wide antimicrobial spectrum
Fast acting: should produce a rapid kill
Not affected by environmental factors: should be active in the presence of organic matter (e.g., blood, sputum, feces) and compatible with soaps, detergents, and other chemicals encountered in use
Nontoxic: should not be harmful to the user or patient
Surface compatibility: should not corrode instruments and metallic surfaces and should not cause the deterioration of cloth, rubber, plastics, and other materials
Residual effect on treated surfaces: should leave an antimicrobial film on the treated surface
Easy to use with clear label directions
Odorless: should have a pleasant odor or no odor to facilitate its routine use
Economical: should not be prohibitively high in cost
Solubility: should be soluble in water
Stability: should be stable in concentrate and use-dilution
Cleaner: should have good cleaning properties
Environmentally friendly: should not damage the environment on disposal

(Modified from Molinari JA, Gleason MJ, Cottone JA, Barrett ED. Comparison of dental surface disinfectants. *Gen. Dent.* 1987;35: 171–175.)

appropriate disinfectant for any medical item and use it in the most efficient way. It should be recognized that excessive costs may be attributed to incorrect concentrations and inappropriate disinfectants. Finally, occupational diseases among cleaning personnel have been associated with the use of several disinfectants such as formaldehyde and glutaraldehyde, and precautions (e.g., gloves, proper ventilation) should be used to minimize exposure *(154)*. Asthma and reactive airway disease may occur in sensitized individuals exposed to any airborne chemical including germicides. Clinically important asthma may occur at levels below ceiling levels regulated by Occupational Safety and Health Administration (OSHA) or recommended by NIOSH. The preferred method of control is to eliminate aerosolization of the chemical (via engineering controls, or substitution) or relocate the worker.

Chemical Disinfectants

Alcohol In the healthcare setting, "alcohol" refers to two water-soluble chemical compounds whose germicidal characteristics are generally underrated: ethyl alcohol and isopropyl alcohol *(155)*. These alcohols are rapidly bactericidal rather than bacteriostatic against vegetative forms of bacteria; they also are tuberculocidal, fungicidal, and virucidal (enveloped viruses but poor activity against some nonenveloped viruses such as parvovirus) *(156)* but do not destroy bacterial spores. Their cidal activity drops sharply when diluted below 50% concentration and the optimum bactericidal concentration is in the range of 60–90% solutions in water (volume/volume) *(157,158)*.

Alcohols are not recommended for sterilizing medical and surgical materials principally because of their lack of sporicidal action and their inability to penetrate protein-rich materials. Fatal postoperative wound infections with *Clostridium* have occurred when alcohols were used to sterilize surgical instruments contaminated with bacterial spores *(159)*. Alcohols have been used effectively to disinfect oral and rectal thermometers, hospital pagers, scissors, CPR manikins, external surfaces of equipment (e.g., ventilator), computer keyboards *(60)*, touch pads, and stethoscopes *(12)*. Alcohol towelettes have been used for years to disinfect small surfaces such as rubber stoppers of multiple-dose medication vials or vaccine bottles.

Alcohols are flammable and consequently must be stored in a cool, well-ventilated area. They also evaporate rapidly and this makes extended exposure time difficult to achieve unless the items are immersed.

Chlorine and Chlorine Compounds Hypochlorites are the most widely used of the chlorine disinfectants and are available in a liquid (e.g., sodium hypochlorite) or solid (e.g., calcium hypochlorite) form. The most prevalent chlorine products in the United States are aqueous solutions of 5.25% to 6.15% sodium hypochlorite, which usually are called *household bleach*. A chlorine-containing product is currently registered by the EPA to kill *C. difficile* spores. They have a broad spectrum of antimicrobial activity (i.e., bactericidal, virucidal, fungicidal, mycobactericidal, sporicidal), do not leave toxic residues, are unaffected by water hardness, are inexpensive and fast acting *(160)*, remove dried or fixed microorganisms and biofilms from surfaces *(138)*, and have a low incidence of serious toxicity *(161,162)*. Sodium hypochlorite at the concentration used in domestic bleach (5.25–6.15%) may produce ocular irritation or oropharygeal, esophageal, and gastric burns *(154,163,164)*. Other disadvantages of hypochlorites include corrosiveness to metals in high concentrations (>500 ppm), inactivation by organic matter, discoloring or "bleaching" of fabrics, release of toxic chlorine gas when mixed with ammonia or acid (e.g., household cleaning agents) *(165)*, and relative stability *(166)*.

Reports have examined the microbicidal activity of a new disinfectant, "superoxidized water." The concept of electrolyzing saline to create a disinfectant or antiseptics is appealing as the basic materials of saline and electricity are cheap and the end product (i.e., water) is not damaging to the environment. The main products of this water are hypochlorous acid (HOCl) and hypochlorite (OCl^-), which constitute free available chlorine. This is also known as *electrolyzed water* and as with any germicide, the antimicrobial activity of superoxidized water is strongly affected by the concentration of the active ingredient (available free chlorine) *(167)*. The free available chlorine concentrations of different superoxidized solutions reported in the literature range from 7 to 180 ppm *(167)*. Data have shown that freshly generated superoxidized water, Sterilox®, is rapidly effective (<2 minutes) in achieving a 5-$\log_{10}$ reduction of pathogenic microorganisms (i.e., *M. tuberculosis*, *M. chelonae*, poliovirus, HIV, MRSA, *E. coli, Candida albicans*, *Enterococcus faecalis, Pseudomonas aeruginosa*) in the absence of organic loading. However, the biocidal activity of this disinfectant was substantially reduced in the presence of organic material (5% horse serum) *(168,169)*.

Hypochlorites are widely used in healthcare facilities in a variety of settings *(160)*. Inorganic chlorine solution is used for disinfecting tonometer heads *(170)* and for spot disinfection of counter tops and floors. A 1:10 to 1:100 dilution of 5.25–6.15% sodium hypochlorite (i.e., household bleach) *(171–174)* or an EPA-registered tuberculocidal disinfectant *(22)* has been recommended for decontaminating blood spills. For small spills of blood (i.e., drops of blood) on noncritical surfaces, the area can be disinfected with a 1:100 dilution of 5.25–6.15% sodium hypochlorite or an EPA-registered tuberculocidal disinfectant. Because hypochlorites and other germicides are substantially inactivated in the presence of blood *(54,175)*, large spills of blood require that the surface be cleaned before an EPA-registered disinfectant or a 1:10 (final concentration) solution of household bleach is applied. If there is a possibility of a sharps injury, there should be an initial decontamination *(154,176)*, followed by cleaning and terminal disinfection (1:10 final concentration) *(54)*. Extreme care should always be employed to prevent percutaneous injury. At least 500 ppm available chlorine for 10 minutes is recommended for decontamination of cardiopulmonary resuscitation training manikins. Other uses in healthcare include as an irrigating agent in endodontic treatment and for disinfecting laundry, dental appliances, hydrotherapy tanks *(40)*, regulated medical waste before disposal *(160)*, applanation tonometers, *(177)* and the water distribution system in hemodialysis centers and hemodialysis machines *(12)*. Disinfection with a 1:10 dilution of concentrated sodium hypochlorite (i.e., bleach) has been shown to be effective in reducing environmental contamination in patient rooms and in reducing *C. difficile* infection rates in hospital units where there is a high endemic *C. difficile* infection rate or in an outbreak setting (11*,178,179*). Recently, Hacek and colleagues reported that the use of bleach (1:10 dilution) in the rooms of all patients with CDI at terminal room cleaning made a sustained, significant impact on reducing the rate of healthcare-associated CDI in a healthcare system *(180)*.

Chlorine has long been favored as the preferred disinfectant in water treatment. Hyperchlorination of a *Legionella*-contaminated hospital water system *(40)* resulted in a dramatic decrease (30% to 1.5%) in the isolation of *L. pneumophila* from water outlets and a cessation of healthcare-associated Legionnaires' disease in the affected unit *(181,182)*. Chloramine T and hypochlorites have been used in disinfecting hydrotherapy equipment *(12)*.

Hypochlorite solutions in tapwater at a pH > 8 stored at room temperature (23°C) in closed, opaque plastic containers may lose up to 40–50% of their free available chlorine level over a period of 1 month. Thus, if a user wished to have a solution containing 500 ppm of available chlorine at day 30, a solution containing 1,000 ppm of chlorine should be prepared at time 0. There is no decomposition of sodium hypochlorite solution after 30 days when stored in a closed brown bottle *(166)*.

Glutaraldehyde Glutaraldehyde is a saturated dialdehyde that has gained wide acceptance as a high-level disinfectant and chemical sterilant *(183)*. Aqueous solutions of glutaraldehyde are acidic and generally in this state are not sporicidal. Only when the solution is "activated" (made alkaline) by use of alkalinizing agents to pH 7.5 to 8.5 does the solution become sporicidal. Once "activated," these solutions have a shelf-life of minimally 14 days because of the polymerization of the glutaraldehyde molecules at alkaline pH levels. This polymerization blocks the active sites (aldehyde groups) of the glutaraldehyde molecules that are responsible for its biocidal activity.

Novel glutaraldehyde formulations (e.g., glutaraldehyde-phenol-sodium phenate, potentiated acid glutaraldehyde, stabilized alkaline glutaraldehyde) produced in the past 40 years have overcome the problem of rapid loss of activity (e.g., use- life: 28 to 30 days) while generally maintaining excellent microbicidal activity *(12,184,185)*. However, it should be recognized that antimicrobial activity is dependent not only on age but also on use conditions such as dilution and organic stress. The use of glutaraldehyde-based solutions in healthcare facilities is common because of their advantages that include excellent biocidal properties; activity in the presence of organic matter (20% bovine serum); and noncorrosive action to endoscopic equipment, thermometers, rubber, or plastic equipment. The advantages, disadvantages, and characteristics of glutaraldehyde are listed in Table 80-3.

The *in vitro* inactivation of microorganisms by glutaraldehydes has been extensively investigated and reviewed *(186)*. Several investigators showed that ≥2% aqueous solutions of glutaraldehyde, buffered to pH 7.5 to 8.5 with sodium bicarbonate, were effective in killing vegetative bacteria in <2 minutes; *M. tuberculosis*, fungi, and viruses in <10 minutes; and spores of *Bacillus* and *Clostridium* species in 3 hours *(186,187)*. Spores of *Clostridium difficile* are more rapidly killed by 2% glutaraldehyde than are spores of other species of *Clostridium* and *Bacillus (188,189)*, this includes the hypervirulent binary toxin stains of *C. difficile* spores (WA Rutala, Unpublished Results, October 2009). There have been reports of microorganisms with relative resistance to glutaraldehyde, including some mycobacteria (*Mycobacterium chelonae*, *M. avium-intracellulare, M. xenopi*) *(190,191)*, *Methylobacterium mesophilicum (192)*, *Trichosporon*, fungal ascospores (e.g., *Microascus cinereus*, *Cheatomium globosum*), and *Cryptosporidium (193)*. *M. chelonae* persisted in a 0.2% glutaraldehyde solution used to store porcine prosthetic heart valves *(194)* and a large outbreak of *M. massiliense* infections in Brazil after videolaparoscopy equipment, used for different elective cosmetic procedures (e.g., liposuction), was highly tolerant to 2% glutaraldehyde *(195)* Porins may have a role in the resistance of mycobacteria to glutaraldehyde and OPA *(196)*.

Dilution of glutaraldehyde during use commonly occurs and studies show a glutaraldehyde concentration decline after a few days of use in an automatic endoscope washer *(197)*. This occurs because instruments are not thoroughly dried and water is carried in with the instrument, which increases the solution's volume and dilutes its effective concentration. This emphasizes the need to ensure that semicritical equipment is disinfected with an acceptable concentration of glutaraldehyde. Data suggest that 1.0% to 1.5% glutaraldehyde is the minimum effective concentration for >2% glutaraldehyde solutions when used as a high-level disinfectant *(197–199)*. Chemical test strips or liquid chemical monitors are available for determining whether an effective concentration of glutaraldehyde is present despite repeated use and dilution. The frequency of testing should be based on how frequently the solutions are used (e.g., used daily, test daily; used weekly, test before

TABLE 80-3

Summary of Advantages and Disadvantages of Chemical Agents Used as Chemical Sterilants[a] or as High-Level Disinfectants

Sterilization Method	*Advantages*	*Disadvantages*
Peracetic acid plus hydrogen peroxide	• No activation required • Odor or irritation not significant	• Materials compatibility concerns (lead, brass, copper, zinc) both cosmetic and functional • Limited clinical experience • Potential for eye and skin damage
Glutaraldehyde	• Numerous use studies published • Relatively inexpensive • Excellent materials compatibility	• Respiratory irritation from glutaraldehyde vapor • Pungent and irritating odor • Relatively slow mycobactericidal activity • Coagulates blood and fixes tissue to surfaces • Allergic contact dermatitis • Glutaraldehyde vapor monitoring recommended
Hydrogen peroxide	• No activation required • May enhance removal of organic matter and microorganisms • No disposal issues • No odor or irritation issues • Does not coagulate blood or fix tissues to surfaces • Inactivates Cryptosporidium • Use studies published	• Material compatibility concerns (brass, zinc, copper, and nickel/silver plating) both cosmetic and functional • Serious eye damage with contact
Ortho-phthalaldehyde	• Fast acting high-level disinfectant • No activation required • Odor not significant • Excellent materials compatibility claimed • Does not coagulate blood or fix tissues to surfaces claimed • Does not require special venting or air monitoring	• Stains skin, mucous membranes, clothing, and environmental surfaces • Repeated exposure may result in hypersensitivity in some patients with bladder cancer • More expensive than glutaraldehyde • Eye irritation with contact • Slow sporicidal activity
Peracetic acid	• Rapid sterilization cycle time (30–45 min) • Low-temperature (50–55°C) liquid immersion sterilization • Environment-friendly byproducts (acetic acid, O_2, H_2O) • Fully automated • Single-use system eliminates need for concentration testing • Standardized cycle • May enhance removal of organic material and endotoxin • No adverse health effects to operators under normal operating conditions • Compatible with many materials and instruments • Sterilant flows through scope facilitating salt, protein, and microbe removal • Rapidly sporicidal • Provides procedure standardization (constant dilution, perfusion of channel, temperatures, exposure)	• Potential material incompatibility (e.g., aluminum anodized coating becomes dull, ureteroscopes) • Used for immersible instruments only • Biological indicator may not be suitable for routine monitoring • One scope or a small number of instruments can be processed in a cycle • More expensive (endoscope repairs, operating costs, purchase costs) than high-level disinfection • Serious eye and skin damage (concentrated solution) with contact • Point-of-use system, no sterile storage
Accelerated hydrogen peroxide (2.0%); high-level disinfectant	• No activation required • No odor • Nonstaining • No special venting requirements • Manual or automated applications • 12-mo shelf life, 14-d reuse • 8 min at 20°C high-level disinfectant claim	• Material compatibility concerns due to limited clinical experience • Antimicrobial claims not independently verified • Organic material resistance concerns due to limited data

[a]All products effective in presence of organic soil, relatively easy to use, and have a broad spectrum of antimicrobial activity (bacteria, fungi, viruses, bacterial spores, and mycobacteria). The above characteristics are documented in the literature; contact the manufacturer of the instrument and sterilant for additional information. All products listed above are FDA-cleared as chemical sterilants except OPA, which is an FDA-cleared high-level disinfectant. (Modified from Rutala WA, Weber DJ. Disinfection of endoscopes: review of new chemical sterilants used for high-level disinfection. *Infect Control Hosp Epidemiol* 1999;20:69–76.)

use; used 30 times per day, test each tenth use), but the strips should not be used to extend the use life beyond the expiration date. Data suggest the chemicals in the test strip deteriorate with time *(200)*, and a manufacturer's expiration date should be placed on the bottles. The bottle of test strips should be dated when opened and used for the period of time indicated on the bottle (e.g., 120 days). The results of test strip monitoring should be documented. The glutaraldehyde test kits have been preliminarily evaluated for accuracy and range *(200)*, but the reliability has been questioned *(201)*. The concentration should be considered unacceptable or unsafe when the test indicates a dilution below the product's minimum effective concentration or MEC (generally to 1.0 to 1.5% glutaraldehyde or lower) by the indicator not changing color.

Glutaraldehyde is used most commonly as a high-level disinfectant for medical equipment such as endoscopes *(176)*, spirometry tubing, dialyzers, transducers, anesthesia and respiratory therapy equipment, hemodialysis proportioning and dialysate delivery systems, and reuse of laparoscopic disposable plastic trocars *(12)*. Glutaraldehyde is noncorrosive to metal and does not damage lensed instruments, rubber or plastics. The FDA-cleared labels for high-level disinfection with >2% glutaraldehyde at 25°C range from 20 to 90 minutes depending upon the product. However, multiple scientific studies and professional organizations support the efficacy of >2% glutaraldehyde for 20 minutes at 20°C (11,*22,39*). Minimally, follow this latter recommendation. Glutaraldehyde should not be used for cleaning noncritical surfaces as it is too toxic and expensive.

Chemical colitis (presents clinically with severe abdominal pain, bloody and mucoid diarrhea, rectal bleeding, and tenesmus 48–72 hours after colonoscopy) believed due to glutaraldehyde exposure from residual disinfecting solution in the endoscope solution channels has been reported and is preventable by careful endoscope rinsing *(154)*. One study found that residual glutaraldehyde levels were higher and more variable after manual disinfection (<0.2–159.5 mg/L) than after automatic disinfection (0.2–6.3 mg/L) *(202)*. Similarly, keratopathy and corneal decompensation were caused by ophthalmic instruments that were inadequately rinsed after soaking in 2% glutaraldehyde *(203)*.

Glutaraldehyde exposure should be monitored to ensure a safe work environment. In the absence of an OSHA PEL, if the glutaraldehyde level is higher than the ACGIH ceiling limit of 0.05 ppm, it would be prudent to take corrective action and repeat monitoring *(204)*.

Hydrogen Peroxide The literature contains several accounts of the properties, germicidal effectiveness, and potential uses for stabilized hydrogen peroxide in the healthcare setting. Published reports ascribing good germicidal activity to hydrogen peroxide have been published and attest to its bactericidal, virucidal, sporicidal, and fungicidal properties *(205–208)*. The advantages, disadvantages, and characteristics of hydrogen peroxide are listed in Table 80-3. As with other chemical sterilants, dilution of the hydrogen peroxide must be monitored by regularly testing the minimum effective concentration (i.e., 7.5 to 6.0%). Compatibility testing by Olympus America of the 7.5% hydrogen peroxide found both cosmetic changes (e.g., discoloration of black anodized metal finishes) *(176)* and functional changes with the tested endoscopes (Olympus, October 15, 1999, written communication).

Commercially available 3% hydrogen peroxide is a stable and effective disinfectant when used on inanimate surfaces. It has been used in concentrations from 3 to 6% for the disinfection of soft contact lenses (e.g., 3% for 2–3 hours) *(205,209)*, tonometer biprisms, ventilators, fabrics *(210)*, and endoscopes *(128)*. Hydrogen peroxide was effective in spot disinfecting fabrics in patients' rooms *(210)*. Corneal damage from a hydrogen peroxide–soaked tonometer tip that was not properly rinsed has been reported *(211)*.

An accelerated hydrogen peroxide–based technology has been recently introduced into healthcare for disinfection of noncritical environmental surfaces and patient equipment *(212)*, and high-level disinfection of semicritical equipment such as endoscopes *(213)*. Accelerated hydrogen peroxide contains very low levels of anionic and nonionic surfactants that act with hydrogen peroxide to produce microbicidal activity. These ingredients are considered safe for humans and benign for the environment. It is prepared and marketed in several concentrations from 0.5% to 7%. The lower concentrations (0.5%) are designed for the disinfection of hard surfaces, while the higher concentrations (2%) are recommended for use as high-level disinfectants. A 0.5% accelerated hydrogen peroxide demonstrated bactericidal and virucidal activity in 1 minute and mycobactericidal and fungicidal activity in 5 minutes *(212)*. It is more costly than other low-level disinfectants such as quaternary ammonium compounds. The product is claimed to have an excellent antimicrobial performance and a favorable safety profile. Another hydrogen peroxide–based technology has also been used for equipment cleaning *(140)*.

As mentioned, a high-level disinfectant based on AHP (2.0%) is available for heat-sensitive semicritical medical devices including manual and automatic reprocessing of flexible endoscopes. It is odorless, nonstaining, ready to use, and has a 12-month shelf life and a 14-day reuse life. This product has demonstrated sporicidal activity, with a reduction in viability titer of >6-$\log_{10}$ in 6 hours at 20°C, but also mycobactericidal, fungicidal, and virucidal activity with a contact time of 8 minutes. It is reported to be a relatively mild solution for end users and is considered to be compatible with flexible endoscopes. It is slightly irritating to skin and mildly irritating to eyes according to accepted standard test methods (same as 3% topical hydrogen peroxide) *(213)*. AHP (7%) can be reused for several days and retain its broad-spectrum antimicrobial activity *(214)*.

Iodophors Iodine solutions or tinctures have long been used by health professionals, primarily as antiseptics on skin or tissue. The FDA has not cleared any liquid chemical sterilant/high-level disinfectants with iodophors as the main active ingredient. However, iodophors have been used both as antiseptics and disinfectants. An iodophor is a combination of iodine and a solubilizing agent or carrier; the resulting complex provides a sustained-release reservoir of iodine and releases small amounts of free iodine in aqueous solution. The best known and most widely used iodophor is povidone-iodine, a compound of polyvinylpyrrolidone with iodine. This product and other iodophors retain the germicidal efficacy of iodine but, unlike iodine, are generally nonstaining and are relatively free of toxicity and irritancy *(215)*.

There are several reports that documented intrinsic microbial contamination of antiseptic formulations of povidone-iodine and poloxamer-iodine *(216,217)*. It was found that "free" iodine (I_2) contributes to the bactericidal activity of iodophors, and dilutions of iodophors demonstrate more rapid bactericidal action than does a full-strength povidone-iodine solution. Therefore, iodophors must be diluted according to the manufacturers' directions to achieve antimicrobial activity.

Published reports on the *in vitro* antimicrobial efficacy of iodophors demonstrate that iodophors are bactericidal, mycobactericidal, and virucidal but may require prolonged contact times to kill certain fungi and bacterial spores *(19,218–221)*.

Besides their use as an antiseptic, iodophors have been used for the disinfection of blood culture bottles and medical equipment such as hydrotherapy tanks and thermometers. Antiseptic iodophors are not suitable for use as hard-surface disinfectants because of concentration differences. Iodophors formulated as antiseptics contain less free iodine than those formulated as disinfectants *(222)*. Iodine or iodine-based antiseptics should not be used on silicone catheters as the silicone tubing may be adversely affected *(223)*.

Ortho-phthalaldehyde (OPA) Ortho-phthalaldehyde is a high-level disinfectant that received FDA clearance in October 1999. It contains at least 0.55% OPA and it has supplanted glutaraldehyde as the most commonly used high-level disinfectant in the United States. OPA solution is a clear, pale-blue liquid with a pH of 7.5. The advantages, disadvantages, and characteristics of OPA are listed in Table 80-3.

Studies have demonstrated excellent microbicidal activity in *in vitro* studies *(12,176,193,224–229)* including superior mycobactericidal activity (5-$\log_{10}$ reduction in 5 minutes) compared to glutaraldehyde. Walsh and colleagues also found OPA effective (>5-$\log_{10}$ reduction) against a wide range of microorganisms, including glutaraldehyde-resistant mycobacteria and *Bacillus atrophaeus* spores *(227)*.

OPA has several potential advantages compared to glutaraldehyde. It has excellent stability over a wide pH range (pH 3–9), is not a known irritant to the eyes and nasal passages, does not require exposure monitoring, has a barely perceptible odor, and requires no activation. OPA, like glutaraldehyde, has excellent material compatibility. A potential disadvantage of OPA is that it stains proteins gray (including unprotected skin) and thus must be handled with caution *(176)*. However, skin staining would indicate improper handling that requires additional training and/or personal protective equipment (PPE) (gloves, eye and mouth protection, fluid-resistant gowns). OPA residues remaining on inadequately water-rinsed transesophageal echocardiogram probes may leave stains of the patient's mouth. Meticulous cleaning, using the correct OPA exposure time (e.g., 12 minutes in the United States; 5 minutes at 25°C in an AER), and copious rinsing of the probe with water should eliminate this problem. Since OPA has been associated with several episodes of anaphylaxis following cystoscopy *(230)*, the manufacturer has modified its instructions for use of OPA and contraindicates the use of OPA as a disinfectant for reprocessing all urological instrumentation for patients with a history of bladder cancer. PPE should be worn when handling contaminated instruments, equipment, and chemicals *(225)*. In addition, equipment must be thoroughly rinsed to prevent discoloration of a patient's skin or mucous membrane. The minimum effective concentration of OPA is 0.3% and that concentration is monitored by test strips designed specifically for the OPA solution. OPA exposure level monitoring found that the concentration during the disinfection process was significantly higher in the manual group (median: 1.43 ppb) than in the automatic group (median: 0.35 ppb). These findings corroborate other findings that show that it is desirable to introduce automatic endoscope reprocessors to decrease disinfectant exposure levels among scope reprocessing technicians *(231)*.

Peracetic Acid Peracetic, or peroxyacetic acid, is characterized by a very rapid action against all microorganisms. Special advantages of peracetic acid are its lack of harmful decomposition products (i.e., acetic acid, water, oxygen, hydrogen peroxide), it enhances removal of organic material *(232)* and leaves no residue. It remains effective in the presence of organic matter and is sporicidal even at low temperatures. Peracetic acid can corrode copper, brass, bronze, plain steel, and galvanized iron, but these effects can be reduced by additives and pH modifications. The advantages, disadvantages, and characteristics of peracetic acid are listed in Table 80-3.

Peracetic acid will inactivate gram-positive and gram-negative bacteria, fungi, and yeasts in <5 minutes at <100 ppm. In the presence of organic matter, 200 to 500 ppm is required. For viruses, the dosage range is wide (12–2,250 ppm), with poliovirus inactivated in yeast extract in 15 minutes with 1,500 to 2,250 ppm. An automated machine using peracetic acid to reprocess heat-sensitive devices such as endoscopes and their accessories is used in the United States *(233,234)*. In this system, a 35% concentration of peracetic acid is diluted to 0.2% with filtered water at a temperature of 50°C. Since the rinse water is tapwater that has been filtered and exposed to ultraviolet rays, it is not sterile. Therefore, the final processed devices are not sterile (FDA, April 6, 2010). Simulated-use trials have demonstrated excellent microbicidal activity *(234–238)*, and three clinical trials have demonstrated both excellent microbial killing and no clinical failures leading to infection *(239–241)*. Three clusters of infection using the peracetic acid automated endoscope reprocessor were linked to inadequately processed bronchoscopes when inappropriate channel connectors were used with the system *(242,243)*. These clusters highlight the importance of training, proper model-specific endoscope connector systems, and quality control procedures to ensure compliance with endoscope manufacturer's recommendations and professional organization guidelines. A high-level disinfectant available in the United Kingdom contains 0.35% peracetic acid. Although this product is rapidly effective against a broad range of microorganisms *(244,245)*, it tarnishes the metal of endoscopes and is unstable, resulting in only a 24-hour use life *(245)*.

Peracetic Acid with Hydrogen Peroxide Three chemical sterilants are FDA-cleared that contain peracetic acid plus hydrogen peroxide (0.08% peracetic acid plus 1.0% hydrogen peroxide, 0.23% peracetic acid plus 7.35% hydrogen peroxide, and 8.3% hydrogen peroxide plus 7.0% peracetic acid).

The advantages, disadvantages, and characteristics of peracetic acid with hydrogen peroxide are listed in Table 80-3.

The bactericidal properties of peracetic acid plus hydrogen peroxide have been demonstrated *(246)*. Manufacturer's data demonstrated that this combination of peracetic acid plus hydrogen peroxide inactivated all microorganisms with the exception of bacterial spores within 20 minutes. The 0.08% peracetic acid plus 1.0% hydrogen peroxide product was effective in inactivating a glutaraldehyde-resistant mycobacteria *(247)*.

The combination of peracetic acid and hydrogen peroxide has been used for disinfecting hemodialyzers *(248)*. The percentage of dialysis centers using a peracetic acid with hydrogen peroxide–based disinfectant for reprocessing dialyzers increased from 5% in 1983 to 62% in 2001 *(249)*.

Phenolics Phenol has occupied a prominent place in the field of hospital disinfection since its initial use as a germicide by Lister in his pioneering work on antiseptic surgery. In the past 40 years, however, work has been concentrated upon the numerous phenol derivatives or phenolics and their antimicrobial properties. Phenol derivatives originate when a functional group (e.g., alkyl, phenyl, benzyl, halogen) replaces one of the hydrogen atoms on the aromatic ring. Two phenol derivatives commonly found as constituents of hospital disinfectants are ortho-phenylphenol and ortho-benzyl-para-chlorophenol.

Published reports on the antimicrobial efficacy of commonly used phenolics showed that they were bactericidal, fungicidal, virucidal, and tuberculocidal *(12,19,53,76,218, 250–253)*.

Many phenolic germicides are EPA-registered as disinfectants for use on environmental surfaces (e.g., bedside tables, bedrails, laboratory surfaces) and noncritical medical devices. Phenolics are not FDA-cleared as high-level disinfectants for use with semicritical items but could be used to preclean or decontaminate critical and semicritical devices prior to terminal sterilization or high-level disinfection.

The use of phenolics in nurseries has been questioned because of the occurrence of hyperbilirubinemia in infants placed in bassinets where phenolic detergents were used *(254)*. In addition, Doan and coworkers demonstrated bilirubin level increases in phenolic-exposed infants compared to nonphenolic-exposed infants when the phenolic was prepared according to the manufacturers' recommended dilution *(255)*. If phenolics are used to clean nursery floors, they must be diluted according to the recommendation on the product label. Phenolics (and other disinfectants) should not be used to clean infant bassinets and incubators while occupied. If phenolics are used to terminally clean infant bassinets and incubators, the surfaces should be rinsed thoroughly with water and dried before the infant bassinets and incubators are reused *(22)*.

Quaternary Ammonium Compounds The quaternary ammonium compounds are widely used as surface disinfectants. There have been some reports of healthcare-associated infections associated with contaminated quaternary ammonium compounds used to disinfect patient-care supplies or equipment such as cystoscopes or cardiac catheters *(256,257)*. As with several other disinfectants (e.g., phenolics, iodophors), gram-negative bacteria have been found to survive or grow in them (258).

Results from manufacturers' data sheets and from published scientific literature indicate that the quaternaries sold as hospital disinfectants are generally fungicidal, bactericidal, and virucidal against lipophilic (enveloped) viruses; they are not sporicidal and generally not tuberculocidal or virucidal against hydrophilic (nonenveloped) viruses *(19,49,50,52,53,92,218,259,260)*. Best et al. and Rutala et al. demonstrated the poor mycobactericidal activities of quaternary ammonium compounds *(49,218)*.

The quaternaries are commonly used in ordinary environmental sanitation of noncritical surfaces such as floors, furniture, and walls. They have demonstrated sustained antimicrobial activity against VRE for 48 hours *(59)*. EPA-registered quaternary ammonium compounds are appropriate to use when disinfecting medical equipment that come into contact with intact skin (e.g., blood pressure cuffs).

Pasteurization

Pasteurization is not a sterilization process; its purpose is to destroy all pathogenic microorganisms with the exception of bacterial spores. The time-temperature relation for hot-water pasteurization is generally >70°C (158°F) for 30 minutes. The water temperature and time should be monitored as part of a quality assurance program *(261)*. Pasteurization of respiratory therapy *(262,263)* and anesthesia equipment *(264)* is a recognized alternative to chemical disinfection.

Ultraviolet Light

Ultraviolet light (UV) has been recognized as an effective method for killing microorganisms. It has been suggested for use in healthcare for several purposes to include air disinfection, room decontamination (see section Room Decontamination below), surface disinfection, biofilm disinfection *(265)*, and ultrasound probe disinfection *(266)*. Contaminated ultrasound probes can potentially transmit pathogens. When the probe is only in contact with the patient's skin, there is a low risk of infection and low-level disinfection is recommended; however, a higher level of disinfection is recommended when the probe contacts mucous membranes or nonintact skin. An evaluation of a new disinfection procedure for ultrasound probes using ultraviolet light demonstrated the median microbial reduction for UV was 100%, 87.5% for antiseptic wiping, and 88% for dry wiping *(266)*.

Surface disinfection with ultraviolet light (100–280 nm) has been evaluated with three hospital-related surfaces, namely, aluminum (bed railings), stainless steel (operating tables), and scrubs (laboratory coats). *Acinetobacter baumannii* were inoculated on small coupons (10^3 or 10^5/coupon) and exposed to 90 Joule/m^2. This exposure was effective in the inactivation of *Acinetobacter* from the metal coupon surfaces but ineffective in the decontamination of scrubs *(267)*.

REPROCESSING SEMICRITICAL ITEMS

Semicritical items represent the greatest risk of disease transmission as far more healthcare associated infections have been caused by semicritical items than critical or noncritical items (11). There is virtually no documented

risk of transmitting infectious agents to patients via noncritical items *(35)* when they are used as noncritical items and do not contact nonintact skin and/or mucous membranes. Critical items have a high risk of infection if such an item is contaminated with any microorganism; however, sterilization cycles that are designed for hospitals are usually based on the overkill approach. The time required for a 6-$\log_{10}$ reduction of highly resistant spores by the process is considered a half-cycle, and the full-cycle exposure time is the time for the half cycle doubled. Thus, a sterilization process can achieve a 12-$\log_{10}$ reduction of highly resistant spores while medical/surgical devices are contaminated with low numbers of microorganisms (85% of instruments <100 bacteria) after use in surgery *(268)*. This results in a huge margin of safety and a sterility assurance level of 10^{-6}, which means there is <1 chance in 1 million that a contaminant will survive on a medical product after the sterilization process. In contrast, semicritical items (e.g., gastrointestinal endoscopes), by virtue of the body cavities they enter, may be contaminated with a 1 billion bacteria *(269)*. A further complication is that many of these devices are constructed in a way that is very difficult to properly clean them (e.g., long, narrow lumens) before the high-level disinfection procedure. Thus, the result is a device with a sterility assurance level of 10^{0} to 10^{-3}, which means there is a greater chance that a contaminant will survive on a medical device after the high-level disinfection procedure than after sterilization (i.e., >1 in 1,000 chance that a contaminant will survive) *(270)*. Thus, reprocessing semicritical items has a narrower margin of safety, and any deviation from the reprocessing protocol can lead to the survival of microorganisms and an increased risk of infection.

Reprocessing of Endoscopes

Physicians use endoscopes to diagnose and treat numerous medical disorders. While endoscopes represent a valuable diagnostic and therapeutic tool in modern medicine and the incidence of infection associated with use has been reported as very low (about 1 in 1.8 million procedures) *(271)*, more healthcare-associated outbreaks have been linked to contaminated endoscopes than to any other medical device *(5–7,272,273)*. In order to prevent the spread of healthcare-associated infections, all heat-sensitive endoscopes (e.g., gastrointestinal endoscopes, bronchoscopes, nasopharygoscopes) must be properly cleaned and at a minimum subjected to high-level disinfection following each use. High-level disinfection can be expected to destroy all microorganisms although when high numbers of bacterial spores are present, a few spores may survive.

Flexible endoscopes, by virtue of the types of body cavities they enter, acquire high levels of microbial contamination (bioburden) during each use *(274)*. For example, the bioburden found on flexible gastrointestinal endoscopes following use has ranged from 10^{5} colony-forming units (CFU)/mL to 10^{10} CFU/mL, with the highest levels being found in the suction channels *(228,274–276)*. The average load on bronchoscopes before cleaning was 6.4×10^{4} CFU/mL. Cleaning reduces the level of microbial contamination by 4- to 6-$\log_{10}$. *(130,277)*. Using HIV-contaminated endoscopes, several investigators have shown that cleaning completely eliminates the microbial contamination on the scopes *(127,278)*. Similarly, other investigators found that ETO sterilization or high-level disinfection (soaking in 2% glutaraldehyde for 20 minutes) was effective only when the device was first properly cleaned *(279)*.

FDA maintains a list of cleared liquid chemical sterilants/high-level disinfectants that can be used to reprocess heat-sensitive medical devices, such as flexible endoscopes. Users can access and view the list at http://www.fda.gov/cdrh/ode/germlab.html *(27)*. At this time, the FDA-cleared and marketed formulations include ≥2.4% glutaraldehyde, 0.55% ortho-phthalaldehyde (OPA), 1.12% glutaraldehyde with 1.93% phenol/phenate, 7.35% hydrogen peroxide with 0.23% peracetic acid, 1.0% hydrogen peroxide with 0.08% peracetic acid, hypochlorite and hypochlorous acid system (650–675 ppm free available chlorine), 2.0% accelerated hydrogen peroxide, 3.4% glutaraldehyde with 26% isopropanol, 8.3% hydrogen peroxide with 7.0% peracetic acid, and 7.5% hydrogen peroxide *(27)*. These products have excellent antimicrobial activity; however, some oxidizing chemicals (e.g., 7.5% hydrogen peroxide, and 1.0% hydrogen peroxide with 0.08% peracetic acid) have been reported to cause cosmetic and functional damage to endoscopes *(176)*. Users should check with device manufacturers for information on germicide compatibility with their device. If the germicide is FDA-cleared, then it is safe when used according to the label directions; however, professionals should review the scientific literature as new data may become available regarding human safety or materials compatibility. ETO sterilization of flexible endoscopes is infrequent because it requires a lengthy processing and aeration time (e.g., 12–15 hours) and is a potential hazard to staff and patients. Three products that are commonly used for reprocessing endoscopes in the United States are ortho-phthalaldehyde; glutaraldehyde; and an automated, liquid chemical sterilant processing system that uses peracetic acid *(183)*. Ortho-phthalaldehyde has replaced glutaraldehyde in many healthcare facilities as it possesses several potential advantages compared to glutaraldehyde: no known irritation to the eyes and nasal passages, does not require activation or exposure monitoring, and has a 12-minute high-level disinfection claim in the United States *(176)*. Disinfectants that are not FDA-cleared and should not be used for reprocessing endoscopes include iodophors, alcohols, quaternary ammonium compounds, and phenolics. These solutions may still be in use outside the United States, but their use should be strongly discouraged because of lack of proven efficacy against all microorganisms or materials incompatibility.

The FDA's clearance of the contact conditions listed on germicide labeling is based on the manufacturer's test results. They conduct the testing under worst-case conditions for germicide formulation (i.e., minimum recommended concentration of the active ingredient) and include organic soil. Typically, manufacturers use 5% serum as the organic soil and hard water as examples of organic and inorganic challenges. The soil is used to represent the organic loading to which the device is exposed during actual use and that would remain on the device in the absence of cleaning. This method assures that the contact conditions provides complete elimination of the test mycobacteria (e.g., 10^{5} to 10^{6} *Mycobacteria tuberculosis* in organic soil and dried on a scope) if inoculated in the most difficult areas for the disinfectant to penetrate and contact in the absence

of cleaning, and thus, provides a margin of safety *(280)*. For 2.4% glutaraldehyde that requires a 45-minute immersion at 25°C to achieve high-level disinfection (i.e., 100% kill of *Mycobacterium tuberculosis*), FDA itself does not conduct testing, but relies solely on the disinfectant manufacturer's data. Users can find the contact conditions for cleared high-level disinfectants/chemical sterilants at http://www.fda.gov/cdrh/ode/germlab.html. It is important to note that data suggest that *M. tuberculosis* levels can be reduced by at least 8-$\log_{10}$ with cleaning (4-$\log_{10}$) *(130,275,276,281)* followed by chemical disinfection for 20 minutes at 20°C (4- to 6-$\log_{10}$) *(130,282–284)*. Based on these data, APIC *(285)*, the Society of Gastroenterology Nurses and Associates (SGNA) *(36,286–288)* the ASGE *(3)*, American College of Chest Physicians *(273)*, and a multisociety guideline *(39)* recommend alternative contact conditions with 2% glutaraldehyde to achieve high-level disinfection based on articles in the literature (e.g., that equipment be immersed in 2% glutaraldehyde at 20°C for at least 20 minutes for high-level disinfection) *(3,25,51,130,282,288–294)*. It is FDA's position that if the user chooses to use alternative contact conditions, they assume liability. In the absence of several well-designed experimental scientific studies regarding alternative exposure times of high-level disinfectants, the manufacturers' recommendations to achieve high-level disinfection should be followed. Currently, such data are available only for 2% glutaraldehyde solutions.

Dilution of glutaraldehyde during use commonly occurs and studies show a glutaraldehyde concentration decline after a few days of use in an automatic endoscope washer *(197,295)*. This occurs because instruments are not thoroughly dried and water is carried in with the instrument, which increases the solution's volume and dilutes its effective concentration *(296)*. This emphasizes the need to ensure that semicritical equipment is disinfected with an acceptable concentration of glutaraldehyde. Data suggest that 1.0% to 1.5% glutaraldehyde is the minimum effective concentration for >2% glutaraldehyde solutions when used as a high-level disinfectant *(197–199,297)*. Chemical test strips or liquid chemical monitors *(296,298)* are available for determining whether an effective concentration of glutaraldehyde is present despite repeated use and dilution. The frequency of testing should be based on how frequently the solutions are used (e.g., used daily, test daily; used weekly, test before use; used 30 times per day, test each tenth use), but the strips should not be used to extend the use life beyond the expiration date. Data suggest the chemicals in the test strip deteriorate with time *(200)*, and a manufacturer's expiration date should be placed on the bottles. The bottle of test strips should be dated when opened and used for the period of time indicated on the bottle (e.g., 120 days). The results of test strip monitoring should be documented. The glutaraldehyde test kits have been preliminarily evaluated for accuracy and range *(200)*, but the reliability has been questioned *(201)*. Manufacturers of some, but not all, chemical test strips, for ensuring the minimum effective concentration of the high-level disinfectant is present, recommend the use of quality control procedures to ensure the strips perform properly. If the manufacturer of the chemical test strip recommends a quality control procedure, comply with the manufacturer's recommendations. The concentration should be considered unacceptable or unsafe when the test indicates a dilution below the product's minimum effective concentration or MEC (generally to 1.0 to 1.5% glutaraldehyde or lower) by the indicator not changing color.

Flexible endoscopes are particularly difficult to disinfect *(299)* and easy to damage because of their intricate design and delicate materials *(300)*. Meticulous cleaning must precede any sterilization or high-level disinfection of these instruments. Failure to perform good cleaning may result in a sterilization or disinfection failure, and outbreaks of infection may occur. Several studies have demonstrated the importance of cleaning in experimental studies with the duck hepatitis B virus *(279,301)*, HIV *(302)*, and *Helicobacter pylori (303)*.

Examining healthcare-associated infections related only to endoscopes through July 1992, Spach found that 281 infections were transmitted by gastrointestinal endoscopy and 96 were transmitted by bronchoscopy. The clinical spectrum ranged from asymptomatic colonization to death. *Salmonella* species and *P. aeruginosa* repeatedly were identified as causative agents of infections transmitted by gastrointestinal endoscopy, and *M. tuberculosis* (TB), atypical mycobacteria, and *P. aeruginosa* were the most common causes of infections transmitted by bronchoscopy *(273)*. Major reasons for transmission were inadequate cleaning, improper selection of a disinfecting agent, failure to follow recommended cleaning and disinfection procedures *(5,7,35,272)*, damaged endoscopes *(304)* and flaws in endoscope design *(305,306)*, or automated endoscope reprocessors *(6,272)*. Failure to follow established guidelines has continued to lead to infections associated with gastrointestinal endoscopes *(7)* and bronchoscopes *(6,273)*. Potential device-associated problems should be reported to the FDA's Center for Devices and Radiologic Health. One multistate investigation found that 23.9% of the bacterial cultures from the internal channels of 71 gastrointestinal endoscopes grew ≥100,000 colonies of bacteria after completion of all disinfection/sterilization procedures (9 of 25 facilities were using a product that has been removed from the marketplace [6 facilities using 1:16 glutaraldehyde phenate], is not FDA-cleared as a high-level disinfectant [an iodophor] or no disinfecting agent) and before use on the next patient *(307)*. It should be acknowledged that the incidence of postendoscopic procedure infections resulting from an improperly processed endoscope has not been rigorously assessed.

Recommendations for the cleaning and disinfection of endoscopic equipment have been published and should be strictly followed *(3,36,39,273,285–288,308–311)*. Unfortunately, audits have shown that personnel do not consistently adhere to guidelines on reprocessing *(312–314)*, and outbreaks of infection continue to occur *(306,315–317)*. In order to ensure that reprocessing personnel are properly trained, there should be initial and annual competency testing for each individual who reprocesses endoscopic instruments *(36,243)*.

In general, endoscope disinfection involves five steps after leak testing: (1) clean—mechanically clean internal and external surfaces, including brushing internal channels and flushing each internal channel with water and a detergent or enzymatic cleaners (leak testing is recommended for endoscopes before immersion); (2) disinfect—immerse endoscope in high-level disinfectant (or chemical sterilant)

and perfuse (eliminates air pockets and ensures contact of the germicide with the internal channels) disinfectant into all accessible channels such as the suction/biopsy channel and air/water channel and expose for a time recommended for specific products; (3) rinse—rinse the endoscope and all channels with sterile water, filtered water (commonly used with AERs) or tapwater (i.e., high-quality potable water that meets federal clean water standards at the point of use); (4) dry—rinse the insertion tube and inner channels with alcohol and dry with forced air after disinfection and before storage; and (5) store—store the endoscope in a way that prevents recontamination and promotes drying (e.g., hung vertically). Drying the endoscope (steps 3 and 4) is essential to greatly reduce the chance of recontamination of the endoscope by microorganisms that may be present in the rinse water *(39,318)*. Because tapwater may contain low levels of microorganisms *(319)*, some have suggested that only sterile water (which may be prohibitively expensive) *(320)* or AER-filtered water be used. The suggestion to use only sterile water or filtered water is not consistent with published guidelines that allow tapwater with an alcohol rinse and forced air drying *(3,36,285,288)* or the scientific literature *(37,283)*. In addition, there has been no evidence of disease transmission when tapwater followed by an alcohol rinse and forced air drying has been used. AERs produce filtered water via passage through a bacterial filter (e.g., 0.2 μm). In addition to the endoscope reprocessing steps, a protocol should be developed that assures the user knows whether an endoscope has been appropriately cleaned and disinfected (e.g., using a room or cabinet for processed endoscopes only) or has not been reprocessed. Confusion can result when users leave endoscopes on movable carts, and it is unclear whether the endoscope has been processed or not. While one guideline has recommended that an endoscope (e.g., a duodenoscope) should be reprocessed immediately before its use *(310)*, other guidelines do not require this activity *(3,36,287,288)* and with the exception of the Association of periOperative Registered Nurses (AORN), professional organizations do not recommend that reprocessing be repeated so long as the original processing is done correctly. Based on studies that have assessed the microbiological stability of endoscopes after high-level disinfection, it appears that reprocessing after storage for a week or 2 weeks is unnecessary *(321–323)*. As part of a quality assurance program, healthcare facility personnel may consider random bacterial surveillance cultures of processed endoscopes to ensure high-level disinfection or sterilization *(6,324–327)*, although some investigators have suggested it is too time consuming and costly and process controls are preferable *(328)*. Reprocessed endoscopes should be free of microbial pathogens except for small numbers of relatively avirulent microbes that represent exogenous environmental contamination (e.g., coagulase-negative *Staphylococcus*, *Bacillus* species, diphtheroids). It has also been suggested that the final rinse water used during endoscope reprocessing be microbiologically cultured at least monthly *(329)*. The microbiologic standard that should be met has not been set and the value of routine endoscope cultures has not been shown *(330)*. In addition, neither the routine culture of reprocessed endoscopes nor the final rinse water has been validated by correlating viable counts on an endoscope to infection following an endoscopic procedure. If culturing of reprocessed endoscopes were done, sampling the endoscope would assess water quality as well as other important steps (e.g., disinfectant effectiveness, exposure time, cleaning) in the reprocessing procedure. A number of methods for sampling endoscopes and water have been described *(40,322,325,331–334)*. Novel approaches (e.g., ATP) to evaluate the effectiveness of endoscope cleaning *(150,152)* or endoscope reprocessing *(335)* have also been evaluated, but there is no accepted method for assessing the outcome of endoscope reprocessing.

The carrying case used to transport clean and reprocessed endoscopes outside of the healthcare environment should not be used to store an endoscope or to transport the instrument within the healthcare facility. A contaminated endoscope should never be placed in the carrying case as the case can also become contaminated. When the endoscope is removed from the case and properly reprocessed and put back in the case, the endoscope can become recontaminated by the case. If the carrying case becomes contaminated, it should be discarded (Olympus America, June 2002, written communication).

Infection preventionists should ensure that institutional policies are consistent with national guidelines and conduct infection control rounds periodically (e.g., at least annually) in areas where endoscopes are reprocessed to make certain there is compliance with policy. Breaches in policy should be documented and corrective action instituted. Some studies suggest the assurance of quality for endoscopic use could be achieved through process control (e.g., minimum effective concentration, training) as opposed to product control (i.e., microbiological monitoring) *(328)*. In incidents in which endoscopes were not exposed to a high-level disinfection process, all patients were assessed for possible acquisition of human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). A 14-step method for managing a failure incident associated with high-level disinfection or sterilization has been described *(336)*. The possible transmission of bloodborne pathogens and other infectious agents highlights the importance of rigorous infection control *(337,338)*.

Automated Endoscope Reprocessors Automated endoscope reprocessors (AER) offer several advantages compared to manual reprocessing: they automate and standardize several important reprocessing steps; *(339–341)* reduce the likelihood that an essential reprocessing step will be skipped; reduce personnel exposure to high-level disinfectants or chemical sterilants; provide significant microbial reduction *(342)* and filtered tap water; and remove established biofilms and retards biofilm generation *(343)*. Disadvantages associated with some AERs include: generally does not eliminate cleaning; failure and outbreaks have been linked to poorly designed reprocessors; and does not monitor high-level disinfectant concentration. Failure of AERs has been linked to outbreaks of infections *(344)* or colonization *(6,345)*, and the AER water filtration system may not be able to reliably provide "sterile" or bacteria-free rinse water *(346,347)*. It is critical that correct connectors between the AER and the device are established to ensure complete flow of disinfectants and rinse water *(6,348)*. In addition, some

endoscopes such as the duodenoscopes (e.g., endoscopic retrograde cholangiopancreatography [ERCP]) contain features (e.g., elevator-wire channel) that require a flushing pressure that is not achieved by some AERs and must be reprocessed manually using a 2- to 5-mL syringe. There is a need for further development and redesign of AERs *(6,349)* and endoscopes *(300,350)* so that they do not represent a potential source of infectious agents. The potential for transmission of infection during endoscopy remains a concern for healthcare workers and patients (11).

A variety of capabilities has been incorporated into the available AERs, and these capabilities have been recently summarized *(351)*. All models have disinfection and rinsing cycles, and some have detergent cleaning, alcohol flush, and/or extended forced-air-drying cycles. Additional features may include variable cycle times; printed documentation of the process; low-intensity ultrasound waves; high-level disinfectant vapor recovery systems; heating to optimize the high-level disinfectants efficacy; a variable number of endoscopes processed per cycle; automated leak testing; automated detection of channel obstructions; and table top, floor standing and cart-mounted models *(351)*.

Not all reprocessors are compatible with all high-level disinfectants or with endoscopes from all manufacturers. Newer AERs should offer benefits over older models. One AER integrates cleaning and has achieved an FDA-cleared cleaning claim (Evo-Tech™). The users must continue to do the "bedside" cleaning (wipe external surfaces and flush each lumen with a detergent solution) and then place the scope directly (within one hour) into the Evo-Tech™ machine. This eliminates the labor-intensive manual cleaning. It also automatically detects leaks, alcohol is flushed through the channels prior to cycle completion to promote drying, and the AER integrates minimum effective concentration (MEC) monitoring. In addition, the printer provides complete monitoring of critical cycle parameters including MEC of the high-level disinfectant (ortho-phthalaldehyde), disinfection time, channel blockage detection, temperature, pressure, and time to ensure compliance throughout the process. Manufacturer's residual data for cleaning of the internal channels as well as external insertion tube surfaces were below the limit of <8.5 μg/cm^2. Another AER (Reliance) requires a minimal number of connections to the endoscope channels and uses a control boot (housing apparatus that creates pressure differentials to ensure connector-less fluid flow through all channels that are accessible through the endoscope's control handle channel ports). Data demonstrate that the soil and microbial removal effected by Reliance washing phase was equivalent to that achieved by optimal manual cleaning. For example, there was >99% reduction in protein and hemoglobin and both methods reduced the level of residual organic material to below 6.4 μg/cm^2 *(352)*.

Tonometers

Disinfection strategies for other semicritical items (e.g., applanation tonometers, rectal/vaginal probes, cryosurgical instruments, and diaphragm fitting rings) are highly variable. Currently, FDA requests that the device manufacturer include at least one validated cleaning and disinfection/sterilization protocol in the labeling for their device. As with all medications and devices, users should be familiar with the label instructions. One study revealed that no uniform technique was in use for disinfection of applanation tonometers, with disinfectant contact times varying from <15 sec to 20 minutes *(38)*. In view of the potential for transmission of viruses (e.g., herpes simplex virus [HSV], adenovirus 8, or HIV) *(353)* by tonometer tips, CDC has recommended *(354)* that the tonometer tips be wiped clean and disinfected for 5–10 minutes with either 3% hydrogen peroxide, 5,000 ppm chlorine, 70% ethyl alcohol, or 70% isopropyl alcohol. However, more recent data suggest that 3% hydrogen peroxide and 70% isopropyl alcohol are not effective against adenovirus capable of causing epidemic keratoconjunctivitis and similar viruses and should not be used for disinfecting applanation tonometers *(90,177,355)*. For this reason, the current CDC guideline recommends to wipe clean tonometer tips and then disinfect them by immersing for 5 to 10 minutes in either 5,000 ppm chlorine or 70% ethyl alcohol (11*,90,170,177,354,355*). Structural damage to Schiotz tonometers has been observed with a 1:10 sodium hypochlorite (5,000 ppm chlorine) and 3% hydrogen peroxide *(356)*. After disinfection, the tonometer should be thoroughly rinsed in tapwater and air dried before use.

Because a short and simple decontamination procedure is desirable in the clinical setting, swabbing the tonometer tip with a 70% isopropyl alcohol wipe is sometimes practiced *(357)*. Preliminary reports suggest that wiping the tonometer tip with an alcohol swab and then allowing the alcohol to evaporate may be an effective means of eliminating HSV, HIV, and adenovirus *(357–359)*. However, since these studies involved only a few replicates and were conducted in a controlled laboratory setting, further studies are needed before this technique can be recommended. In addition, two reports have found that disinfection of pneumotonometer tips between uses with a 70% isopropyl alcohol wipe contributed to outbreaks of epidemic keratoconjunctivitis caused by adenovirus type 8 *(360,361)*.

Endocavitary Probes

Vaginal probes are used in sonographic scanning. A vaginal probe and all endocavitary probes without a probe cover are semicritical devices as they have direct contact with mucous membranes (e.g., vagina, rectum, pharynx). While one could argue that the use of the probe cover changes the category, the CDC guideline proposes that a new condom/probe cover should be used to cover the probe for each patient, and since condoms/probe covers may fail *(362–365)*, high-level disinfection of the endocavitary probe also should be performed (11). The relevance of this recommendation is reinforced with the findings that sterile transvaginal ultrasound probe covers have a very high rate of perforations even before use (0%, 25%, and 65% perforations from three suppliers) *(365)*. After oocyte retrieval use, Hignett and Claman found a very high rate of perforations in used endovaginal probe covers from two suppliers (75% and 81%) i, while Amis and coworkers *(366)* and Milki and Fisch *(362)* demonstrated a lower rate of perforations after use of condoms (0.9% and 2.0%, respectively). Rooks and coworkers found that condoms were superior to commercially available probe covers for covering the ultrasound probe (1.7% for condoms versus 8.3% leakage for probe covers) *(367)*. These studies underscore the need for routine probe disinfection between examinations. Although most ultrasound manufacturers recommend the

use of 2% glutaraldehyde for high-level disinfection of contaminated transvaginal transducers, the use of this agent has been questioned *(368)* because it may shorten the life of the transducer and may have toxic effects on the gametes and embryos *(369)*. An alternative procedure for disinfecting the vaginal transducer has been offered by Garland and deCrespigny *(370)*. It involves the mechanical removal of the gel from the transducer, cleaning the transducer in soap and water, wiping the transducer with 70% alcohol or soaking it for 2 minutes in 500 ppm chlorine, and rinsing with tapwater and air drying. The effectiveness of this and other methods *(366)* has not been validated in either rigorous laboratory experiments or in clinical use. High-level disinfection with a product (e.g., hydrogen peroxide) that is not toxic to staff, patients, probes, and retrieved cells should be used until such time as the effectiveness of alternative procedures against microbes of importance at the cavitary site is demonstrated by well-designed experimental scientific studies. Other probes such as rectal, cryosurgical, and transesophageal probes/devices should also be subjected to high-level disinfection between patients.

Ultrasound probes may also be used during surgical procedures and have contact with sterile body sites. These probes may be covered with a sterile sheath to reduce the level of contamination on the probe and reduce the risk of infection. However, since the sheath does not provide complete protection of the probe, the probes should be sterilized between each patient use as with other critical items. If this is not possible, minimally high-level disinfect the probe and cover it with a sterile probe cover.

Some cryosurgical probes are not fully immersible. When reprocessing these probes, the tip of the probe should be immersed in a high-level disinfectant for the appropriate time (e.g., 20 minutes exposure with 2% glutaraldehyde) and any other portion of the probe that could have mucous membrane contact could be disinfected by immersion or wrapping (or wiping) with a cloth soaked in a high-level disinfectant in order to allow the recommended contact time. After disinfection, the probe should be rinsed with tapwater and dried before use. Healthcare facilities that use nonimmersible probes should replace them as soon as possible with fully immersible probes.

One study showed that the use of a high-quality, snugly fitting, sterile, disposable polyurethane sheath on a nasopharyngoscopes during a clinical examination, combined with enzymatic detergent cleaning and disinfection with 70% ethanol, can provide a reliably decontaminated, patient-ready instrument that eliminates the need for high-level disinfection of nasopharyngoscopes *(371)*. If other studies corroborate the integrity of the sterile polyurethane sheaths used in nasopharyngoscopy (or other procedures), this practice may be an option to high-level disinfection.

Thus, the CDC guideline states that even if probe covers have been used, clean and high-level disinfect other semicritical devices such as rectal probes, vaginal probes, and cryosurgical probes with a product that is not toxic to staff, patients, probes, and retrieved germ cells (if applicable). Use a high-level disinfectant at the FDA-cleared exposure time. When probe covers are available, use a probe cover or condom to reduce the level of microbial contamination. Do not use a lower category of disinfection or cease to follow the appropriate disinfectant recommendations when using probe covers because these sheaths and condoms may fail. Following high-level disinfection, rinse all items. Use sterile water, filtered water, or tapwater followed by an alcohol rinse for semicritical equipment that will have contact with the mucous membranes of the upper respiratory tract (e.g., nose, pharynx, esophagus) (11).

Prostate Biopsy Probes

Transrectal ultrasound (TRUS)–guided prostate biopsies are among the most common outpatient diagnostic procedures performed in urology practice to evaluate patients for prostate cancer after an elevated prostate-specific antigen level or abnormal digital rectal examination findings *(372)*. It involves obtaining multiple prostate tissue cores by passing a disposable biopsy needle through a needle guide under ultrasound guidance. All prostatic biopsy procedures likely result in contamination of the probe with blood or feces. During this procedure, the transducer assembly is generally covered with a barrier sheath *(373)*. Breaches in the reprocessing of prostate biopsy probes can pose a risk of disease transmission *(372,374)*.

Disinfection or sterilization of ultrasound transducer components is based on the function or use of each component. Since the biopsy needle penetrates sterile tissue for biopsy, it should be sterile. Ideally, the needle guide should be sterilized between patient uses. However, if this is not possible (i.e., clinic does not have a sterilizer as biopsy needles are likely purchased as single-use sterile devices), then high-level disinfection after disassembly and cleaning is acceptable as it has contact with mucous membranes but not sterile tissue. The FDA alert *(373)* and a CDC article *(372)* recommend that the needle guide be sterilized as the biopsy needle contacts the needle guide before it penetrates sterile tissue. This recommendation is inconsistent with current recommendation for the disinfection of endoscopes. It is currently recommended that gastrointestinal endoscopes be high-level disinfected minimally but that medical devices that pass through the endoscope and enter sterile tissue (biopsy forceps) be sterilized. There is no recommendation that the lumen or channel through which they pass should also be sterilized. One possible explanation for the inconsistency in this FDA recommendation is that the gastrointestinal endoscopes are high-level disinfected as there is no practical way to sterilize them, while the reusable needle guide for prostate probes can be sterilized (MJ Arduino, August 2006, written communication). While a barrier sheath is used on the transducer assembly during the biopsy procedure, the sheath is compromised by the penetration of the needle *(373)*. Although prostate probes and other endocavitary probes are often covered with a disposable sheath or condom *(373)*, such covers do not adequately protect the probe from microbial contamination due to leakage, (9%) *(375)* and thus the use of a cover does not alter the requirement for high-level disinfection minimally (11). FDA specifies the use of a sterile barrier sheath in their recommendation for reprocessing reusable ultrasound transducer assemblies *(373)*. It is appropriate to use a sterile barrier sheath when an ultrasound probe is entering a sterile body cavity, but when the probe is entering the rectum the need for a sterile barrier sheath is unclear.

All semicritical and critical medical devices must be thoroughly cleaned with enzymatic or nonenzymatic detergents before it is subjected to a high-level disinfection or

sterilization process., respectively. Brushes should be used, when possible, to effectively clean the transducer assemblies, especially the lumens. One investigation showed that the needle guide and prostate probe can be effectively disinfected with glutaraldehyde, but the needle guide must be disassembled from the transducer assembly *(376)*.

The FDA issued a Public Health Notification in June 2006 as a result of follow-up to the Department of Veterans Affairs (VA), Veterans Health Administration Patient Safety Alert related to a particular company's ultrasound transducer assemblies. During patient safety rounds, the lumen of a needle guide of an ultrasound transducer assembly was found to be soiled. The FDA guidance consisted of several steps (see http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062086.htm for the complete method recommend by the FDA). We have evaluated the FDA steps and suggest some modifications (Table 80-4). Do not reuse items labeled for single use (e.g., single-use biopsy needles). Additional recommendations may be available in the operator's manuals or user guides. It is important that these recommendations be consistent with disinfection and sterilization guidelines/principles or that these recommendations have been validated by appropriate scientific studies. Do not use any disinfectant that can cause irreparable damage to the materials used to construct the probe. For example, if an alcohol rinse is not compatible with the probe, rinse with sterile water (not filtered water, or tap water) and do not rinse with alcohol. These recommendations could be adapted to all ultrasonic prostate probes to include those with an external needle guide attachment.

TABLE 80-4

Recommendations for Reprocessing Transrectal Ultrasound Prostate Biopsy Probes[a]

Cleaning
- Clean immediately after use
- Disassemble the transducer (remove needle guide from the probe)
- Brush clean (if possible) or flush each lumen and thoroughly clean all surfaces of reusable components with enzymatic or nonenzymatic detergent
- Rinse with tap water
- Dry with disposable cloth/towel or air dry
- Visibly inspect the entire device to ensure it is clean

High-Level Disinfection or Sterilization
- Steam sterilize all heat-stable reusable components
- Alternatively, high-level disinfect the probe and the needle guide separately following disassembly
- High-level disinfect all heat sensitive components (ensure disinfectant reaches all areas inside the lumens and the minimum effective concentration of the high-level disinfectant is monitored)
- Rinse with sterile water, filtered water, or tap water (FDA specifies sterile water for rinsing)
- If filtered water or tap water is used, follow with an alcohol rinse (not immersion of the probe in alcohol) to enhance drying (and no residual water is left for microbial growth)
- Dry the device
- Appropriately store the device to ensure the device is not recontaminated

[a]Users should be familiar with the manufacturer's recommendations for use and disinfection of the specific device used by the facility. (Modified from Rutala WA, Gergen MF, Weber DJ. Disinfection of a probe used in ultrasound-guided prostate biopsy. *Infect Control Hosp Epidemiol* 2007;28.)

Infrared Coagulation (IRC)

Infrared coagulation is a widely used method for treating hemorrhoids. The procedure involves applying infrared light to compress and seal hemorrhoid veins. The manufacturer of the device sells a sterile disposable sheath and states removing and soaking lightguides between procedures is no longer required. The manufacturer also states that the lightguide is damaged by immersion in a disinfectant as the lightguide is not sealed at the end and disinfectant gets between the quartz glass and the covering.

As mentioned, the CDC guideline recommends immersion for reprocessing endocavitary probes with covers because integrity of the cover is compromised. Since the lightguide cannot be immersed, we investigated an alternative procedure. This procedure involved wiping the probe for 2 minutes with a 1:10 bleach (5,000 ppm) and after that is completed, wipe the probe with sterile water and let the probe air dry. This procedure has been found effective in eliminating >6-$\log_{10}$ reduction (7.8×10^6) of *Mycobacterium terrae* and is used at our hospital for decontamination of the sheathed device after use *(377)*.

Laryngoscopes

Laryngoscopes are routinely used to view the vocal cords and larynx and for airway management. It typically consists of a blade that connects to a handle, which usually contains two batteries that powers the light source. Limited guidelines are available for reprocessing laryngoscope blades and handles, and hospital practices vary *(378,379)*. For example, some guidelines and hospitals low-level disinfect the handle as it does not have direct contact with a mucous membrane, and others recommend that the handle be high-level disinfected to prevent disease transmission. While blades have been linked to healthcare-associated infections, handles have not been directly linked to healthcare-associated infections (HAIs), but contamination with blood and other potentially infected materials during clinical use suggests its potential *(380)* and the blade and handle function together. When patient-ready handles were evaluated for blood or bacterial contamination, a high incidence of contamination was found *(380,381)*. For this reason, it is ideal that the blades and handles be high-level disinfe cted or sterilized even if a protective barrier or sheath is used during the procedure.

DISINFECTION OF SURFACES

Room Decontamination Units (Hydrogen Peroxide Vapor and Ultraviolet Light)

Surface disinfection of noncritical surfaces and equipment is normally performed by manually applying a liquid disinfectant to the surface with a cloth, wipe, or mop. Recent

studies have identified significant opportunities in hospitals to improve the cleaning of frequently touched objects in the patient's immediate environment (65*,382,383*). For example, of 20,646 standardized environmental surfaces (14 types of objects), only 9,910 (48%) were cleaned at terminal room cleaning (65). Epidemiologic studies have shown that patients admitted to rooms previously occupied by individuals infected or colonized with MRSA (384), VRE *(385)*, or *C. difficile (386)* are at significant risk of acquiring these microorganisms from contaminated environmental surfaces. These data have led to the development of room decontamination units that avoid the problems associated with the thoroughness of terminal cleaning activities in patient rooms.

Hydrogen peroxide vapor (HPV) has been used increasingly for the decontamination of biological safety cabinets and rooms in healthcare (387*,388–397*). These investigators found that HPV is a highly effective method for eradicating various pathogens (e.g., MRSA, *M. tuberculosis*, *Serratia*, *Clostridium difficile* spores, *Clostridium botulinum* spores) from rooms, furniture, and equipment. This room decontamination system has not only been found to be effective in eradicating pathogens from contaminated surfaces but has also been found to significantly reduced the incidence of *C. difficile* infection rates (387). Otter et al. *(398)* reported that the HPV decontamination required a mean time of 2 hours and 20 minutes, compared with 32 minutes for conventional cleaning. A summary of the advantages and disadvantages of hydrogen peroxide vapor for room decontamination is shown in Table 80-5.

Ultraviolet C light units have also been proposed for room decontamination. One unit (Tru-D) uses an array of UV sensors, which determines and targets shadowed areas to deliver a measured dose of UV energy that destroys microorganisms. This unit is fully automated, activated by a hand-held remote, and the room ventilation does not need to be modified. It uses UV-C (254 nm range) to decontaminate surfaces. It measures UV reflected from walls,

TABLE 80-5

Advantages and Disadvantages for Room Decontamination by Hydrogen Peroxide Vapor (HPV) and Ultraviolet C

Room Decontamination	*Advantages*	*Disadvantages*
HPV	• Efficacious (reliable biocidal activity) against wide range of pathogens (e.g., kills ~6 logs spores) • Surfaces and equipment decontaminated • Decrease incidence of disease (*C. difficile*) • Residue free and does not give rise to health and safety concerns (aeration units convert HPV into oxygen and water) • Uniform distribution in the room via an automated dispersal system • Useful for disinfecting complex equipment and furniture	• Contribution of the environment to disease transmission ~5% • Only done at terminal disinfection (not daily cleaning) • Rapid recontamination of the environment • All patients must be removed from the area • Decontamination takes ~3–5 h (bed turnover time: 72 min) • HVAC system must be disabled to prevent unwanted dilution of HPV during the exposure; room sealed with tape • Costs • Does not remove dust and stains that are important to patients/visitors • Sensitive parameters-HP concentration 280 ppm, temperature: 26–28°C, relative humidity: 48–57% • Long-term use exposure damage from microcondensation to sensitive electronics may occur? • Does not remove dust and stains
UVC	• Reliable biocidal activity against a wide range of pathogens (e.g., kills 3–4 logs vegetative bacteria) • Surfaces and equipment decontaminated • Room decontamination is rapid (~15 m) for vegetative bacteria • HVAC system does not need to be disabled • Room does not need to be sealed • It is residual free and does not give rise to health and safety concerns • No consumable products, so costs are capital equipment and staff time • Good distribution of UV energy via an automated monitoring system	• Do not know if use decreases the incidence of HAIs • Only done at terminal disinfection (i.e., not daily cleaning) • All patients and staff must be removed from the room/area • Capital equipment costs are substantial • Does not remove dust and stains • Sensitive use parameters (e.g., UV dose delivered)

(Modified from Rutala WA, Weber DJ. Disinfection and sterilization in healthcare facilities. In: Lautenbach E, Woeltje KF, Malani PN, eds. *Practical healthcare epidemiology*. Chicago, IL: University of Chicago Press, 2010:61–80.)

ceiling, floors, or other treated areas and calculated the operation time to deliver the programmed lethal dose for pathogens *(399)*. After UV dose is delivered, it will power down and an audible alarm will notify the operator. In one study, the effectiveness of UV-C radiation of MRSA, VRE, and MDR-*Acinetobacter* on surfaces was >99.9% within 15 minutes and 99.84% for C. difficile spores with 50 minutes. In rooms occupied by patients with MRSA, UV-C irradiation of <15 minutes reduced MRSA per surface site from 384 CFU to 19 CFU and reduced the number of positive samples for MRSA from 20.3% (81/400) to 0.5% (2/400) *(400)*.

OTHER DISINFECTION ISSUES

OSHA Bloodborne Pathogen Standard

In December 1991, the OSHA promulgated a standard entitled "Occupational Exposure to Bloodborne Pathogens" to eliminate or minimize occupational exposure to bloodborne pathogens *(401)*. One component of this requirement is that all equipment and environmental and working surfaces be cleaned and decontaminated with an appropriate disinfectant after contact with blood or other potentially infectious materials. While the OSHA standard does not specify the type of disinfectant or procedure, the OSHA original compliance document *(402)* suggested that a germicide must be tuberculocidal to kill the HBV (e.g., phenolic, chlorine). However, in February 1997, OSHA amended its policy and stated that EPA-registered disinfectants that are labeled as effective against HIV and HBV would be considered as appropriate disinfectants "…provided such surfaces have not become contaminated with agent(s) or volumes of or concentrations of agent(s) for which higher level disinfection is recommended." When bloodborne pathogens other than HBV or HIV are of concern, OSHA continues to require the use of EPA-registered tuberculocidal disinfectants or hypochlorite solution (diluted 1:10 or 1:100 with water) *(172,403)*. Recent studies demonstrate that, in the presence of large blood spills, a 1:10 final dilution of EPA-registered hypochlorite solution initially should be used to inactivate bloodborne viruses *(54,404)* to minimize risk of disease to the healthcare worker from percutaneous injury during the clean-up process.

Emerging Pathogens (*Cryptosporidium*, *Helicobacter pylori*, *Escherichia coli* O157:H7, Rotavirus, Human Papillomavirus, Norovirus, Severe Acute Respiratory Syndrome [SARS] Coronavirus, Avian Influenza Virus (H5N1), Novel Influenza H1N1, Hepatitis C Virus, Creutzfeldt-Jacob Disease (CJD), Antibiotic-resistant bacteria [VRE, MRSA])

Emerging pathogens are of growing concern to the general public and infection preventionists. Relevant pathogens include *Cryptosporidium parvum*, *Helicobacter pylori*, *E. coli* O157:H7, rotavirus, human papillomavirus, norovirus, SARS coronavirus, avian influenza virus, novel influenza H1N1, hepatitis C virus, CJD, multidrug-resistant bacteria such as MRSA. The susceptibility of each of these pathogens to chemical disinfectants/sterilants has been studied. With the exceptions discussed below, all of these emerging pathogens are susceptible to currently available chemical disinfectants/sterilants (11*,229,405*).

Cryptosporidium *Cryptosporidium* is resistant to chlorine at concentrations used in potable water. *C. parvum* is not completely inactivated by most disinfectants used in healthcare including ethyl alcohol *(193)*, glutaraldehyde *(193,406)*, 5.25% hypochlorite *(193)*, peracetic aci *(193)*, ortho-phthalaldehyde *(193)*, phenol *(193,406)*, povidone-iodine *(193,406)*, and quaternary ammonium compounds *(193)*. The only chemical disinfectants/sterilants able to inactivate greater than a 3-$\log_{10}$ reduction of *C. parvum* were 6% and 7.5% hydrogen peroxide *(193)*. Sterilization methods will fully inactivate *C. parvum*, including steam *(193)*, ETO, *(193,407)* and hydrogen peroxide gas plasma *(193)*. Although most disinfectants are ineffective against *C. parvum*, current cleaning and disinfection practices appear satisfactory to prevent healthcare-associated transmission. For example, endoscopes are unlikely to represent an important vehicle for the transmission of *C. parvum* because the results of bacterial studies indicate mechanical cleaning will remove approximately 10^4 microorganisms and drying rapidly results in loss of *C. parvum* viability (e.g., 30 minutes, 2.9-$\log_{10}$ decrease, and 60 minutes, 3.8-$\log_{10}$ decrease) *(193)*.

E. coli O157:H7 Chlorine at approximately 1 ppm has been found capable of eliminating approximately 4-$\log_{10}$ of *E. coli* O157:H7 within 1 minute in a suspension test *(95)*. Electrolyzed oxidizing water at 23°C was effective in 10 minutes in producing a 5-$\log_{10}$ decrease in *E. coli* O157:H7 inoculated onto kitchen cutting boards *(408)*. The following disinfectants eliminated >5-$\log_{10}$ of *E. coli* O157:H7 within 30 seconds: a quaternary ammonium compound, a phenolic, a hypochlorite (1:10 dilution of 5.25% bleach), and ethanol *(48)*.

Helicobacter pylori Data are available on the susceptibility of *H. pylori* to disinfectants. Using a suspension test, Akamatsu and colleagues assessed the effectiveness of a variety of disinfectants against nine strains of *H. pylori (93)*. Ethanol (80%) and glutaraldehyde (0.5%) killed all strains within 15 seconds; chlorhexidine gluconate (0.05%, 1.0%), benzalkonium chloride (0.025%, 0.1%), alkyldiaminoethylglycine hydrochloride (0.1%), povidone-iodine (0.1%), and sodium hypochlorite (150 ppm) killed all strains within 30 seconds. Both ethanol (80%) and glutaraldehyde (0.5%) retained similar bactericidal activity in the presence of organic matter, while the other disinfectants showed reduced bactericidal activity. In particular, the bactericidal activity of povidone-iodine (0.1%) and sodium hypochlorite (150 ppm) was markedly decreased in the presence of dried yeast solution with killing times increased to 5 to 10 minutes and 5 to 30 minutes, respectively. Disinfection of experimentally contaminated endoscopes using 2% glutaraldehyde (10, 20, 45 minutes exposure times) or the peracetic acid system (with and without active peracetic acid) has been demonstrated to be effective in eliminating *H. pylori (291)*. Epidemiologic investigations of patients who had undergone endoscopy with endoscopes mechanically washed and disinfected with 2.0% to 2.3% glutaraldehyde have revealed no evidence of person-to-person transmission of *H. pylori (303,409)*.

Rotavirus An outbreak of healthcare-associated rotavirus gastroenteritis on a pediatric unit has been reported *(410)*. Person-to-person via the hands of healthcare workers was proposed as the mechanism of transmission. Prolonged survival of rotavirus on environmental surfaces (90 minutes to more than 10 days at room temperature) and hands

(>4 hours) has been demonstrated. Rotavirus suspended in feces can survive for a longer period of time *(411,412)*. Vectors for this infection have included air, hands, fomites, water, and food *(412)*. Products with demonstrated efficacy (>3-$\log_{10}$ reduction in virus) against rotavirus within 1 minute include 95% ethanol, 70% isopropanol, some phenolics, 2% glutaraldehyde, 0.35% peracetic acid, and some quaternary ammonium compounds *(52,413–415)*. In a human challenge study, a disinfectant spray (0.1% ortho-phenylphenol and 79% ethanol), sodium hypochlorite (800 ppm free chlorine), and a phenol-based product (14.7% phenol diluted 1:256 in tapwater) when sprayed onto contaminated stainless steel disks were effective in interrupting the transfer of a human rotavirus from stainless steel disk to fingerpads of volunteers after an exposure time of 3 to 10 minutes. A quaternary ammonium product (7.05% quaternary ammonium compound diluted 1:128 in tapwater) and tapwater allowed transfer of virus *(47)*.

Human Papillomavirus Human papillomavirus (HPV) is an extremely common sexually acquired infection and is considered the cause of cervical cancer. While there are limited data regarding the inactivation of HPV by disinfectants because *in vitro* replication of complete virions has only been achieved recently, a pseudotype HPV-16 and a bovine papillomavirus were used in an infectivity assay to evaluate potential methods of disinfecting HPV-contaminated surfaces *(416)*. In this study, the bovine papillomavirus demonstrated substantial sensitivity to 70% ethanol, and all infectivity was eliminated for pseudotype HPV-16 virions. Studies with the bovine papillomavirus have shown a 99.9% inactivation with a 0.3% povidone-iodine solution *(417)*.

Pandemic Influenza The effect of chlorine on the H5N1 subtype of the avian influenza virus was evaluated. Free chlorine concentrations typically used in drinking water treatment (0.52 to 1.08 ppm) were sufficient to inactivate the virus by >3-$\log_{10}$ with an exposure time of 1 minute *(418)*. Common disinfectants (e.g., 70% ethanol, 70% propanol) and detergents were effective in inactivating influenza A virus H1N1 within 1 minute in surface and suspension tests *(57)*.

Norovirus More is known about the inactivation of norovirus (members of the family *Caliciviridae* and important causes of gastroenteritis in humans) even though they cannot easily be grown in tissue culture. Improper disinfection of environmental surfaces contaminated by the feces or vomitus of infected patients is believed to play a role in the spread of noroviruses in some settings *(419,420)*. Prolonged survival of a norovirus surrogate (i.e., feline calicivirus [FCV], a closely related cultivable virus) has been demonstrated (e.g., at room temperature, FCV in a dried state survived for between 18 and 21 days) *(260)*. Because of the limited ability to culture noroviruses, data are based on surrogates such as murine norovirus or feline calicivirus or an assessment for the presence of human norovirus genome by RT-PCR. Both methods have important drawbacks. The surrogate viruses may not mimic the susceptibililty of human noroviruses to germicides and the use of RT-PCR may detect nonviable norovirus (421).

Inactivation studies with FCV have shown the effectiveness of chlorine, glutaraldehyde, and iodine-based products, whereas the quaternary ammonium compound, detergent, and ethanol failed to inactivate the virus completely *(260)*. Sattar also evaluated the effectiveness of several disinfectants against the feline calicivirus and found that bleach diluted to 1,000 ppm of available chlorine reduced infectivity of FCV by 4.5 logs in 1 minute. Other effective (reduction factor of >4-$\log_{10}$ in virus) disinfectants included accelerated hydrogen peroxide-5,000 ppm (3 minutes); chlorine dioxide-1,000 ppm chlorine (1 minute); a mixture of four quaternary ammonium compounds-2,470 ppm (10 minutes); 79% ethanol with 0.1% quaternary ammonium compound (3 minutes); and 75% ethanol (10 minutes) *(422)*. Gehrke et al. *(423)* showed that 70% ethanol and 70% 1-propanol reduced FCV by a 3- to 4-$\log_{10}$ reduction in 30 seconds, and Whitehead and McCue showed >4-$\log_{10}$ reduction with 100 ppm chlorine in a 1-minute contact time *(424)*.

SARS or Severe Acute Respiratory Syndrome The CDC announced that a previously unrecognized human virus from the coronavirus family is the cause of a recently described syndrome of SARS or Severe Acute Respiratory Syndrome *(425)*. Two coronaviruses that are known to infect humans causes approximately one-third of common colds and may cause gastroenteritis. The virucidal efficacy of chemical germicides against coronavirus has been investigated. Sattar et al. *(355)* investigated the activity of several disinfectants against coronavirus 229E and found several disinfectants were effective after a 1-minute contact time including sodium hypochlorite (at a free chlorine concentration of 1,000 ppm and 5,000 ppm), 70% ethyl alcohol, and povidone-iodine (1% iodine). Saknimit et al. *(426)* showed that 70% ethanol, 50% isopropanol, 0.05% benzalkonium chloride, 50 ppm iodine in iodophor, 0.23% sodium chlorite, 1% cresol soap, and 0.7% formaldehyde inactivated >3 logs of two animal coronaviruses (mouse hepatitis virus, canine coronavirus) after a 10-minute exposure time. Sizun et al. *(427)* demonstrated the activity of povidone-iodine against human coronaviruses 229E and OC43. Since the SARS coronavirus is stable in feces and urine at room temperature for at least 1–2 days (World Health Organization, 2003; http://www.who.int/csr/sars/survival_2003_05_04/en/index.html), surfaces may be a possible source of contamination and lead to infection with the SARS coronavirus and should be disinfected. The antiviral action of common disinfectants (0.21% sodium hypochlorite, 0.23% pine oil, or 0.10% of a quaternary compound with 79% of ethanol) against murine hepatitis virus, a surrogate for SARS coronavirus, demonstrated a 3-$\log_{10}$ reduction or better in a 30-second contact time *(56)* Until more precise information is available, assume the environment in which SARS patients are housed is heavily contaminated and thoroughly disinfect the room and equipment daily and after the patient is discharged. Use EPA-registered disinfectants or 1:100 dilution of household bleach and water for surface disinfection and disinfection on noncritical patient-care equipment. High-level disinfection and sterilization of semicritical and critical medical devices, respectively, does not need to be altered for patients with known or suspected SARS.

Creutzfeldt Jakob Disease (CJD) The prions of CJD and other transmissible spongiform encephalopathies exhibit an unusual resistance to conventional chemical and physical decontamination methods. Because the CJD agent

is not readily inactivated by conventional disinfection and sterilization procedures and because of the invariably fatal outcome of CJD, the procedures for disinfection and sterilization of the CJD prion have been both cautious and controversial for many years. Recommendations for disinfection and sterilization of prion-contaminated medical devices are as follows (428). Instruments should be kept wet or damp until they are decontaminated, and they should be decontaminated as soon as possible after use. Dried films of tissue are more resistant to prion inactivation by steam sterilization compared to tissues that were kept moist. This may relate to the rapid heating that occurs in the film of dried material compared to the bulk of the sample, and the rapid fixation of the prion protein in the dried film *(429)*. It also appears that prions in the dried portions of the brain macerates are less efficiently inactivated than undisturbed tissue. For high-risk tissues (brain, spinal cord, and eyes), high-risk patients, and critical or semicritical medical devices, it is recommended to clean the device and sterilize by one of four methods, using steam sterilization as recommended in the scientific literature (428,*430*) (option 1 or 2) or using a combination of sodium hydroxide and autoclaving as recommended by the World Health Organization *(431)* (option 3 or 4):

1. Autoclave at 134°C for 18 minutes in a prevacuum sterilizer.
2. Autoclave at 132°C for 1 hour in a gravity displacement sterilizer.
3. Immerse in 1N NaOH [1N NaOH is a solution of 40 g NaOH in 1 L of water] for 1 hour; remove and rinse in water, then transfer to an open pan and autoclave [121°C gravity displacement or 134°C porous or prevacuum sterilizer] for 1 hour.
4. Immerse instruments in 1N NaOH for 1 hour and heat in a gravity displacement sterilizer at 121°C for 30 minutes. However, the combination of sodium hydroxide and steam sterilization may be deleterious to surgical instruments, sterilizers, as well as sterilizer operators who would be breathing vaporized chemicals unless engineering controls or use of PPE prevents exposure *(432)*.

The temperature should not exceed 134°C because under certain conditions the effectiveness of autoclaving actually declines as the temperature is increased (e.g., 136°C, 138°C) *(433)*. Prion-contaminated medical devices that are impossible or difficult to clean should be discarded. Flash sterilization should not be used for reprocessing. To minimize environmental contamination, noncritical environmental surfaces should be covered with plastic-backed paper and when contaminated with high-risk tissues the paper should be properly discarded. Environmental surfaces (noncritical) contaminated with high-risk tissues (e.g., laboratory surfaces) should be cleaned and then spot decontaminated with a 1:10 dilution of hypochlorite solutions (428).

To minimize the possibility of use of neurosurgical instruments that have been potentially contaminated during procedures performed on patients in whom CJD is later diagnosed, healthcare facilities should consider using the sterilization guidelines outlined above for neurosurgical instruments used during brain biopsy done on patients in whom a specific lesion has not been demonstrated (e.g., by magnetic resonance imaging or computerized tomography scans). Alternatively, neurosurgical instruments used in such patients could be disposable *(430)* or instruments quarantined until the pathology of the brain biopsy is reviewed and CJD excluded (428).

Multidrug-Resistant Microorganisms There are no data to show that antibiotic-resistant bacteria are less sensitive to the liquid chemical germicides than antibiotic-sensitive bacteria at currently used germicide contact conditions and concentrations *(434)*. Several studies have found antibiotic-resistant hospital strains of common healthcare-associated pathogens (i.e., *Enterococcus*, *P. aeruginosa*, *Klebsiella pneumoniae*, *E. coli*, *S. aureus*, and *S. epidermidis*) to be equally susceptible to disinfectants as antibiotic-sensitive strains *(48,435–437)*. The susceptibility of glycopeptide-intermediate *S. aureus* was similar to vancomycin-susceptible, methicillin-resistant *S. aureus (438)*. Based on these data, routine disinfection and housekeeping protocols do not need to be altered because of antibiotic resistance provided the disinfection method is effective *(439,440)*. A study that evaluated the efficacy of selected cleaning methods (e.g., QUAT-sprayed cloth, and QUAT-immersed cloth) for eliminating VRE found that currently used disinfection processes are likely highly effective in eliminating VRE. Despite the *in vitro* effectiveness of disinfectants, it is critical that the disinfectant have contact with the contaminated surface in order to remove and/or inactivate the pathogen *(439)*.

Disinfection of HBV-, HCV-, HIV- or Tuberculosis-Contaminated Devices

The CDC recommendation for high-level disinfection of HBV-, HCV-, HIV- or tuberculosis-contaminated devices is appropriate because experiments have demonstrated the effectiveness of high-level disinfectants to inactivate these and other pathogens that may contaminate semicritical devices *(53,94,172,218,278,293,302,404,441–457)*. Nonetheless, some healthcare facilities have modified their disinfection procedures when endoscopes are used with a patient known or suspected to be infected with HBV, HIV, or *M. tuberculosis (38,458)*. This is inconsistent with the concept of Standard Precautions that presumes that all patients are potentially infected with bloodborne pathogens *(172)*. Several studies have highlighted the inability to distinguish HBV- or HIV-infected patients from noninfected patients on clinical grounds *(459–461)*. It also is likely that mycobacterial infection will not be clinically apparent in many patients. In most instances, hospitals that altered their disinfection procedure used ETO sterilization on the endoscopic instruments because they believed this practice reduced the risk of infection *(38,458)*. ETO is not routinely used for endoscope sterilization because of the lengthy processing time. Endoscopes and other semicritical devices should be managed the same way whether or not the patient is known to be infected with HBV, HCV, HIV, or *M. tuberculosis*.

An evaluation of a manual disinfection procedure to eliminate HCV from experimentally contaminated endoscopes provided some evidence that cleaning and 2% glutaraldehyde for 20 minutes should prevent transmission *(455)*. Using experimentally contaminated hysteroscopes, Sartor and colleagues detected HCV by polymerase chain

reaction (PCR) in one (3%) of 34 samples following cleaning with a detergent, but no samples were positive following treatment with a 2% glutaraldehyde solution for 20 minutes *(292)*. Rey and colleagues demonstrated complete elimination of HCV (as detected by PCR) from endoscopes used on chronically infected patients following cleaning and disinfection for 3 to 5 minutes in glutaraldehyde *(290)*. Similarly, Chanzy and coworkers used PCR to demonstrate complete elimination of HCV following standard disinfection of experimentally contaminated endoscopes *(455)*, while Ishino and colleagues found that endoscopes used on patients who were positive for HCV antibody had no detectable HCV RNA after high-level disinfection *(462)*. The inhibitory activity of a phenolic and a chlorine compound on HCV showed that the phenolic inhibited the binding and replication of HCV, but the chlorine was ineffective, probably due to its low concentration and its neutralization in the presence of organic matter *(463)*. Recent experiments using cell-culture grown HCV showed 0.5% glutaraldehyde, 0.05% peracetic acid, and ethanol were able to completely inactivate HCV within 1 minute *(55)*.

Inactivation of Biothreat Agents

Recent publications have highlighted the concern about the potential for biological terrorism *(464,465)*. The CDC has categorized several agents as "high priority" because they can be easily disseminated or transmitted person-to-person, cause high mortality, and are likely to cause public panic and social disruption *(466)*. These agents include *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), variola major (smallpox), *Clostridium botulinum* toxin (botulism), *Francisella tularensis* (tularemia), filoviruses (Ebola hemorrhagic fever, Marburg hemorrhagic fever); and arenaviruses (Lassa [Lassa fever], Junin [Argentine hemorrhagic fever]), and related viruses *(466)*.

A few comments can be made regarding the role of sterilization and disinfection of potential agents of bioterrorism. First, the susceptibility of these agents to germicides *in vitro* is similar to other related pathogens. For example, variola is similar to vaccinia *(219)* and *B. anthracis* is similar to *B. atrophaeus* (formerly *B. subtilis*) *(467)*. Thus, one can extrapolate from the larger database available on the susceptibility of genetically similar microorganisms. Second, many of the potential bioterrorist agents are stable enough in the environment that contaminated environmental surfaces or fomites could lead to transmission of agents such as *B. anthracis*, *F. tularensis*, variola major, *C. botulinum* toxin, and *C. burnetii (468)*. Third, data suggest that current disinfection and sterilization practices are appropriate for the management of patient-care equipment and environmental surfaces when potentially contaminated patients are evaluated and/or admitted in a healthcare facility following exposure to a bioterrorist agent. For example, sodium hypochlorite may be used for surface disinfection (see http://www.epa.gov/pesticides/factsheets/chemicals/bleachfactsheet.htm). In instances where the healthcare facility is the site of a bioterrorist attack, environmental decontamination may require special decontamination procedures (e.g., chlorine dioxide gas for anthrax spores; see http://www.epa.gov/pesticides/factsheets/chemicals/chlorinedioxidefactsheet.htm). The effectiveness of sporicides to decontaminate rooms, buildings, and surfaces contaminated with biothreat agents is being investigated by the EPA and others *(469,470)*. These studies demonstrate that the effectiveness of sporicides varies based on many factors such as surface composition, exposure conditions, and method of application. For example, one study found that spraying or spreading chlorine dioxide resulted in only a 1-$\log_{10}$ reduction against *B. anthracis* (Sterne strain) because the chlorine dioxide gas was rapidly vaporized from the solutions compared to an 8-$\log_{10}$ reduction with aqueous chlorine dioxide in sealed tubes *(471)*. Use of disinfectants for decontamination following a bioterrorist attack requires crises exemption from the EPA (see http://www.epa.gov/opprd001/section18/). Of only theoretical concern is the possibility that a bioterrorist agent could be engineered to be less susceptible to disinfection and sterilization processes.

Toxicological, Environmental, and Occupational Concerns

Health hazards associated with the use of germicides in healthcare vary from mucous membrane irritation to death, with the latter involving accidental injection by mentally disturbed patients *(472)*. While variations exist in the degree of toxicity *(154,473–475)*, all disinfectants should be used with the proper safety precautions *(476)* and for the intended purpose only.

The key factors associated with assessing the health risk of a chemical exposure include the duration, intensity (i.e., how much chemical is involved), and route (e.g., skin, mucous membranes, and inhalation) of the exposure. Toxicity may be acute or chronic. Acute toxicity usually results from an accidental spill of a chemical substance. The exposure of personnel is sudden and often produces an emergency situation. Chronic toxicity results from repeated exposure to low levels of the chemical over a prolonged period. The responsibility for informing workers of the chemical hazards in the workplace and implementing control measures rests with the employer. The OSHA Hazard Communication Standard (29 CFR 1910.1200, 1915.99, 1917.28, 1918.90, 1926.59, and 1928.21) requires manufacturers and importers of hazardous chemicals to develop Material Safety Data Sheets (MSDSs) for each chemical or mixture of chemicals. Employers must have MSDSs readily available to employees who work with the products and thus may be exposed.

Exposure limits have been published for many chemicals used in healthcare to aid in providing a safe environment and are discussed in each section of this guideline as relevant. Only the exposure limits published by OSHA carry the legal force of regulations. OSHA publishes a limit as a time-weighted average (TWA), that is, the average concentration for a normal 8-hour work day and a 40-hour work week to which nearly all workers may be repeatedly exposed to a chemical without adverse health effects. For example, the permissible exposure limit (PEL) for ETO is 1.0 ppm, 8 hour TWA. The National Institute for Occupational Safety and Health (NIOSH) develops recommended exposure limits (RELs). RELs are occupational exposure limits recommended by NIOSH as being protective of worker health and safety over a working lifetime. This limit is frequently expressed as a 40-hour TWA exposure for up to 10 hours per day during a 40-per-hour work week. These exposure limits are designed for inhalation exposures.

Irritant and allergic affects may occur below the exposure limits, and skin contact may result in dermal effects or systemic absorption apart from inhalation. The current RELs can be accessed via the NIOSH webpage (www.cdc.gov/niosh). Guidelines on exposure limits are also provided by the American Conference of Governmental Industrial Hygienists (ACGIH) *(477)*. Additionally, information about workplace exposures and methods to reduce them (e.g., work practices, engineering controls, PPE) is available on the OSHA (www.osha.gov) and the NIOSH websites.

Some states have excluded the disposal of certain chemical germicides (e.g., glutaraldehyde, formaldehyde, and some phenols) or limited certain concentrations via the sewer system. These rules are intended to minimize environmental harm. If healthcare facilities exceed the maximum allowable concentration for a chemical (e.g., ≥5.0 mg/L), they have three options. First, they can switch to alternative products. For example, they can change from glutaraldehyde to another disinfectant for high-level disinfection or from phenolics to quaternary ammonium compounds for low-level disinfection. Second, the healthcare facility can collect the disinfectant and dispose of it as a hazardous chemical. Third, they can use a commercially available small-scale treatment method (e.g., neutralize glutaraldehyde with glycine).

The safe disposal of regulated chemicals is important throughout the medical community. In the case of disposal of large volumes of spent solutions, users may decide to neutralize the microbicidal activity prior to disposal (e.g., glutaraldehyde). This can be accomplished by reaction with chemicals such as sodium bisulfite *(478,479)* or glycine *(480)*.

European authors have suggested that disinfection by heat rather than chemicals should be used for instruments and ventilation therapy equipment. The concerns for chemical disinfection include the toxic side effects for the patient caused by chemical residues on the instrument or object; occupational exposure to toxic chemicals; and the danger of recontamination by rinsing the disinfectant with microbially contaminated tapwater *(481)*.

***Clostridium difficile*: Role of the Environment and Disinfection Prevention Strategies** *Clostridium difficile* is an enteric bacterial pathogen that causes an infection that results in a broad spectrum of disease ranging from mild diarrhea to life-threatening pseudomembraneous colitis. Although *C. difficile* infection (CDI) has been frequently encountered in hospitals and long-term care facilities for many years, the rates in the United States have tripled from 2000 to 2005, and disease morbidity and mortality have also increased *(178,482–484)*. This trend has been associated with the emergence of a new, highly virulent strain of *C. difficile* that produces greater quantities of toxins A and B and a separate binary toxin. To effectively manage this disease and keep informed of its changing epidemiology, optimal strategies in CDI surveillance, diagnosis, treatment, antibiotic control, and infection prevention are warranted *(485)*. This chapter only considers the role of the environment in transmission and the infection prevention strategies that prevent transmission.

The two major reservoirs of *C. difficile* in healthcare settings are humans, who are colonized or infected, and inanimate objects. Patients with symptomatic intestinal infection are thought to be major reservoir. The three mechanisms of transfer of *C. difficile* in the healthcare setting are: (a) direct transfer of *C. difficile* from a colonized or infected patient to the environment (e.g., rectal thermometer, commode, over-the-bed table) and contact by another patient and inoculation into the mouth (Fig. 80-2, section A); (b) direct transfer from a colonized or an infected patient to a healthcare worker via contact and transfer via hands to a noncolonized or noninfected patient (Fig. 80-2, section B); and (c) indirect transfer via healthcare worker contact (or any other person) with the contaminated environment and transfer to a noncolonized or noninfected patient (Fig. 80-2, section C) *(486)*. These modes of transmission can be prevented by infection prevention strategies such as Contact Precautions, hand hygiene with soap and water, and removing or inactivating the *C. difficile* spores from the inanimate environment (environmental surfaces or patient-care equipment).

Several factors facilitate the environmental route of transmission with *C. difficile*. First, *C. difficile* contaminates the environment of patients colonized or infected with *C. difficile*. Second, the *C. difficile* spore can survive in the hospital environment for up to 5 months *(487)*, whereas the vegetative bacteria die, due to desiccation, within 15 minutes in room air *(488)*. Vegetative *C. difficile* can remain viable on moist surfaces for up to 3 hours in room air. These data suggest that moist surfaces in hospitals (e.g., toilets, sinks, moist dressings) may provide a suitable environment for vegetative *C. difficile* to persist for several hours *(488)*. The spore is also more resistant to the effect of the gastric acids in the stomach *(489)*. Thus, the spore is the more likely bacterial form that is important in disease transmission that must be inactivated and/or removed by surface disinfection. Since the *C. difficile* spores are more likely involved in disease transmission than are vegetative bacteria, a claim based only on the vegetative bacteria would likely be potentially misleading and be incompletely effective in preventing disease transmission. Thus, the recent EPA letter preventing claims based on the inactivation of vegetative bacteria is both soundly based in science and judicious public health policy (F. Sanders, EPA, written communication, September 2008). Third, since spores are relatively resistant to inactivation by low-level disinfectants, a higher level of disinfection is needed to prevent an environmental mode of spread.

Transmission of *C. difficile* to a patient via transient hand carriage on healthcare workers' hands is thought to be the most likely mode of transmission (Fig. 80-2, sections B and C). Transient hand carriage can occur through patient or environmental contact. Fifty-nine percent of 35 healthcare workers had positive cultures for *C. difficile* from their hands after direct contact with a culture-positive patient *(490)*. *C. difficile* can be found at multiple sites of patients with CDI including groin, chest, abdomen, forearm, and hands and can be transferred to the care provider's hands *(491)*.

While healthcare workers are the most likely mode of transmission, the hands may become contaminated by either patient contact or contact with a contaminated environment or both. *C. difficile* contamination has been found in rooms of patients that are colonized or infected with

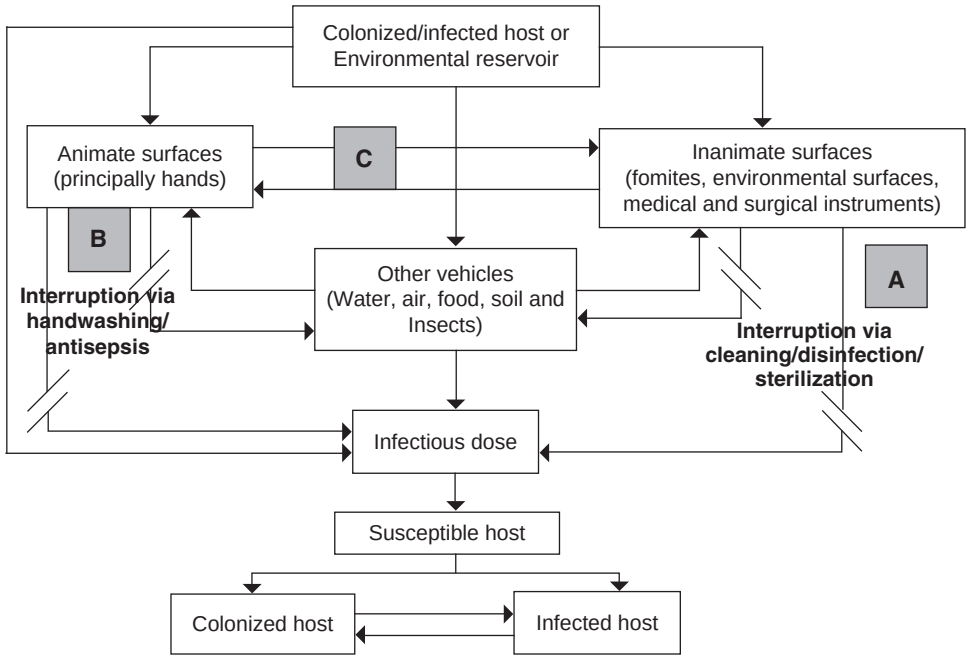

FIGURE 80-2 Transmission of *Clostridium difficile* via animate and inanimate surfaces. The three mechanisms of transfer of *C. difficile* in the healthcare setting are: (i) direct transfer of *C. difficile* from a colonized or an infected patient to the environment (e.g., rectal thermometer, commode, over-the-bed table) and contact by another patient and inoculation into the mouth (**section A**); (ii) direct transfer from a colonized or an infected patient to a healthcare worker via contact and transfer via hands to a noncolonized or noninfected patient (**section B**); and (iii) indirect transfer via healthcare worker contact with the contaminated environment and transfer to a noncolonized or noninfected patient (**section C**).

C. difficile, and the spores can persist on hard surfaces for months *(487)*. For example, *C. difficile* contamination has been found on 49% of sites in rooms occupied by patients with *C. difficile* infection and 29% of sites in rooms occupied by asymptomatic carriers *(490)*. Contamination of the environment and patient-care equipment occurs through fecal shedding or through the contaminated hands of the patient or healthcare workers *(489)*. There are several observations that demonstrate that contaminated environmental surfaces are important in the acquisition of *C. difficile* to include the incidence of CDI is significantly associated with the proportion of culture-positive environmental sites and epidemiological evidence that the use of sodium hypochlorite for environmental cleaning may significantly reduce the incidence of CDI. Data also demonstrate that the frequency of positive personnel hand cultures was strongly correlated with the density of environmental contamination *(492)*. For example, hand contamination was 0% when environmental contamination was 0–25%, 8% when environmental contamination was 25–50%, and 36% of the hand cultures positive when environmental contamination was >50% *(493)*. Additionally, the use of an effective antimicrobial (i.e., chlorine) significantly decreased environmental contamination in rooms of patients with *C. difficile*. For example, Eckstein observed nine of the rooms (90%) of patients with CDI had one or more positive cultures prior to cleaning with 1:10 dilution of bleach versus 2 (20%) after cleaning *(494)*. Kaatz et al. recovered *C. difficile* from 31% of the environmental samples. When the ward was disinfected with unbuffered hypochlorite (500 ppm available chlorine), surface contamination decreased to 21% of the initial levels and the CDI outbreak ended. Phosphate-buffered hypochlorite (1,600 ppm available chlorine) was even more effective in reducing environmental *C. difficile* levels, with a resultant 98% reduction in surface contamination *(495)*.

With increasing CDI rates, clearly there is a need for more effective infection prevention strategies. Strategies to prevent patient ingestion of spores consist of traditional infection prevention strategies that target the environment, hand hygiene, and barrier precautions such as Contact Precautions *(178)*. Two strategies have been shown to be effective at interrupting disease transmission during CDI clusters or epidemic periods: effective room decontamination by surface disinfection with sodium hypochlorite to minimize environmental contamination; and the use of effective barrier precautions (especially gloves) during patient contact to prevent transmission *(178)*.

Studies have shown that admission to a room previously occupied by a patient with MRSA (384), VRE *(385)*, or *C. difficile (386)* significantly increases the odds of acquiring the drug-resistant microorganisms. These studies demonstrate the importance of effective room disinfection or eliminating the pathogen from the environment. Pathogen survival of environmental surfaces or patient-care equipment may be attributable to ineffective products (i.e., disinfectants that don't kill the pathogen) or poor practices (i.e., all surfaces are not wiped or a poor technique that does not remove the pathogen) *(383)*.

Since *C. difficile* is shed in the feces, any surface or device that becomes contaminated by feces or hands can serve as a reservoir for *C. difficile* spores. The frequency of *C. difficile* contamination in patients' rooms may vary

from approximately 10% to >50% (387,*487,492–502*). The *C. difficile* spore load on environmental surfaces in healthcare facilities is low. To our knowledge, seven studies assessed the microbial load of *C. difficile* on environmental surfaces and most studies usually found <10 colonies of *C. difficile* on sampled surfaces found to be contaminated (387,*487,493–495,497,502*). Two studies reported more than 100 colonies; one reported a range of "1 to >200" and one study that sampled several sites with a sponge found 1,300 colonies. The heaviest contamination is found on floors but other sites frequently found contaminated are windowsills, commodes, toilets, call buttons, scales, blood pressure cuffs, toys, bathtubs, tables, light switches, phones, door handles, mops, electronic thermometers, and feeding tube equipment. These spores will remain in the environment for months unless physical removed or inactivated by disinfectants. Most low-level disinfectants used in healthcare (e.g., alcohol, quaternary ammonium compounds, phenolics) are not effective against *C. difficile* spores, while higher-level disinfectants kill the spores (e.g., glutaraldehyde, 5,000 ppm chlorine)(Unpublished data, WA Rutala, December 2008) *(179)*.

The importance of environmental contamination in disease transmission is emphasized by the epidemiological findings that disinfection with sodium hypochlorite (i.e., bleach) has been shown to be effective in reducing environmental contamination in patient rooms and in reducing CDI rates in hospital units where the rate of CDI is high (defined as >3 cases per 1,000 patient days). In an intervention study, the incidence of CDI for bone marrow transplant patients decreased significantly, from 8.6 to 3.3 cases per 1,000 patient days after the environmental disinfection was switched from a quaternary ammonium compound to 1:10 dilution of concentrated hypochlorite solution (i.e., bleach) in the rooms of patients with CDI *(498)*. When the protocol was reversed and a quaternary ammonium compound was reintroduced to those units, rates returned to the high baseline rate of 8.1 cases per 1,000-patient days. No reduction in CDI rates was seen among neurosurgical ICU and medicine patients for whom baseline rates were 3.0 and 1.3 cases per 1,000 patient days. Three other studies have also provided epidemiological data that demonstrates the effectiveness of chlorine disinfection in reducing *C. difficile* spores on environmental surfaces and reduces the incidence of *C. difficile*. *(492,495,503)*. For this reason, the use of bleach (1:10 dilution of concentrated bleach) is recommended by the Centers for Disease Control and Prevention during outbreaks of CDI (11). One application of bleach covering all surfaces to allow a sufficient wetness for ≥ 1 minute contact time is recommended. A dilution of bleach with water normally takes 1 to 3 minutes to dry. For sporadic CDI cases where there is no epidemic or recognized cross transmission of *C. difficile*, hospitals can use their regular EPA-registered disinfectant for disinfection of patient rooms. Recently, room disinfection by vaporized hydrogen peroxide has also been found to reduce *C. difficile* incidence rates (387).

In summary, environmental interventions are an important part of a comprehensive strategy in preventing transmission of *C. difficile* in a healthcare setting. The use of chlorine during hyperendemic and epidemic periods has been shown to reduce environmental contamination with *C. difficile* and to reduce the incidence of *C. difficile* infection rates. Interventions, such as chlorine, aimed at optimizing environmental disinfection are an important component of our infection prevention strategies.

Dental Instruments

Scientific articles and increased publicity about the potential for transmitting infectious agents in dentistry have focused attention on dental instruments as possible agents for pathogen transmission *(504,505)*. The American Dental Association recommends that surgical and other instruments that normally penetrate soft tissue or bone (e.g., extraction forceps, scalpel blades, bone chisels, periodontal scalers, and surgical burs) be classified as critical devices that should be sterilized after each use or discarded. Instruments that are not intended to penetrate oral soft tissues or bone (e.g., amalgam condensers, and air/water syringes) but may come in contact with oral tissues are classified as semicritical but are recommended to be sterilized after each use if the instruments are heat tolerant *(506,507)*. If a semicritical item is heat sensitive, it should, at a minimum, be processed with high-level disinfection *(507,508)*. Handpieces can be contaminated internally with patient material and should be heat sterilized after each patient. Handpieces that cannot be heat sterilized should not be used *(509)*. Methods of sterilization that may be used for critical or semicritical dental instruments and materials that are heat-stable include steam under pressure (autoclave), chemical (formaldehyde) vapor, and dry heat (e.g., 320°F for 2 hours). The steam sterilizer is the method most commonly used by dental professionals *(510)*. All 3 sterilization procedures can be damaging to some dental instruments, including steam-sterilized handpieces *(511)*. Heat-tolerant alternatives are available for most clinical dental applications and are preferred *(507)*.

CDC has divided noncritical surfaces in dental offices into clinical contact and housekeeping surfaces *(507)*. Clinical contact surfaces may be touched frequently with gloved hands during patient care or surfaces that may become contaminated with blood or other potentially infectious material and subsequently contact instruments, hands, gloves, or devices (e.g., light handles, switches, dental x-ray equipment, chair-side computers). Barrier protective coverings (e.g., clear plastic wraps) may be used for these surfaces particularly those that are difficult to clean (e.g., light handles, chair switches). The coverings should be changed when visibly soiled, when damaged, and on a routine basis (e.g., between patients). Disinfect protected surfaces at the end of the day or if contamination is evident. If not barrier-protected, these surfaces should be disinfected between patients with an intermediate-disinfectant (i.e., EPA-registered hospital disinfectant with tuberculocidal claim) or low-level disinfectant (i.e., EPA-registered hospital disinfectant with an HBV and HIV label claim) *(401,403,507)*.

Most housekeeping surfaces need to be cleaned only with a detergent and water or an EPA-registered hospital disinfectant, depending on the nature of the surface and the type and degree of contamination. When housekeeping surfaces are visibly contaminated by blood or body substances, however, prompt removal and surface disinfection is a sound infection control practice and required by OSHA *(401,507)*.

Several studies have demonstrated variability among dental practices while trying to meet these recommendations *(512,513)*. For example, 68% of respondents believed they were sterilizing their instruments but did not use appropriate chemical sterilants or exposure times and 49% of respondents did not challenge autoclaves with biological indicators *(512)*. Other investigators using biological indicators have found a high portion (15–65%) of positive spore tests after assessing the efficacy of sterilizers used in dental offices. In one study of Minnesota dental offices, operator error, rather than mechanical malfunction *(514)*, caused 87% of sterilization failures. Common factors in the improper use of sterilizers include chamber overload; low temperature setting; inadequate exposure time; failure to preheat the sterilizer; and interruption of the cycle.

Disinfection in the Hemodialysis Unit

Hemodialysis systems include hemodialysis machines, water supply, water treatment systems, and the distribution system. During hemodialysis, patients have acquired bloodborne viruses and pathogenic bacteria *(515–517)*. Cleaning and disinfection are important components of infection control in a hemodialysis center. Disinfectants used to reprocess hemodialyzers, hemodialysis machines, and water treatment systems are regulated by the EPA and the FDA.

Disinfection on noncritical surfaces (e.g., dialysis bed or chair, countertops, external surfaces of dialysis machines, and equipment [scissors, hemostats, clamps, blood pressure cuffs, stethoscopes]) should be done with an EPA-registered disinfectant unless the item is visibly contaminated with blood in which case a tuberculocidal agent (or a disinfectant with specific label claims for HBV and HIV) or a 1:100 dilution of a hypochlorite solution (500–600 ppm free chlorine) should be used *(516,518)*. This procedure accomplishes two goals, i.e., it removes soil on a regular basis and maintains an environment that is consistent with good patient care. Disinfection of hemodialyzers is accomplished with peracetic acid, formaldehyde, glutaraldehyde, heat pasteurization with citric acid, and chlorine-containing compounds *(519)*. Disinfection of hemodialysis systems is normally accomplished by chlorine-based disinfectants (e.g., sodium hypochlorite), aqueous formaldehyde, heat pasteurization, ozone, or peracetic acid *(520,521)*. All products must be used according to the manufacturers' recommendations. Some dialysis systems use hot-water disinfection for the control of microbial contamination.

At its high point, 82% of U.S. chronic hemodialysis centers were reprocessing (i.e., reuse) dialyzers for the same patient using high-level disinfection *(519)*. However, one of the large dialysis organizations has decided to phase out reuse, and as of 2002 the percentage of dialysis facilities reprocessing hemodialyzers had dropped to 63% *(522)*. The two commonly used disinfectants to reprocess dialyzers were peracetic acid and formaldehyde; 72% used peracetic acid and 20% used formaldehyde to disinfect hemodialyzers. Another 4% of the facilities either used glutaraldehyde or heat pasteurization in combination with citric acid *(522)*. Detailed infection control recommendations, to include disinfection and sterilization and the use of dedicated machines for HBsAg-positive patients, in the hemodialysis setting may be found in two reviews *(515,516)*. Recommended practices for the reuse of hemodialyzers have been published by the Association for the Advancement of Medical Instrumentation *(523)*.

Disinfection in Ambulatory Care, Home Care, and the Home

With the advent of managed healthcare, increasing numbers of patients are now being cared for in ambulatory care and in home settings. Many patients cared for in these settings may have communicable diseases, immunocompromising conditions, or invasive devices. Therefore, adequate disinfection in these settings is necessary to provide a safe patient environment. Since the ambulatory care setting (i.e., outpatient facilities) provides the same infection risk as the hospital, the Spaulding classification scheme described in this guideline should be followed (Table 80-1) *(22)*.

The home environment should be a much safer setting than hospitals or ambulatory care. Epidemics should not be a problem and cross infection should be rare. The healthcare provider is responsible for providing the responsible family member information on infection control procedures to follow in the home including hand hygiene, proper cleaning and disinfection of equipment, and safe storage of cleaned and disinfected devices. Among the products recommended for home disinfection of reusable objects are bleach, alcohol, and hydrogen peroxide. It has been recommended by APIC that reusable objects (e.g., tracheostomy tubes) that touch mucous membranes be disinfected by immersion in 70% isopropyl alcohol for 5 minutes, or 3% hydrogen peroxide for 30 minutes. Additionally, a 1:50 dilution of 5.25%–6.15% sodium hypochlorite (household bleach) for 5 minutes should be effective *(160,166,524)*. Noncritical items (e.g., blood pressure cuffs, crutches) can be cleaned with a detergent. Blood spills should be handled as per OSHA regulations as described in a previous section. In general, sterilization of critical items is not practical in homes but theoretically could be accomplished by chemical sterilants or boiling. Single-use disposable items can be used or reusable items sterilized in a hospital *(525,526)*.

Some environmental groups advocate "environmentally safe" products as alternatives to commercial germicides in the home-care setting. These alternatives (e.g., ammonia, baking soda, vinegar, Borax, liquid detergent) are not registered with the EPA and should not be used for disinfecting because they are ineffective against *S. aureus*. Borax, baking soda, and detergents are also ineffective against *Salmonella typhi* and *E. coli*; however, undiluted vinegar and ammonia are effective against *S. typhi* and *E.coli (48,527,528)*. Common commercial disinfectants designed for home use have also been found effective against selected antibiotic-resistant bacteria *(48)*.

Public concerns have been raised that the use of antimicrobials in the home may promote the development of antibiotic-resistant bacteria *(529,530)*. This issue is unresolved and needs to be considered further via scientific and clinical investigations. While the public health benefits resulting from the use of disinfectants in the home environment are unknown, it is known that many sites in the home kitchen and bathroom are microbially contaminated *(531)*, the use of hypochlorites results in a marked reduction of bacteria *(532)*, and good standards of hygiene (e.g., food hygiene, hand hygiene) may have an impact on reducing infections arising in the home *(533,534)*. It is also known from laboratory studies that many commercially prepared

household disinfectants are effective against common pathogens *(48)* and can interrupt surface-to-human transmission of pathogens *(44)*. The "targeted hygiene concept," which means identifying situations and areas (e.g., food preparation surfaces and bathroom) where there is a risk of transmission of pathogens, may be a reasonable way to identify when disinfection may be appropriate *(535)*.

Susceptibility of Antibiotic-Resistant Bacteria to Disinfectants

As with antibiotics, reduced susceptibility (or acquired "resistance") of bacteria to disinfectants can arise by either chromosomal gene mutation or the acquisition of genetic material in the form of plasmids or transposons *(71–74,533,536)*. When there is a change in bacterial susceptibility that renders an antibiotic ineffective against an infection previously treatable by that antibiotic, the bacteria are referred to as "resistant." In contrast, reduced susceptibility to disinfectants does not correlate with failure of the disinfectant because concentrations used in disinfection still greatly exceed the cidal level. Thus, the word "resistance" when applied to these changes is incorrect, and the preferred term is reduced susceptibility or increased tolerance *(71,537)*. Currently, there are no data to show that antibiotic-resistant bacteria are less sensitive to the liquid chemical germicides than antibiotic-sensitive bacteria at currently used germicide contact conditions and concentrations *(434)*.

MRSA and VRE are recognized as important healthcare-associated agents. It has been known for years that some antiseptics and disinfectants are, on the basis of minimum inhibitory concentrations (MICs), somewhat less inhibitory to *S. aureus* strains that contain a plasmid-carrying gene encoding resistance to the antibiotic gentamicin *(71)*. For example, Townsend et al. found that gentamicin resistance also encodes reduced susceptibility to propamidine, quaternary ammonium compounds, and ethidium bromide *(538)*, and Brumfitt and associates found MRSA strains less susceptible than methicillin-sensitive *S. aureus* (MSSA) strains to chlorhexidine, propamidine, and the quaternary ammonium compound cetrimide *(539)*. Al-Masaudi et al. found the MRSA and the MSSA strains to be equally sensitive to phenols and chlorhexidine, but MRSA strains were slightly more tolerant to quaternary ammonium compounds *(540)*. Studies have established the involvement of two gene families (*qac*CD [now referred to as *smr*] and *qac*AB) in providing protection against agents that are components of disinfectant formulations such as quaternary ammonium compounds. Tennant and coworkers propose that staphylococci evade destruction because the protein specified by the *qac*A determinant is a cytoplasmic-membrane-associated protein involved in an efflux system that actively reduces intracellular accumulation of toxicants such as quaternary ammonium compounds to intracellular targets *(541)*.

Other studies demonstrated that plasmid-mediated formaldehyde tolerance is transferable from *Serratia marcescens* to *E. coli (542)* and plasmid-mediated quaternary ammonium tolerance is transferable from *S. aureus* to *E. coli (543)*. Tolerance to mercury and silver is also plasmid borne *(71–74,536)*.

Since the concentrations of disinfectants used in practice are much higher than the MICs observed, even for the more tolerant strains, the clinical relevance of these observations is questionable. Several studies have found antibiotic-resistant hospital strains of common healthcare-associated pathogens (i.e., *Enterococcus, P. aeruginosa, Klebsiella pneumoniae, E. coli*, *S. aureus*, and *S. epidermidis*) to be equally susceptible to disinfectants as antibiotic-sensitive strains *(48,435–437)*. The susceptibility of glycopeptide-intermediate *S. aureus* was similar to vancomycin-susceptible, methicillin-resistant *S. aureus*. *(438)* Based on these data, routine disinfection and housekeeping protocols do not need to be altered because of antibiotic resistance provided the disinfection method is effective *(439,440)*. A study that evaluated the efficacy of selected cleaning methods (e.g., QUAT-sprayed cloth, and QUAT-immersed cloth) for eliminating VRE found that currently used disinfection processes are likely highly effective in eliminating VRE. However, surface disinfection must involve contact with all contaminated surfaces *(439)*.

Lastly, does the use of antiseptics or disinfectants facilitate the development of disinfectant-tolerant microorganisms? Based on current evidence and reviews *(529,530,536,537,544)*, the development of enhanced tolerance to disinfectants in response to disinfectant exposure can occur. However, it is not important in clinical terms since the level of tolerance is low and unlikely to compromise the effectiveness of disinfectants where much higher concentrations are used *(537,545)*.

The issue of whether low-level tolerance to germicides selects for antibiotic-resistant strains is unsettled but may depend on the mechanism by which tolerance is attained. For example, changes in the permeability barrier or efflux mechanisms may affect susceptibility to antibiotics and germicides, but specific changes to a target site may not. Some researchers have suggested that the use of disinfectants or antiseptics (e.g., triclosan) could facilitate the development of antibiotic-resistant microorganisms *(529,530,546)*. While there is evidence in laboratory studies of low-level resistance to triclosan, the concentrations of triclosan in these studies were low (generally <1 μg/mL) and dissimilar from the higher levels used in antimicrobial products (2,000–20,000 μg/mL) *(82,547)*. Thus, researchers can create laboratory-derived mutants that demonstrate reduced susceptibility to antiseptics or disinfectants. In some experiments, such bacteria have demonstrated reduced susceptibility to certain antibiotics *(530)*. There is no evidence that using antiseptics/disinfectants selects for antibiotic-resistant microorganisms in nature or that mutants survive in nature *(548)*. In addition, there are fundamental differences between the action of antibiotics and disinfectants. Antibiotics are selectively toxic and generally have a single target site in bacteria, thereby inhibiting a specific biosynthetic process. Germicides generally are considered to be nonspecific antimicrobials because of a multiplicity of toxic effect mechanisms or target sites and are broader spectrum in the types of microorganisms against which they are effective *(71,537)*.

The rotational use of disinfectants in some environments (e.g., pharmacy production units) has been recommended and practiced in an attempt to prevent the development of resistant microbes *(549,550)*. Currently, there appears to be rare case reports that appropriately used disinfectants have resulted in a clinical problem

arising from the selection or development of nonsusceptible microorganisms *(77)*.

Contact Times for Surface Disinfectants

An important issue concerning the use of disinfectants for noncritical surfaces in healthcare settings is that the contact time specified on the label of the product is often too long to be practically followed. The labels of most products registered by EPA for use against HBV, HIV, or *M. tuberculosis* (TB) specify a contact time of 10 minutes. The only way an institution can achieve a contact time of 10 minutes is to reapply the surface disinfectant 5–6 times to the surface as the typical dry time for a water-based disinfectant is 1.5–2 minutes and currently, healthcare facilities like UNC Health Care are achieving surface disinfection of noncritical patient-care items and environmental surfaces by one application of a disinfectant and requiring a >1 minute dry time. Long contact time, such as 10 minutes, are not practical for disinfection of environmental surfaces in a healthcare setting and requiring housekeeping staff to follow label directions for actions with no proven benefit to employee or patient safety may serve to reduce efforts proven to improve patient outcomes.

Multiple scientific papers have demonstrated significant microbial reduction with contact times of 30 to 60 seconds, and these studies are the basis for the CDC guideline of at least 1 minute for surface disinfection of noncritical surfaces *(42–50,52–57,90–95)*. Equally important as disinfectant contact time is the application of the disinfectant to the surface or the equipment to ensure that all contaminated surfaces and non-critical patient-care equipment are wiped as current studies demonstrate that only approximately 50% of high-risk objects are cleaned at terminal cleaning. Additionally, there are no data that demonstrate improved infection prevention by a 10-minute contact time versus a 1-minute contact time.

Currently, some EPA-registered disinfectants have contact times from 1 to 3 minutes and EPA will approve a shortened contact time for any product for which the manufacturers will submit confirmatory efficacy data. By law, all applicable label instructions on EPA-registered products must be followed, but we are not aware of an EPA enforcement action against healthcare facilities for "off label" use of a surface disinfectant although there have been citations reported from the Joint Commission and CMS.

Microbial Contamination of Disinfectants

Contaminated disinfectants and antiseptics have been occasional vehicles of healthcare-associated infections and pseudoepidemics for more than 50 years. A summary of the published reports describing contaminated disinfectants and antiseptic solutions leading to healthcare-associated infections has been published (258*,551*). Since this summary, additional reports have been published *(552–555)*. When examining the reports of disinfectants found contaminated with microorganisms, there are several noteworthy observations. Perhaps most importantly, high-level disinfectants/liquid chemical sterilants have not been associated with outbreaks due to intrinsic or extrinsic contamination. Another feature of these outbreaks has been that members of the genus *Pseudomonas* (e.g., *P. aeruginosa*) are the most frequent isolates from contaminated disinfectants, being the agents recovered from 80% of the contaminated products. Their ability to remain viable or grow in use-dilutions of disinfectants is unparalleled. This survival advantage for *Pseudomonas* is presumably due to their nutritional versatility, their unique outer membrane that constitutes an effective barrier to the passage of germicides, and/or efflux systems *(556)*. While the concentrated solutions of the disinfectants have not been demonstrated to be contaminated at the point of manufacture, Newman et al. found that an undiluted phenolic may be contaminated by a *Pseudomonas* sp. during use *(557)*. In most of the reports that describe illness associated with contaminated disinfectants, the product was used to disinfect patient-care equipment such as cystoscopes, cardiac catheters, and thermometers. The germicides used as disinfectants that were reported contaminated include chlorhexidine, quaternary ammonium compounds, phenolic, and pine oil.

The following control measures should be instituted to reduce the frequency of bacterial growth in disinfectants and the threat of serious healthcare-associated infections from the use of such contaminated products *(551)*. First, some disinfectants should not be diluted and those that are must be prepared correctly to achieve the manufacturer's recommended use-dilution. Second, infection preventionists must learn from the literature what inappropriate activities result in extrinsic contamination (i.e., at the point of use) of germicides and train users to prevent their recurrence. Common sources of extrinsic contamination of germicides in the reviewed literature are the water to make working dilutions, contaminated containers, and general contamination of the hospital areas where the germicides are prepared and/or used. Third, stock solutions of germicides must be stored as indicated on the product label. Currently, the EPA verifies manufacturers' efficacy claims against microorganisms. These measures should provide assurance that products that meet the EPA registration requirements are capable of achieving a certain level of antimicrobial activity when used as directed.

New Products and Issues in Disinfection

Several recent issues in disinfection that require comments will be briefly discussed. First, toxic anterior segment syndrome (TASS), which is an increasingly reported complication of cataract surgery. TASS is a sterile postoperative inflammatory reaction caused by a noninfectious substance that enters the anterior segment of the eye, resulting in toxic damage to intraocular tissues. The induction of TASS may be associated with specific products such as balanced salt solution, detergent (enzymatic and nonenzymatic) residues, bacterial endotoxins, preservatives, foreign matter, and residues from sterilization processing. Staff involved in reprocessing ocular instruments should be properly instructed in thoroughly cleaning and rinsing instruments prior to sterilization. Recommended practices related to reprocessing and preventing TASS are published by several professional organizations and government agencies (CDC, FDA, American Association of Medical Instrumentation, American Society of Cataract and Refractive Surgery, American Society of Ophthalmic Registered Nurses) *(558–563)*. Second, the use of bactericidal surface materials, such as copper and its alloys, might constitute a way to

minimize the spread of healthcare-associated pathogens. Effective inhibition of healthcare-associated pathogens by copper and alloys was best when the copper content was >55%. The use of copper-containing materials for surfaces in the hospital environment may be an adjunct for the prevention of HAIs and requires further evaluation *(564,565)*. Some strains of bacteria may be resistant to the toxic properties exerted by dry metallic copper surfaces *(566,567)*. Copper-based biocides have also been shown to have an antibacterial effect *(568)*. Third, antimicrobial coatings (e.g., polymer-encapsulated chlorine-dioxide-coated surfaces) continue to be investigated. One product provides a slow sustained release of gaseous chlorine dioxide at a rate sufficient to inhibit bacterial growth for 28 days. These investigations may offer a new direction for providing persistent microbicidal properties on surfaces *(569,570)*. Fourth, the use of atmospheric nonthermal plasma as a disinfectant for objects contaminated with bacteria such as MRSA also warrants further study *(571)*.

There are several issues that affect the reprocessing of semicritical items (items that touch mucous membranes) such as endoscopes, endocavitary probes, and laryngoscopes. First, there are new high-level disinfectants that include a 2% accelerated hydrogen peroxide *(213)*, an 8.3% hydrogen peroxide with 7.0% peracetic acid, and a 3.4% glutaraldehyde with 26% isopropanol *(572)*. Second, since breaches of high-level disinfection and sterilization guidelines are not uncommon, a 14-step protocol was developed to aid infection preventionists in the evaluation of potential disinfection and sterilization failures *(336)*. Third, prevention of disease transmission associated with laryngoscopes, prostate biopsy probes, and endoscopes requires adequate reprocessing of the device. Several recent papers review the recommendations for reprocessing semicritical medical devices that have been associated with disease transmission *(39,376,378,573)*.

Regarding the disinfection of noncritical items such as environmental surfaces, there are several noteworthy observations. First, and importantly, Carling and colleagues used an invisible fluorescent targeting method that assessed whether high-touch objects in a patient's room were cleaned as part of terminal disinfection procedure. They found that 50% of a standardized set of 14 objects were not cleaned at all. This information should be used to develop focused administrative and educational interventions that incorporate ongoing feedback to the environmental services staff to improve cleaning and disinfection practices *(383)*. For example, healthcare facilities may need to introduce the use of checklists or other tools (e.g., invisible fluorescent dyes) to ensure complete cleaning of all potentially contaminated surfaces. The inadequacy of terminal room disinfection likely explains why admission to a room previously occupied by an MRSA-positive patient or a VRE-positive patient significantly increased the odds of acquisition for MRSA and VRE (384). These observations highlight the importance of cleaning all surfaces and all accessible equipment each time cleaning is done in patient rooms. Second, healthcare facilities have started to use a microfiber mopping technique rather than a conventional, cotton string mop to clean floors. The microfiber system demonstrated superior microbial removal compared with cotton string mops when used with a detergent cleaner *(60)*. Third, an accelerated hydrogen peroxide product (0.5%) that claims virucidal, bactericidal, fungicidal, and tuberculocidal activity has been introduced into the United States for disinfection of noncritical environmental surfaces and equipment *(212)*. Fourth, a diverse group of pathogenic microorganisms were killed within 5 seconds by a steam disinfection system and therefore may represent a novel alternative to liquid chemical disinfectants *(574)*. Fourth, a new antimicrobial containing glucoprotamin (0.5%) as the active ingredient has proved to be very effective against bacterial clinical isolates in 1 minute *(575)*.

CONCLUSION

When properly used, disinfection and sterilization can ensure the safe use of invasive and noninvasive medical devices. The method of disinfection and sterilization depends on the intended use of the medical device: critical items (contact sterile tissue) must be sterilized prior to use; semicritical items (contact mucous membranes or nonintact skin) must be high-level disinfected; and noncritical items (contact intact skin) should receive low-level disinfection. Cleaning should always precede high-level disinfection and sterilization. Current disinfection and sterilization guidelines must be strictly followed.

Since semicritical equipment has been associated with reprocessing errors that result in patient lookback and patient notifications, it is essential that control measures be instituted to prevent patient exposures *(336)*. Before new equipment (especially semicritical equipment as the margin of safety is less than that for sterilization) *(270)* is used for patient care on more than one patient, reprocessing procedures for that equipment should be developed. Staff should receive training on the safe use and reprocessing of the equipment and be competency tested. Infection control rounds or audits should be conducted annually in all clinical areas that reprocess semicritical devices to ensure adherence to the reprocessing standards and policies. Results of infection control rounds should be provided to the unit managers and deficiencies in reprocessing should be corrected and the corrective measures documented to infection control within 2 weeks.

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CHAPTER 81

Sterilization and Pasteurization in Healthcare Facilities

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Since ancient times, man has understood the importance of heat and water as purifying agents. One of the first references to purifying rituals using heat and water is found in the Old Testament, describing the cleaning procedures for warriors' blood-contaminated weapons and clothing after the battle:

> *"Purify every garment, everything made of leather, everything woven of goat's hair, and everything made of wood. Only the gold, the silver, the bronze, the iron, the lead, everything that can endure the fire, you shall put through the fire, and it shall be clean; and it shall be purified with the water of purification.[1] But all that cannot endure fire you shall put through water."*
>
> *Numbers 31:20, 22-23 (New King James Version)*

Although mankind held a vague concept that an unseen presence was associated with the spread of disease, scientific awareness and acceptance of the microbial world emerged in Europe beginning in 1677 with Anton van Leeuwenhoek's invention of the microscope. Over the next 300 years, the great names in microbiology and medicine (e.g., Lazzaro Spallanzani, Louis Pasteur, and Robert Koch) advanced our understanding of the microbial world, all of which instituted efforts in the civilized world to develop the means to control infectious diseases through environmental sanitation, personal hygiene, and processes to preserve and protect food and water. The canning industry was among the first to employ pressurized steam sterilization to inactivate spoilage microorganisms, thereby rendering containerized food products safe to eat even after long periods of storage. In fact, *Geobacillus stearothermophilus* (formerly *Bacillus stearothermophilus*), the source of the highly resistant bacterial endospores used today as the reference standard in the design and monitoring of steam autoclave cycles, is a common food spoilage microorganism.

The findings and conclusions in this chapter are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Any use of mention of trade names in this chapter is for identification purposes only and does not represent any endorsement by either the CDC or the U.S. Public Health Service.

[1]Also known as "water of separation"—a presumably alkaline infusion of select herbs and ritually prepared animal ashes.

It has been little more than 110 years since the development of formal procedures for the sterilization of instruments and medical devices, liquids, and other materials used in hospitals. At that time, there was a growing appreciation for the role of microorganisms in the transmission of infectious diseases and for the necessity of sterile materials in surgery and other hospital activities. Although infection prevention as we know it today was in its infancy, scientists both in hospitals and in the medical device industry began to sterilize instruments and materials used in patient treatments (1).

Historically, physical methods (e.g., steam under pressure in steam autoclaves, dry heat in sterilizing ovens) have played the predominant role for sterilizing devices, equipment, and supplies in hospitals and industry. Since the 1950s, however, the number of heat-sensitive devices that must be sterilized using low-temperature processes has increased. Those low-temperature sterilization processes available to hospitals may employ gases, gas plasmas, or liquid chemicals, whereas the medical device industry typically uses gas (ethylene oxide, ETO) or irradiation for terminal sterilization. Exposure of heat-sensitive materials to short-cycle substerilizing temperatures (e.g., pasteurization [60–75°C for 5–15 minutes]) is common in the food industry but of limited use in the medical arena in the United States.

The material in this chapter centers on a review of the general principles of sterilization and pasteurization as currently performed primarily in US healthcare facilities. Discussion of the sterilization methods used in industry (e.g., irradiation), as well as an in-depth review of the mathematical/engineering basis of sterilization, is beyond the scope of this chapter. The reader is referred to two excellent texts for more detailed information on these topics (*2,*3). This chapter also does not discuss the use of liquid chemicals for disinfection as this topic is thoroughly covered in Chapter 80. Furthermore, the day-to-day operations and maintenance of sterilizers and all the attendant processes, occupational safety, construction, regulations, and quality control aspects, are addressed in Chapter 70.

DEFINITIONS

Over the years, the terms "sterilization," "sterile," "decontamination," and "disinfection" have often been used

interchangeably, thereby leading to considerable confusion among healthcare personnel. For "sterile" and "sterilization," we view these, respectively, in the context of the *state* of sterility, as the *process* of sterilization and the *application* of sterilization. Any device or solution is considered to be sterile when it is completely free of all microorganisms, either living or inert (i.e., viruses, bacterial endospores, or fungal spores) (1). This *state* of sterility is the objective of the sterilization procedure, and viewed in this context, the definition is categorical and absolute (i.e., an item is either sterile or it is not). An interesting dilemma arises with fluids "sterilized" via filtration, using bacteriologic filters (nominal pore size of 0.2 μm) for this purpose. Such filtered liquids are often labeled as "sterile," but the pore size of the filters used is large enough to permit the passage of viruses or certain pleomorphic or cell wall–deficient gram-negative bacterial species (e.g., species of *Pseudomonas, Proteus, and Stenotrophomonas*), *Mycoplasma* spp., or *Mycobacterium* spp. (including *Mycobacterium tuberculosis* and waterborne nontuberculous mycobacteria) to the filtrate. Therefore, in the most practical sense of the term, such liquids do not meet the strict definition of "sterile" (4). This is especially true if the fluid being filtered has a potentially high microbial content (e.g., untreated, contaminated water or, not infrequently, water from the piping and tubing systems of treated public/institutional water supplies). An exception is noted for the end-stage filtration of "finished" liquids in the production of pharmaceutical and medical products that have been subjected to one or more rigorous prefiltration purification steps.

Sterilization is the use of a physical, chemical (liquid, gas, or plasma), or irradiation process to destroy all microorganisms including large numbers of highly resistant bacterial endospores. A *sterilization procedure,* on the other hand, cannot be categorically defined. Rather, the procedure is defined as a process, after which the probability of a microorganism surviving on an item is <1 in 1 million (10^{-6}). This is referred to as the *sterility assurance level* (SAL), and the attendant concepts are used by the medical device industry to design and monitor sterilization cycles for wide varieties and large quantities of medical devices.

The *application* of sterilization takes into account additional considerations (e.g., the Spaulding terminology used in the classification of materials subjected to various germicidal processes). Dr. E. H. Spaulding in 1972 *(5)* devised a classification scheme for reusable medical devices and instruments to determine the appropriate terminal reprocessing step for each of these items. Such medical devices and instruments were categorized as "critical," "semi-critical," or "noncritical" based on the manner in which they come into contact with patients and the corresponding risk of infection transmission during their use. *Critical* instruments or devices, the first category, are so called because of the substantial risk of infection if the item is contaminated with microorganisms at the time of use (i.e., with these instruments, sterility is *critical*). These are instruments or objects that are introduced directly into the human body, either into or in contact with the bloodstream or normally sterile areas of the body. Examples include needles, scalpels, transfer forceps, cardiac catheters, implants, and also the inner surface components of extracorporeal bloodflow devices, such as those of the heart–lung oxygenator and the blood side of artificial kidneys (hemodialyzers). These items must be meticulously cleaned, then sterilized by a validated sterilization process before use on the next patient, thereby minimizing the potential for disease transmission. Instruments or devices in the second category are classified as *semi-critical* in terms of the risk of infection, and examples are flexible gastrointestinal endoscopes, bronchoscopes, endotracheal and aspirator tubes, respiratory therapy equipment, and vaginal speculа. Although these items come in contract with mucous membranes, they do not ordinarily come into contact with the bloodstream or a sterile body site during normal use. Sterilization of many of these items, although desirable and cost-effective if they can withstand steam autoclaving, is not absolutely essential (i.e., according to Spaulding's classification, it is *semi-critical* that they be sterile at the time of use). At a minimum, semi-critical instruments or devices should be subjected to the comparatively potent heat or chemical treatment referred to as *high-level disinfection*—a process that is discussed in detail in Chapter 80. Instruments, devices, or surfaces that come into direct or indirect contact only with intact skin during routine use (e.g., backboards, blood pressure cuffs, and stethoscopes) have only minimal risk of disease transmission. The sterility of these surfaces and devices is *noncritical*. For some of these items and surfaces, washing with soap and water may be the only between-use process necessary. Medical equipment used routinely in patient care is typically cleaned and disinfected routinely, but care must be used to minimize damage to and malfunction of electronic medical equipment when using liquid cleaners and disinfectants. Cleaning and application of low- to intermediate-level disinfection for noncritical surfaces are defined and discussed in Chapter 80.

GENERAL FACTORS AFFECTING STERILIZATION PROCESSES

A significant consideration in assessing the effectiveness of a sterilization process is the overall *resistance* level of the target microbial population. Resistance can be categorized as *intrinsic* or *extrinsic. Intrinsic resistance* is the innate capacity of a particular microbial cell to resist a specific potentially lethal treatment. *Extrinsic resistance*, in contrast, describes the added challenge that inert organic matter and other extraneous materials or configurations (e.g., mated surfaces such as forceps' hinges) pose to a sterilizing process. Organic matter, soil, patient material, or charred matter can diminish the effectiveness of the sterilizing treatment. It follows that high numbers of the most highly resistant microorganisms and large amounts of organic matter present on a device or surface will contribute significantly to the overall resistance of the population to inactivation and therefore, both of these contaminants should be minimized prior to sterilization or any other terminal reprocessing. Meticulous cleaning of devices, instruments, and surfaces is therefore an enormously important first step that will ensure the overall success of the process.

Intrinsic Resistance

Microorganisms vary widely in their responses to physical and chemical stresses. Among the various categories of

microorganisms, the species that form bacterial endospores possess the highest level of intrinsic resistance to sterilization processes, and because of this, they are consistently used as standard challenge microorganisms when initially designing and engineering a sterilization cycle and also when monitoring in-use performance of sterilizer equipment in the healthcare setting. Intrinsic resistance stems from innate and specific biophysical and biochemical properties of the particular strain of the spore-forming bacterium. These properties can be affected by external factors such as pH and the ionic concentration of growth and sporulation media, all of which can have pronounced effects on spore resistance to heat. Endospores are more readily inactivated at low pH because pH can affect ionic adsorption to the spore surface, which in turn can affect heat stability *(6)*. In contrast, yeasts in low pH media can exhibit increased resistance to heat *(2)*. With respect to thermal resistance of bacterial endospores, Powell, in 1953, identified dipicolinic acid (DPA) (pyridine-2, 6-dicarboxylic acid) as closely associated with thermoresistance *(7)*. This chemical is found in correspondingly high levels in all endospores with significant resistance to heat, but is absent in the vegetative bacterial cells *(8)*. When sterilization researchers developed the inactivation kinetic rates (survival curves) for various bacterial endospores, they observed that endospores first emerge from a dormant state, and the cellular energy required to do this is called "activation energy." This is the initial step in the inactivation process and also occurs prior to cellular growth. Grecz et al., in 1972, determined that this step involved the dissolution of a calcium salt of DPA. The rate of DPA loss is proportional to levels of intrinsic thermal resistance of the endospores *(9)*. Endospores of different genera and species often demonstrate widely differing levels of intrinsic resistance to different sterilizing agents. A classic example of this observation is seen with heat applications. For moist heat sterilizing processes, endospores of *G. stearothermophilus* provide the greatest challenge for this process, whereas their resistance to dry heat is very low. *Bacillus atrophaeus* (formerly *B. subtilis* var. *niger*) endospores have greater resistance to dry heat than to moist heat (3). Another example illustrates this point. A curious, extremely slow-growing bacterium, *Bacillus xerothermodurans*, was isolated from soil collected near the National Aeronautics and Space Administration (NASA) Vehicle Assembly Building (VAB) at Cape Kennedy, FL, in the 1970s *(10,11)*. Endospores of this microorganism exhibited an extreme level of intrinsic resistance to dry heat (i.e., at 125°C, the length of time needed to reduce the number of surviving spores by 90% was **139 hours**). In contrast, endospores of *B. atrophaeus*, the standard challenge microorganism used to design and monitor dry heat or ETO sterilization cycles, showed a 90% reduction of surviving spores when exposed for 15 *minutes* to dry heat at 125°C. In other words, *B. xerothermodurans* is >500-fold more resistant to inactivation by dry heat than is *B. atrophaeus*. Interestingly, endospores of *B. xerothermodurans* are extremely sensitive to inactivation with moist heat (i.e., a 90% reduction of surviving spores occurs when exposed to moist heat at 80°C for **61 minutes**). Although serving as an illustration of the spectrum of spore resistance, these contrasting extremes offer little practicality for this novel microorganism being used as a biological indicator. It may, however, eventually serve as a useful research tool in the ongoing study of microbial resistance to heat.

Extrinsic Resistance

The presence of soil, organic matter, and/or bioburden on the surface of a medical device or instrument will interfere with the ability of the sterilant to make contact with those surfaces, thereby interfering with and diminishing the effectiveness of the sterilization process. The protective effect of organic matter has been recognized for several decades. With respect to moist heat (e.g., steam under pressure) sterilizing processes, the presence of residual organic matter can extend the time to inactivate bacterial endospores by six to eight times compared with the time required to inactivate spores in a less organically contaminated milieu *(12)*. Further, organic bioburden not only provides physical protection but may also contain massive numbers of microorganisms with widely varying levels of resistance, thereby increasing the potential for highly resistant microorganisms to be present. Bioburden and inorganic matter can pose challenges for other sterilizing processes as well. Dry heat is an oxidative process, and anything that prevents oxygen from reaching its targets will confer resistance (3,*13,14*). For example, the inclusion of bacterial endospores inside inorganic, water-soluble crystals can extend the dry-heat inactivation times by 15-fold to 20-fold *(15)*.

Cleaning

Cleaning is a process using water and any of a variety of salts, surfactants, ultrasonic energy, or enzymes to break covalent bonds between surfaces and visible soils, organic matter, and microorganisms, thereby enabling the dispersion and removal of these foreign materials from the item. Cleaning is, therefore, absolutely essential in efforts to enhance the efficacy of any terminal reprocessing step and is equally important for both sterilization and disinfection processes (4). A number of instrument design factors can pose challenges to effective cleaning. These include the presence of lumens, closely mated surfaces, acute angles, springs and valves, inaccessible areas, and roughened surfaces (16). Cleaning can be done manually, removing soil via water, detergent, and physical scrubbing, or by using an automated process such as enzymatic detergents and ultrasonic cleaners. Ultrasonic cleaning involves waves of acoustic energy in liquid, using cavitation and implosion to loosen soils from surfaces (17). An efficient cleaning process is capable of reducing microbial bioburden on instrument surfaces by several orders of magnitude. A number of researchers have demonstrated that microbial bioburden on typical medical instruments is generally low ($<10^3$ colony-forming units [CFU]/device) before cleaning, but ≥80% will have $<10^2$ CFU/device after cleaning *(18–20)*. In one series of experiments, Rutala et al. *(20)* observed that approximately 30% of cleaned medical instruments had no detectable contamination by the sampling and culture methods being used. Some of the microorganisms isolated from cleaned instruments have included coagulase-negative *Staphylococcus aureus,* diphtheroids, *Bacillus cereus*, *Bacillus* spp., and *Stenotrophomonas maltophila*. This observation supports the notion that while cleaning is essential to the overall efficacy of any terminal reprocessing, cleaning by itself is not by any means sufficient

to render a critical medical device or instrument safe and ready for use on the next patient. Such devices and instruments must *always* be subjected to a validated sterilization process prior to use.

This question has been asked on many occasions—is it safe to use a reusable medical device with residual foreign material after the device has undergone a sterilization process? The risk of infection in this instance is difficult to estimate, but the current consensus is that this questionable work practice (the state of "sterile but dirty") does not meet a proper surgical standard. The proper course of action in this instance is to return the instrument or lot of instruments to the central sterile supply unit (CSS) to be recleaned and resterilized. Even if the risk of infection is negligible, the possibility exists that such residual foreign matter may cause localized irritation and subsequent inflammation in the surgical site or may trigger an immune response, all of which may contribute to a possible surgical site adverse event. The aesthetics of such a lack of physical cleanliness is self-evident.

Sterility Assurance Levels and Engineering a Sterilization Cycle

Historically, the development of a sterilization cycle involved the determination of a SAL by using a specific biological challenge microorganism (e.g., representative bacterial endospores of *significantly* high resistance), constructing an inactivation curve, and obtaining a *D*-value. Death in this instance is a first order exponential or logarithmic function. In general, a *D-value* is the time required at a specific temperature to inactivate a given microbial population by 90% (i.e., a one $\log_{10}$ reduction, examples of which were given earlier). As mentioned previously, activation energy is required to bring spores out of dormancy as the very first step of inactivation, and when plotted in an inactivation curve, this may distort the initial shape of the curve depending on the innate characteristics of the endospore population being tested (3). *D*-values, therefore, are valid only when treatment temperatures are high enough to discount the effect of activation and the population of challenge microorganisms is of uniform resistance (3). This approach is illustrated in Figure 81-1. The inactivation rate is linear, and the *D*-value can be obtained for a given set of sterilization parameters. In practice, a survivor curve spanning six logs of inactivation can be determined by using quantitative spore assays. A six-$\log_{10}$ reduction in this discussion is considered a *half cycle* (1). An additional six $\log_{10}$ inactivation can be deduced by extrapolation of the linear survivor curve. In other words, the time at temperature required for the half cycle is doubled, resulting in a 12-$\log_{10}$ level of lethality for a *full cycle*. This procedure is used to construct a sterilization cycle with an SAL of 10^{-6}, meaning that the probability of a single survivor in the initial challenge of highly resistant endospores would be 1 in 1 million *(21)*. In the development of sterilization cycles, this approach is extraordinarily conservative. Accordingly, manufacturers of sterilization systems, including low-temperature systems, employ this high degree of conservatism in designing their cycles (Box 81-1).

In reality and as mentioned previously, most reusable medical devices have a bioburden $<10^2$ CFU/device after cleaning, and the residual microorganisms consist primarily of vegetative bacteria that are killed much more rapidly than are bacterial endospores. In the design and validation of the sterilization cycle, a challenge of one million bacterial endospores highly resistant to the process is used, and the survival curves reflect the highly conservative nature of this approach. This design conservativism, in conjunction with consistently efficient instrument and device cleaning, results in a significant level of overkill, thereby ensuring a huge margin of sterilization success and a high degree of patient safety (1,*22*).

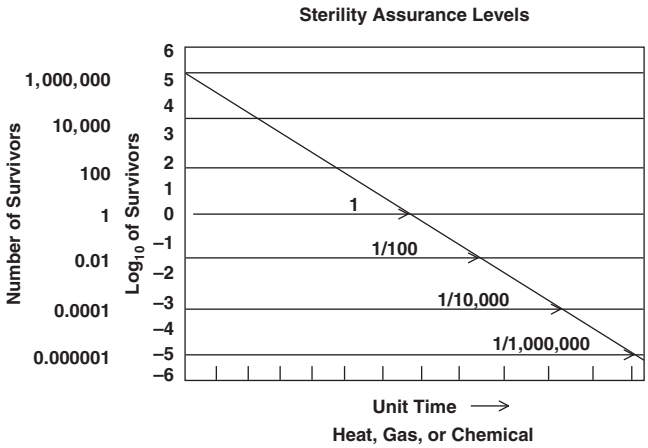

FIGURE 81-1 Numbers of surviving microorganisms compared to a starting population of 1,000,000 microorganisms are as follows: 6 $\log_{10}$ = 1,000,000; 5 $\log_{10}$ = 100,000; 4 $\log_{10}$ = 10,000; 3 $\log_{10}$ = 1,000; 2 $\log_{10}$ = 100; 1 $\log_{10}$ = 10; 0 $\log_{10}$ = 1. Three examples of the probability of a surviving microorganism as inactivation time continues are noted in the chart. (Adapted from Figure 43.2 in Favero MS, Bond WW. Chemical disinfection of medical and surgical materials. In: Block SS, ed. *Disinfection, sterilization, and preservation*. 5th ed. Philadelphia, PA: Lippincott, Williams and Wilkins, 2001:881–917.)

When engineering a sterilization cycle, regardless of the type of sterilant used (e.g., steam under pressure, gas plasma, and dry heat), researchers will take the following parameters into account: time, temperature, relative humidity (RH), pH of any suspending medium used with challenge microorganisms, and a standardized load configuration. Time and temperature, as mentioned previously, are the basic parameters evaluated when constructing inactivation curves and determining *D*-values. RH is defined as the ratio of the actual water vapor pressure in a system

BOX 81-1

Sterilization Cycle Design Considerations

- An assumption that the bioburden on a device is 10^6, consisting of bacterial endospores most resistant to the process
- In challenge tests, the placement of endospores is in the most occluded location in the device
- Use of spores contained in an organic and inorganic burden
- Application of simulated use conditions
- Documentation that a complete cycle produces a six $\log_{10}$ of measurable kill with a 10^{-6} probability that one spore survives

to the saturated water vapor pressure of the system at the same temperature. Water activity is the relative water availability in a cell or spore and depends on the RH *(23)*. There appears to be an inverse relationship between cell resistance and water activity *(23)*. The more water available to cells or spores, the faster the inactivation process whether it be moist heat or dry heat *(24)*.

Standardized sterilizer loading configurations are important for a number of reasons. Regardless of the process used, the sterilant must be able to make contact with all surfaces in the load in order to effect microbial inactivation. Load configurations take into account the packaging of devices, placement in secondary containment, etc., in efforts to identify spatial challenges to sterilant penetration. Such challenges can include "cold spots" in the load where temperature is less than that specified for the cycle and air pockets due to insufficient air evacuation processes. Once the manufacturer of the sterilizer has validated the sterilization cycle parameters and confirmed effectiveness with standardized loads, in-use instructions can then ensure that hospitals will be able to use the equipment effectively and safely.

STERILIZATION PROCESSES

In the United States, the Food and Drug Administration (FDA) recognizes three categories of sterilization methods used to sterilize medical devices in manufacturing settings. As described in draft guidance for industry, these categories are (a) *traditional* sterilization methods, (b) *nontraditional* sterilization methods, and (c) *novel nontraditional* sterilization methods (25). Traditional sterilization methods are those that have a long history of safe and effective use as demonstrated by ample literature, 510(k) clearances or approvals of premarket approval applications, and satisfactory quality systems (QS) inspections, and for which there are voluntary consensus standards for validation that are recognized by the FDA (25). Sterilization methods in the traditional category include dry heat, ETO in a fixed chamber, moist heat, and irradiation (e.g., gamma ray, electron beam). Nontraditional sterilization methods are those that do not have a long history of safe and effective use and for which there are no FDA-recognized standards but for which published information on the validation of these methods exists and for which the FDA has previously evaluated data as part of a QS evaluation and determined the methods to be adequate (25). Hydrogen peroxide gas plasma and ozone are the two methods currently listed under the nontraditional category. Of the six sterilization methods/sterilants listed in these two categories, all with the exception of irradiation are commonly available for use in US healthcare facilities. ETO, hydrogen peroxide gas plasma, and ozone are available in CSS settings as low-temperature processes for heat-sensitive instruments. Novel, nontraditional sterilizing methods are newly developed methods for which there are no FDA-recognized standards, no FDA inspection history, and no FDA comprehensive evaluations of sterilization validation data (25). There is also little or no published information on process validation for these methods. Furthermore, a novel, nontraditional method is one that has not been evaluated by the FDA as part of a QS evaluation and that employs sterilization methods that the FDA has not reviewed and determined to be adequate to provide a reasonable assurance of safe and effective use. Methods included in this category are chlorine dioxide, ETO in a bag, high-intensity light or pulsed light, microwave irradiation, sound wave energy, ultraviolet light, and vaporized chemical sterilant systems (e.g., hydrogen peroxide or peracetic acid [PAA]) (25). These novel, nontraditional methods/sterilants will not be addressed in this chapter, given their current status as emerging, developing technologies.

It is interesting to note that sterilization using liquid chemical sterilants is not included in this FDA discussion of sterilization methods. A liquid chemical sterilization process is by design problematic, time-consuming, and has no procedure or method to ensure or maintain the sterility of the device once it has been removed from the chemical. One possible explanation for the omission is that the draft guidance containing the definitions for the three sterilization method categories is intended for the device industry, and device manufacturers would be asked to identify the sterilization method used to render devices sterile before marketing. In view of the fact that liquid chemical sterilization methods involving device immersion do require long contact times and there is a risk of contamination of the devices upon removal from the chemical, it is unlikely that device manufacturers would employ a liquid chemical sterilization method. Liquid chemical sterilization, however, is a method available for use in the healthcare setting (i.e., the device customer) for the reprocessing of reusable, heat-sensitive devices.

STERILIZATION BY HEAT

Heat-based sterilization processes in healthcare facilities are based on either moist heat (steam under pressure) or, to a lesser degree, dry heat.

Moist Heat (Saturated Steam under Pressure)

Moist heat technology for terminal reprocessing of heat-stable reusable medical instruments and devices is the most common, efficient, and economical sterilization process in use. Furthermore, as a properly conducted sterilizing process, it leaves no chemical residues or byproducts on the surfaces of the medical instruments. Its lethal property is the result of mass transfer of heat to a surface via convection, with steam condensing as it loses heat. Thus, steam kills quickly and efficiently and does this by coagulation and denaturation of enzymes and structural proteins (17). The basic steam sterilizer (autoclave) is a steel-walled chamber surrounded on the sides by a jacket of trapped steam. The autoclave chamber may be sealed at the back of the chamber, or it may be designed as a "pass-through" chamber with doors located at either end. Pressure gauges, safety relief valves, temperature indicators, steam entry portals, and drain vents are some of the main engineered components of this equipment.

One of the major concerns of autoclave design and engineering is the removal of air from the load and the chamber. Although there are several different engineering approaches to air removal, the two main mechanisms used to accomplish air removal are gravity displacement and air evacuation (3). There are three types of general-purpose

steam sterilizers that use these methods of air removal: (a) gravity displacement sterilizers, (b) dynamic air-removal sterilizers, and (c) steam-flush pressure pulse sterilizers (26). Equipment employing vacuum evacuation of air was previously referred to as "prevacuum" or "porous load" sterilizers, but the Association for the Advancement of Medical Instrumentation (AAMI) now identifies these as *dynamic air-removal sterilizers* (27).

Gravity displacement autoclaves are typically used to sterilize nonporous instruments and devices, laboratory media, liquids, and pharmaceutical products; for in-house sterilization of glassware, oils, or powders, see "Dry Heat" below (17). This type of autoclave can range in size from small, tabletop units commonly used in small clinical practice to larger-sized units suitable for CSS operations (26). When engineered on a very large scale, this type of sterilizer is also one of the most commonly used technologies for the decontamination of regulated medical waste. Gravity displacement autoclaves are generally not recommended for terminal reprocessing of dense, porous items because the gravity displacement method of air removal in this situation is very inefficient. Entrapped air in a porous load leads to reduced steam penetration, and subsequently, heating efficiency (17,*28,29*).

In the "conditioning" phase of the sterilization cycle for a gravity displacement autoclave, steam enters the chamber from a portal at the top of the chamber. A water separator unit located at the steam entry portal helps to entrap water mist, removing it from the steam and thereby improving steam quality to ≥98% saturated steam (i.e., <2% water) and also minimizing the wetness of the load during the cycle (3). A steam separator modulates the velocity of the steam entering the chamber so as to minimize steam mixing with the air. Steam is lighter than air, and as steam fills the chamber from the top, air is forced by gravity to exit the chamber at a drain portal located on the floor of the chamber.

A variety of time, temperature, and steam pressure parameters have been validated for these sterilizers, and the reader is referred to the American National Standards Institute (ANSI)/AAMI document ANSI/AAMI ST79:2010 for suggested cycle parameters (27). Users, however, should consult the manufacturer's written instructions for proper and effective operation of specific models of this equipment.

Dynamic air-removal autoclaves make use of a high-speed vacuum pump to remove air at the start of a cycle. Air evacuation can be accomplished in one step or by using several "pulses" of pulling a vacuum (i.e., pressure pulsing). High-vacuum air removal is a one-pulse evacuation. When the chamber pressure reaches a partial pressure <5 mm Hg, the steam is injected into the chamber, and the heating of the load is begun (3). This particular engineering design for a sterilizer has been associated with several problems, including dehydration of certain materials, generation of superheated steam in porous item packs, charring of fabric; accordingly, uses of high-vacuum air-removal sterilizers are being phased out (3). Other versions of dynamic air-removal autoclaves are designed to evacuate the air in several applications of a vacuum, all during the conditioning phase. This pressure-pulsing method of air removal is efficient at removing air entrapped in porous loads (3). Unlike gravity displacement autoclaves, dynamic air-removal sterilizers are known to have problems with air leaks and occasional inadequate air removal (17). The Bowie–Dick test is run on dynamic air-removal sterilizers at the beginning of the day to test for effective air removal (26,27). A Bowie–Dick test sheet is inserted into a porous load (e.g., clean cotton, surgical towels) and placed toward the front of the chamber over the drain. If the conditioning phase of the sterilizer fails to evacuate all entrapped air, a spot will appear on the Bowie–Dick test sheet (27). In this event, the autoclave should be taken out of service pending inspection, repairs, and a successful pass of a subsequent Bowie–Dick test (27).

A third type of general purpose steam sterilizer employs a steam-flush pressure pulse mechanism for air evacuation. Air is evacuated by drawing a vacuum to a predetermined pressure, at which point steam is introduced into the chamber, forcing air out through a vent in the chamber. This air removal process is repeated several times, and during this process, the load gradually comes to the predetermined exposure temperature (3). Unlike the dynamic air removal sterilizers, the steam-flush pressure pulse equipment is not prone to air leaks; Bowie–Dick testing is not required with this type of sterilizer (26).

As with gravity displacement sterilizers, dynamic air-removal equipment manufacturers have validated a variety of time–temperature–steam pressure combinations of parameters, and the ANSI/AAMI ST79:2010 summarizes these in thorough discussions (27). Written instructions of the sterilizer manufacturer must also be consulted when determining the appropriate cycle parameters for each type of recommended loading configuration (e.g., wrapped metal instruments or porous materials).

Sterilization using saturated steam under pressure is a demonstrably economical and effective process. However, there are three areas of concern that impact the proper operation of these pieces of equipment: (a) superheated steam, (b) load wetness, and (c) steam quality (3). Superheat is a temperature excess above the temperature of saturated steam at the same pressure (3). Superheated steam can be generated in several ways. If the temperature in the jacket is higher than the target temperature for the cycle, materials in the load can pick up this heat. When steam is introduced into the chamber, the steam picks up the heat from the load and the walls of the chamber, resulting in superheat in the surface layers of the load (3). Superheat can be deleterious to porous loads (e.g., fabrics). When heat is transferred from steam to fabric, that effect penetrates beyond the surface and into the materials deep in the load. Additionally, heat is released when moisture rehydrates dried materials (e.g., cotton fabrics, paper) *(30,31)*. As a result, temperatures in the center of a porous load can rise and, in some instances, cause charring of the materials.

Excessive load wetness after the completion of a heat cycle can be extremely problematic. In the 1950s, researchers demonstrated that bacteria can pass through wet or damp wrapping materials, thereby contributing to post-process contamination of the load *(32,33)*. Most sterilizers include a drying phase as the last step of the sterilizing process to prevent this unacceptable wetness.

Steam quality is critical to the success of a steam sterilization cycle. Ideal steam for sterilization is 100% saturated

steam by weight (3). The presence of water diminishes the quality of the steam, which in turn affects the efficiency of sterilization and appropriate drying of processed materials (3). Most steam sterilizers are designed to operate most efficiently using high-quality steam (e.g., ≥97% steam). As steam makes contact with the load, heat is released to the load as the steam condenses. The water used to generate the steam is now spread out as a wet film over the entire load *(34)*. A steam sterilizer's dry cycle is engineered to evaporate any water that has not drained out via the chamber steam trap drains (assuming high-quality steam). Diminished quality steam adds more liquid water to the load, and if this is more than the steam sterilizer's drying cycle can evaporate during its cycle, the load will end up with wet packs *(34)*. Items that become extremely wet during the sterilization cycle are correspondingly difficult to dry.

There are a number of causes for diminished steam quality. Boiler problems are often the first to be evaluated in this regard. Boilers must be serviced and maintained by trained personnel. The steam distribution system and piping, if not insulated, can secondarily cause condensation of steam to water en route to the sterilizers *(34)*. Dissolved salts and other minerals in the water used to generate the steam can also affect steam quality.

Flash Sterilization At times, during surgical procedures, a medical instrument in short supply may be inadvertently dropped to the floor or somehow becomes contaminated such that it needs to be cleaned and sterilized as quickly as possible. The process of "flash sterilization" was developed to address this circumstance. Underwood and Perkins outlined the parameters of this process as the sterilization of an *unwrapped* item at 132°C for 3 minutes at 27 to 28 lb of pressure in a gravity displacement sterilizer (17,*35*). Flash sterilization is, therefore, distinguishable from the more conventional "full-cycle sterilization," in which a clean device or instrument is wrapped and sterilized so that it may be stored and maintained in its sterile state for subsequent use *(35)*. Historically, the Centers for Disease Control and Prevention (CDC) recommended against using flash sterilization for routine sterilization of instruments, arguing that the process should not be done as a means of convenience, to avoid having sufficient surgical instrument inventory, or to accelerate the throughput of instruments to the next surgical case *(36,37)*. Additionally, CDC recommended at that earlier time against the use of flash sterilization for reprocessing surgical implants for the following reasons: (a) up until recently there were no rapid, reliable, validated biological indicators (BIs) available for monitoring the flash sterilization procedure; (b) there was a lack of protective wrapping to maintain the sterility of the instrument; (c) there existed a possibility of inadvertent contamination of the instrument during transport from the sterilizer to the sterile operative field in the operating room; and (d) the cycle parameters (time, temperature) were considered nearing minimal effectiveness. However, there are times when flash sterilization of an implant is unavoidable in an emergency. In this situation, the process may be optimized by paying particular attention to thorough record-keeping and documentation of the implant (lot/serial numbers, separate components, etc.), the cleaning and sterilizing parameters used, the technicians performing the reprocessing, the surgical procedure and the surgical team, patient information, day and time of the surgery, etc (17).

Carefully performed by trained personnel using modern equipment, materials, and techniques, flash sterilization can be considered an effective sterilizing process with sufficient SAL (10^{-6}) such that potential patient-to-patient transmission is interrupted with high confidence *(38,39)*. Flash sterilization can be done on heat-stable reusable medical instruments using a steam sterilizer—either a gravity displacement unit or dynamic-air-removal equipment. The instrument(s) must first be meticulously cleaned, thoroughly rinsed, and dried. There are a variety of factors that must be taken into consideration with regard to cycle parameters before running a flash-sterilization process. These include (a) the type of steam sterilizer used; (b) the type of load (nonporous or a mix of porous and nonporous); (c) whether or not the item is wrapped or otherwise contained; (d) the temperature; (e) the exposure time; and (f) whether or not a dry-time phase is part of the cycle. The reader is referred to the ANSI/AAMI ST79:2010 (27) for summary tables of suggested cycle parameters for two configurations of steam sterilizers, but most importantly the healthcare facility wishing to use flash sterilization should consult the sterilizer manufacturer's written instructions for information on validated cycle parameters (27). Additionally, some medical instruments and devices require longer exposure time, making it equally important to consult the manufacturers of these instruments and devices as well. Furthermore, if any sort of containment is used for the instrument or device undergoing flash sterilization, it is imperative to verify that said containment has been cleared by the FDA for this purpose, and the healthcare facility should follow the containment manufacturer's instructions carefully. Wrappers are generally used to facilitate aseptic transport from the sterilizer to the point of immediate use after the instrument has cooled down, whereas rigid containment may be considered for aseptic holding of the instruments for short periods of time (usually <24 hours), depending on the design configuration of the container.

Recently, AAMI convened a working group of professional associations and federal government agencies (including CDC) to consider revisiting flash sterilization as practice and policy. Given the variety of cycle parameters and possible uses for shortened steam sterilization cycles, the group felt that the term "immediate-use steam sterilization" more appropriately identified this process. The working group will release a statement of its findings, but at this writing, the group continued to support these key elements: (a) manufacturer instructions for validated cycle parameters are to be followed, and containment vessels/materials should be confirmed as FDA-cleared; (b) instrument inventories should be sufficient to meet anticipated surgical demand; (c) technicians should be thoroughly trained in all aspects of performing immediate-use steam sterilization; (d) instruments must be thoroughly cleaned before sterilization; and (e) the traditional recommendations *against* performing immediate-use steam sterilization on implants and those instruments for which validated cycle parameters are not available are retained. An additional advisory against the use of immediate-use

steam sterilization for instruments that have been used on patients known or suspected of having Creutzfeld–Jakob disease was also included in the draft statement.

Dry Heat

As mentioned previously, microbial inactivation due to exposure to dry heat is accomplished primarily as an oxidative process (3). Dry-heat sterilizers operate at atmospheric pressure, and although it is a relatively inefficient heat transfer agent, the fluid medium through which heat is dispersed to the surfaces of the load is air (3). Heat is transferred through air movement known as *convection*. Dry-heat sterilizers relying on natural convection due to temperature gradients in the chamber are the *gravity convection* type, while other, more efficient, equipment with fans to help with air movement are the *mechanical convection* or "forced-air" type of dry-heat sterilizers (3).

Dry-heat cycles are characterized by high heat, relatively long exposure periods, and sometimes lengthy lag times (especially in the gravity convection type equipment) as the load items are brought up to temperature. One factor that will impact the effectiveness of a dry heat process is the amount of water (intrinsic moisture) in the materials undergoing sterilization. The lower the RH, the longer the time required for sterilization using dry heat *(23)*. Table 81-1 lists current time–temperature relationships for a variety of dry-heat sterilization cycles.

Dry-heat sterilizers should not be overloaded since air must freely circulate amongst the items in the load in order for proper heat transfer to occur. Dry heat is typically used to sterilize those items that would be damaged by steam and/or moisture or are otherwise impenetrable by steam. Examples of such items are petrolatum, oils, powders, delicate sharp instruments, and glassware (3). One useful application in particular is the use of dry heat to render glassware free of endotoxin residues during sterilization since cycles in steam autoclaves *do not* inactivate endotoxins. An additional benefit to using dry heat is its reduced propensity to corrode materials and dull sharp edges. Some of the obvious disadvantages, however, are (a) high temperature damage to easily charred or combustible materials, (b) long exposure times, (c) damage to some materials due to oxidation, and (d) a potential for distinct temperature zones being generated in the chamber due to improper loading and subsequent inefficient air circulation (3).

TABLE 81-1

Time–Temperature Relationships for Dry Heat Sterilization (3,*40*)

Temperature	*Exposure Time in Minutes*[a]
170°C (340°F)	60
160°C (320°F)	120
150°C (300°F)	150
140°C (285°F)	180
121°C (250°F)	Overnight

[a]Does not include lag time for load to reach temperature.

STERILIZATION WITH GASES

Two gas sterilants have been used in CSS settings:ETO and, more recently, ozone. ETO was the first major sterilant to be used for low-temperature sterilization processes.

Ethylene Oxide

ETO (molecular formula C_2H_4O) was first registered by the U.S. Environmental Protection Agency (EPA) as a pesticide under the provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in 1966 (41). It is a colorless gas with flammable and explosive properties (17). End-use formulations comprise a mixture of ETO and inert gases in varying concentrations to lessen combustible properties. In hospitals and healthcare facilities, ETO is used to sterilize heat-sensitive medical instruments, devices, and some laboratory devices (21 CFR §201). In the United States, approximately 7.4 million pounds of ETO is used for end-use healthcare applications annually (41).

ETO is an alkylating agent that interacts with proteins and nucleic acids (*42,*43). This chemical reaction with cellular components interferes with cell metabolism and replication (17). ETO is broadly antimicrobial, capable of inactivating bacteria, viruses, fungi, and bacterial endospores *(44–47)*.

The length and effectiveness of the ETO sterilization cycle is dependent on several factors: (a) ETO gas concentration, ideally in the range of 450 to 1200 mg/L; (b) temperature, ranging from 37°C to 63°C; (c) RH, ranging from 40% to 80%; and (d) length of the exposure phase (1–6 hours) (17,43,48,*49*). RH as a source of moisture is especially important as this enables ETO to penetrate the load. Gas concentration and temperature modifications may help to shorten the exposure phase of the cycle (17). The effectiveness of the process can be diminished by the presence of salts and organic matter (17,*50*).

There are five phases comprising the ETO sterilization cycle: (a) preconditioning and humidification, (b) gas introduction, (c) exposure, (d) evacuation, and (e) air washes (17). The preconditioning phase accomplishes several things to enhance the effectiveness of the process, namely, the preparation of the chamber by establishing correct humidity and temperature parameters. A vacuum is drawn, and ETO is introduced into the chamber in the next phase. The length of the exposure phase is determined in part by the size and configuration of the load (48). At the completion of the exposure phase, the gas is evacuated and air washes take place.

One of the characteristics of ETO is its ability to penetrate a variety of materials such as polymers and plastics (*42,*43). ETO is also a known carcinogen and toxic substance that, with short-term occupational exposure, can cause respiratory distress, nausea and vomiting, convulsions, muscle weakness, nerve damage, cognitive impairment, and eye and skin irritation *(51,52)*. ETO residuals in implant devices have been known to cause tissue burns in patients, and residuals in ETO-sterilized hollow fiber dialysis membranes have been shown to be neurotoxic (17,*53,54*). To prevent these adverse events, medical instruments and devices subjected to ETO sterilization must be sufficiently aerated to remove ETO residuals. Aeration can take from 8 to 12 hours and is typically performed at 50°C to 60°C (17). AAMI has promulgated a guidance document

detailing allowable ETO limits for devices (48). The use of the processed device (e.g., duration of use, method of use, and repeated use) is factored into allowable residual determinations (17,48). To protect healthcare facility employees from ETO exposure, EPA requires, as of February 28, 2010, that facilities must use a single-chamber process (i.e., sterilization and aeration occurring in the same chamber) when using an ETO sterilizer for the terminal reprocessing of instruments *(55)*.

ETO is currently the principal sterilant that may be used, if judged necessary, to sterilize rigid or flexible endoscopes or other lumened devices, but because some studies have shown that lumen diameter and length may hinder full ETO penetration throughout all channels, it is important for healthcare facility professionals to check with the endoscope manufacturer to determine if ETO sterilization has been validated for the device make and model (17,*50,56,57*). Additionally, the long aeration time required after ETO sterilization is a key factor to consider when determining if this process is suitable for lumened instruments, given the usual demand for rapid endoscopic instrument turnaround. This somewhat problematic and overtly lengthy, expensive process of endoscope sterilization using ETO is perhaps the main reason that virtually all endoscopes—in particular, the flexible ones—are reprocessed using a powerful disinfecting process, *high-level disinfection* (see below [Sterilization with Liquid Chemicals] and more detailed discussion of high-level disinfection in Chapter 80).

Ozone

Ozone has had a long history as a disinfecting gas, with applications typically noted for water and wastewater treatment *(58)*, aquaculture, heating and cooling unit treatment, process water treatment in industry, food processing, and paper pulp bleaching, among others (59). Ozone is an unstable three-atom form of oxygen (O_3) generated by the excitation of molecular oxygen (O_2) into atomic oxygen (O) in an energizing environment allowing the recombination of these atoms to form O_3 (59,*60*). Ozone is a powerful oxidizing agent, and its stability varies with its physical state. In the gaseous phase, the half-life of ozone in ambient atmosphere is approximately 12 hours, whereas in the aqueous phase, the half-life varies from hours to seconds depending on the characteristics of water (e.g., temperature, pH, and UV light) (59).

Ozone has broad antimicrobial properties and has been shown to inactivate bacteria, bacterial endospores, viruses, fungi, and yeasts (59). Greater levels of $\log_{10}$ reduction for bacteria (~4–5 $\log_{10}$) are observed with long contact times (~20 minutes) at concentrations ranging from 0.18 to 0.5 mg/L when the presence of organic matter is kept to a minimum (i.e., an ozone demand-free system) (59). For viruses suspended in water, reductions of 1–4 $\log_{10}$ have been documented for contact times ranging from 10 to 30 seconds at concentrations of 0.14 to 0.5 mg/L (59).

Ozone sterilizers are relatively new to the medical instrument reprocessing marketplace and provide another option for low-temperature sterilization of heat-sensitive reusable devices. As with any sterilizing process, the effectiveness of this process is affected by the presence of organic matter, materials and configurations of the devices (e.g., hinged instruments must be open to ensure gas penetration) and/or chamber loading, and the number and intrinsic resistance of any mixed microbial populations present. Therefore, devices must be thoroughly cleaned, rinsed, and dried before terminal reprocessing. A typical cycle for ozone sterilization involves three phases—two preconditioning and exposure phases followed by a ventilation phase *(61)*. In the preconditioning steps, a vacuum is drawn, humidification occurs, and chamber temperature is increased to slightly above room temperature (30.8–36°C) *(62)*. Ozone is generated within the sterilizer and introduced into the chamber to begin the exposure phase (63). After a brief repressurization of the chamber, these steps are repeated, followed by the ventilation portion of the cycle to remove residual ozone from the chamber *(61,62)*. The cycle time is longer compared to other sterilizers (4.5 hours).

Ozone sterilizers can be used to terminally reprocess a variety of medical instruments made of metal or plastics, but they are not recommended for sterilizing sealed ampoules, fabrics, liquids, or latex/natural rubber products (*62,*63). Laboratory studies of one ozone sterilizer have shown that ozone can penetrate lumens as narrow as 0.5 mm and as long as 70 cm and produce >6 $\log_{10}$ reduction of *G. stearothermophilus (61)*. Manufacturer literature advises that their sterilizer has not been validated for sterilization of surgical implants *(62)*. Devices ready to be sterilized should be packaged in nonwoven materials or reusable rigid sterilization container systems cleared by the FDA for use in ozone sterilizers (63).

STERILIZATION WITH GAS PLASMA

The sterilization of medical instruments and devices using gas plasma technology is a relatively recent development in the healthcare industry, gaining momentum in the 1990s, whereas heat-based and gas technologies have been in use for decades. One of the major factors driving this development was the emergence of medical instruments and devices manufactured from heat-sensitive materials (e.g., plastics and fiber optics). Gas plasma technology provides yet another alternative means of low-temperature sterilization, has reasonably rapid sterilization cycles, and minimizes or eliminates potentially hazardous residuals from being deposited on the instruments.

Plasma is the fourth state of matter. It typically consists of a cloud of ions, electrons, or neutral species, generated by very high temperature or by electric or magnetic fields. The type of plasma used in healthcare facilities is a "glow discharge" or low-temperature plasma (64). The two main methods of generating low-temperature plasmas are direct electric current and the use of radio frequency *(65,66)*. Of these, the radio frequency system is the most common, is easier to design into the equipment, and is characterized by higher ionization efficiencies (64). Plasmas are identified by the type of gas or vapor from which they are formed (64). The FDA-cleared technology marketed in the United States converts an aqueous chemical solution first to vapor in a vacuum, and radio frequency converts the vapor to plasma.

Hydrogen peroxide gas plasma has been shown to effectively inactivate bacterial endospores as well as a wide variety of other microorganisms (17,*44,46,67–70*). The mechanism of sporicidal activity, although not fully understood for this technology, is presumed to be due to the generation of chemical free radicals and other biologically active species as the chemical vapor and plasma are generated *(71)*. These free radicals and active species presumably penetrate and act on essential cell components (i.e., enzymes, nucleic acids, proteins) and disrupt microbial metabolic processes (17). The energy required to produce these active chemical species is very low (1–10 eV) (64). A hydrogen peroxide gas plasma sterilizer has several steps to accomplish before the exposure phase in which plasma is generated. First, a vacuum is drawn in the chamber, and a small amount of 59% aqueous hydrogen peroxide is introduced into the chamber. This is vaporized until a concentration of 6.0 mg/L is reached. Vaporized hydrogen peroxide also has antimicrobial properties and exerts some degree of inactivation in advance of the plasma phase. Pressure in the chamber is reduced, and radio frequency energy of 400 W is applied to the vapor, converting it to the plasma state (64). At the end of the plasma phase, free radicals decay to oxygen and water.

Research and development work by the manufacturer determined that adequate diffusion of the vaporized hydrogen peroxide to all items in the load is important so that the reactive chemical species are right at the surfaces of the items to be sterilized when the plasma is generated. This requires that the packaging or wrapping of the items be designed to allow penetration of the vaporized hydrogen peroxide. Packaging/wrapping materials that are suitable for use with hydrogen peroxide gas plasma sterilizers include Tyvek-Mylar pouches, polypropylene wrapping, or reusable containers cleared by the FDA for use with these sterilizers (63). Additionally, sterilant penetration of lumens with this technology is limited; thus, lumened devices with long or narrow channels cannot be adequately processed with this sterilizer (FDA-cleared versions in the United States). Healthcare facilities are advised to check with the sterilizer manufacturer to identify the lumened instruments that can be successfully sterilized with this equipment (63).

Medical instruments and devices that would normally be damaged by high heat and/or moisture can be processed with this technology with the exception of the following: linens; other materials containing cellulose; powders; liquids; and devices with long, narrow lumens or with blind lumens (63,64,*69*).

STERILIZATION WITH LIQUID CHEMICALS

The Food Quality Protection Act of 1996 exempted from the definition of "pesticide" (previously under FIFRA) the liquid chemical sterilants and high-level disinfectants intended for use in the reprocessing of reusable, clean, critical and semi-critical medical devices *(72)*. This Act conferred upon the FDA sole regulatory jurisdiction over these classes of chemicals used for medical device reprocessing. A "sterilant" is defined as an agent (including select, sufficiently potent liquid chemicals) that destroys all viable forms of microbial life, including high numbers of highly resistant bacterial endospores (1). For the liquid chemical sterilants, these agents must demonstrate this potency under standard laboratory test conditions as specified by the AOAC International (AOAC). Traditionally, a "high-level disinfectant" is a sporicidal germicidal chemical that, under conditions of use, inactivates all microbial pathogens except *high* numbers of the bacterial endospores (1,*15*). FDA further elaborates on this definition of high-level disinfectant with a process aspect, defining a high-level disinfectant as a sterilant used under the same contact conditions, except for a shorter contact time *(72)*.

FDA requires manufacturers of liquid chemical sterilants/high-level disinfectants to submit laboratory data in support of antimicrobial claims as part of the official clearance process. Typically, potency testing using a validated test method for sporicides (AOAC Sporicidal Test 6.3.05: 1995, Official Method 966.04) demonstrates the chemical's capability to inactivate bacterial endospores effectively. Simulated-use tests provide a slightly different perspective on the chemical's performance, namely, to determine the penetrating capability of the germicide and identify the conditions under which the chemical will fail *(72)*. Chemicals to be marketed as high-level disinfectants first have to qualify as a sterilant by passing the AOAC Sporicidal Test and worst-case condition testing with simulated-use tests. Additional potency testing using another AOAC method (6.3.06: 1995, Official Method 965.12, Tuberculocidal Activity of Disinfectants) or a quantitative suspension test *(73)* and simulated-use testing would then be conducted using an appropriate mycobacterial challenge microorganism (e.g., *Mycobacterium terrae, Mycobacterium bovis*) with the same contact conditions except for a shorter contact time *(72)*. Additional details of the methods and data requirements for FDA clearance of these classes of germicides are thoroughly outlined in the agency guidance *(72)*. Historically, all of the germicides tested in this regulatory process had sufficient potency to be cleared as liquid chemical sterilants with indications for device sterilization and use conditions for the chemical to function as a high-level disinfectant. More recently, however, several germicidal chemicals capable of sporicidal activity have failed to meet the stringent criteria as a liquid chemical sterilant but have performed adequately in the simulated-use testing for high-level disinfectants. The FDA has allowed the qualified marketing of these chemicals for indications for high-level disinfection only (e.g., *ortho*-phthalaldehyde, hypochlorite/hypochlorous acid) (74).

Although the terms appear similar, "liquid chemical sterilization" is significantly different from "traditional sterilization." The FDA recognizes that sterilization with liquid chemical sterilants does not deliver to a "sterile field" a device with the same SAL as one sterilized using physical or thermal sterilization methods *(72,75,76)*. Traditional sterilization, from FDA's perspective, is a validated, reliable, economical process used to render a product free of all forms of viable microorganisms (*72,*77). In most cases, thermal methods, such as steam, are used to achieve sterilization. Thermal sterilization methods have been studied and characterized extensively, and it is well known that inactivation kinetics/survivor curves are log-linear for these methods, and therefore, easy to extrapolate. In contrast, the survival

BOX 81-2

Practical Limitations of Liquid Chemical Sterilization Processes

1. Liquid chemical sterilants are very sensitive to extraneous organic material.
2. Liquid chemical sterilants are slower acting compared to heat.
3. Liquid chemical sterilants do not penetrate by convection as compared to heat.
4. The item to be processed cannot be wrapped.
5. Biological monitoring of liquid chemical sterilization is problematic (e.g., the indicator microorganisms cannot be hermetically sealed for validation).
6. The item must be aseptically removed from the liquid with sterile gloves and garb.
7. The item must be handled aseptically and rinsed with sterile water.
8. The rinsed item must be dried with sterile towels.
9. The item must be placed in a sterile container if it is to be transported or is not used immediately.

(Data from references *72,75,76,*77, and *78.*)

curve data for liquid chemical sterilants may not exhibit log-linear kinetics; the shape of the curve can vary on any number of factors including the formulation or chemical stability of the particular sterilant *(72)*.

There are several limitations to the overall efficiency of liquid chemical sterilization. Although a spectrum of oxidative or fixative liquid chemical agents are capable of inactivating large numbers of resistant bacterial endospores, the *process* of liquid chemical sterilization, appropriate only for a limited variety of heat-sensitive instruments, is much more fragile than traditional heat (or gas or irradiation) sterilization because of the limitations listed in Box 81-2.

The users of this fragile method of reprocessing medical instruments must be fully aware that the probability of an SAL of 10^{-6} being presented to a "sterile field" is nil after all the postprocess manipulations. In other words, from a standpoint of killing bacterial endospores, the state of "sterility" (10^6 spores killed in a half-cycle test) *may be* achieved during the exposure/immersion period (see Practical Limitation No. 5 in Box 81-2). However, when the item is simply removed from the liquid, that "state of sterility" no longer exists. The subsequent manipulation of the item further reduces the "assurance level."

Table 81-2 summarizes the theoretical probabilities of contamination and infection for the different types of terminal microbial inactivation processes *(79)*.

Thorough cleaning must precede the terminal reprocessing step. Those critical instruments that are heat-stable should be steam sterilized (1). Those critical instruments that are not heat-stable must be sterilized using a low-temperature sterilization procedure, of which liquid chemical sterilization, as qualified above, is an option. However, given the information in Table 81-2, it should be clear that heat sterilization methods provide an optimal SAL and are the most efficient and cost-effective methods. Therefore, it makes no sense to subject a heat-stable reusable medical instrument or device to a liquid chemical sterilization process. The debit of process efficiency is self-evident, and if given a quest for economy or speed in reprocessing, this practice should be discouraged.

Liquid Chemical Sterilants and High-Level Disinfectants

As of June 2010, 22 FDA-cleared liquid chemical sterilants and high-level disinfectants with general claims of reprocessing reusable medical devices are known to be marketed in the United States. Table 81-3 provides summary information on these chemicals *(80)*. This list does not include chemicals exclusively linked as a component of a machine-liquid chemical "system."

All liquid chemical sterilants are required to demonstrate sufficient potency to kill bacterial endospores, but as is evident from Table 81-3, in many instances the

TABLE 81-2

Theoretical Probabilities of Residual Contamination and Infection Transmission Post–Terminal Reprocessing

Procedure	*Indications*	*Probability of Contamination*	*Probability of Infection*
Heat sterilization	Heat-stable critical devices	10^{-6}	0
Chemical sterilization (long immersion)	Heat-sensitive critical devices	A. 10^{-3} B. 1	A. 0 to ? B. 1 to ?
High-level disinfection (short immersion)	Heat-sensitive semi-critical devices	A. 1–10^{-2} B. 1	A. 1 to ? B. 1 to ?
Low-level disinfection	Noncritical devices; environmental surfaces	1	1 to ?

Note: A. During immersion time. B. After postimmersion manipulation (rinsing with sterile water, drying with sterile towels, aseptic transport to a sterile field or to a sterile container).
(Modified from Favero MS. Current sterilization procedures accomplished by liquid chemical germicides. In: Favero MS, Gröschel DHM, eds. *ASM symposium of chemical germicides in the health-care field. Current status, evaluation of efficacy and research needs*. Washington, DC: American Society for Microbiology, 1987:13–18.)

TABLE 81-3

Summary of Currently Available, FDA-Cleared Liquid Chemical Sterilants and High-Level Disinfectants *(80)*

Active Ingredient	*510(k) Number*	*Available Concentration*	*Indications for Device Sterilization*		*Indications for High-Level Disinfection*		*Proprietary System*	*Notes*
			Time	*Temperature (°C)*	*Time*	*Temperature (°C)*		
Glutaraldehyde	K051305	2.65%	—	—	5 min	37.8	Yes	Single use
	K012889	3.5%	10 h	20	45 min	25		
	K993042	2.5%	7 h 40 min	35	5 min	35	Yes	AER holds temperature
	K974188	3.2%	10 h	20	40 min	20		
	K974062	3.0%	10 h	25	25 min	25		
	K931592	3.4%	10 h	25	90 min	25		
	K931052	2.5%	10 h	25	90 min	25		
	K924434	2.4%	10 h	25	45 min	25		
	K923744	3.4%	10 h	20–25	20 min	25		
	K914749	2.5%	10 h	22	45 min	22		
	K060618	2.4%	10 h	25	45 min	25		
Glutaraldehyde + isopropanol	K041360	3.4% glutaraldehyde 26% isopropanol	10 h	20	10 min	20		
Hydrogen peroxide + peracetic Acid (PAA)	K041984	8.3% hydrogen peroxide 7.0% PAA	5 h	25	5 min	25		
	K972708	7.35% hydrogen peroxide 0.23% PAA	180 min	20	15 min	20		
	K960513	1.0% hydrogen peroxide 0.08% PAA	8 h	20	25 min	20		
Ortho-phthaldehyde (OPA)	K032959	5.75%	—	—	5 min	50	Yes	Single use
	K030004	0.55%	—	—	12 min (manual) 5 min (AER)	20 (manual) 25 (AER)	Yes	Can be used manually or with AER
	K991487	0.55%	—	—	12 min	20		
	K070627	0.60%	—	—	12 min (manual) 5 min (AER)	20 (manual) 25 (AER)	Yes	Can be used manually or with AER
Hypochlorite + hypochlorous acid	K013280	650–675 FAC	—	—	10 min	25		Single use, generated on site
	K063159	400–450 FAC	—	—	10 min	30		Single use, generated on site
Hydrogen peroxide	K080420	2.0%	—	—	8 min	20		

AER, automated endoscope reprocessor; FAC, free available chlorine.
(Adapted from U.S. Food and Drug Administration. Alternatives to STERIS System 1. Available at *www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm194429.htm*; current as of May 22, 2010. Readers are urged to update this table periodically at *http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm194429.htm*. Accessed May 22, 2010.)

contact time required to achieve liquid chemical sterilization is quite long, making sterilization generally impractical as a process. Furthermore, instrument exposure to some of these potent chemicals for such long periods of time may result in serious damage to the instrument. In these situations, these chemicals are used only at shorter contact times sufficient to inactivate mycobacteria (i.e., to be *tuberculocidal*) and small numbers of endospores (i.e., the process of high-level disinfection). These are the chemicals, listed in Table 81-3, that have no legal clearance or indication for sterilization *(80)*. The use of liquid chemical sterilants for high-level disinfection is discussed in detail in Chapter 80.

Glutaraldehyde

Glutaraldehyde is a saturated dialdehyde related to formaldehyde but it has been shown to be two to eight times more sporicidal than formaldehyde *(81)*. The mode of action of glutaraldehyde on microorganisms is by alkylation, reacting with amino and sulfhydryl groups of proteins and ring nitrogen atoms of purine bases (1). This acts as a protein fixative and disrupts the integrity of nucleic acids. The sporicidal potency of glutaraldehyde can be affected by pH, temperature, and ultrasonic energy (1). The microbiocidal activity of aqueous glutaraldehyde appears to increase when the pH is alkaline but declines after storage or repeated use *(81)*. Neutral to acidic formulations are also sporicidal, and this activity is increased by the addition of heat or in the presence of ultrasonic energy *(82,83)*.

Manufacturer's use instructions indicate the conditions for repeated use of glutaraldehyde formulations and the use-life period for working solutions. Chemical indicators (CIs) are typically used to monitor active ingredient concentration before and during use. In practice, any liquid chemical sterilant used for more than one sterilization (or disinfection) cycle will lose potency for a variety of reasons. These include dilution from repeated exposure to wet or moist instruments, dilution from use in certain automated disinfecting machines, accumulated organic material from improperly cleaned instruments, excessive heating, or other innate chemical degradation (1). In other words, chemical germicides (including glutaraldehyde) invariably lose potency if reused, and the rate of loss is more dependent on patterns and intensity of usage rather than the age of the solution *(84–86)*.

Glutaraldehyde-based germicides are the most widely used liquid chemical sterilant/high-level disinfectant products legally marketed for between-patient reprocessing of heat-sensitive medical instruments and devices. Manufacturer instructions for these products indicate their use *only* as immersion chemicals. That is, there is no indication for the use of glutaraldehyde products as surface disinfectants in any environmental or institutional setting. Proper ventilation and personal protective equipment (e.g., gloves and face protection) are required to prevent toxic or sensitization reactions in healthcare personnel (1).

Hydrogen Peroxide

Hydrogen peroxide has been recognized as a reliable germicide for more than a century. It is available in a stabilized form (2% H_2O_2) and in several low concentration formulations of hydrogen peroxide and PAA. At present, only the hydrogen peroxide/PAA formulations are legally marketed for device sterilization *(80)*. The mode of action is that of an oxidative chemical reaction with cellular components. Hydrogen peroxide in high concentrations is bactericidal, virucidal, and sporicidal *(87,88)*. Hydrogen peroxide in concentrations between 3% and 7% or in mixtures with PAA constitutes a useful class of chemical agents for sterilizing and disinfecting medical devices *(89)*.

Peracetic Acid

PAA, a powerful chemical oxidizer, has been known for decades as an effective antiseptic. In the 1800s, for example, PAA was used as a hand wash product, and it is capable of denaturing proteins and other cellular components (e.g., enzymes) and affects cell wall permeability (17,90,*91*). PAA is a strong, broad-spectrum germicide, with potency demonstrated against gram-positive and gram-negative bacteria, fungi, viruses, and yeasts (17,90). When used as a disinfectant/sterilant, instruments must be meticulously cleaned since organic matter will rapidly diminish the potency of PAA (17,*92*).

It was only recently (within the last 25 years) that the sporicidal properties of PAA were evaluated and put to commercial use. In 1988, the FDA cleared a PAA chemical sterilant as part of a liquid chemical sterilizing system (Steris System 1, S20 sterilant). As a low-temperature sterilizing process, this system was commonly used to terminally reprocess heat-sensitive, lumened devices such as endoscopes and bronchoscopes. In 2008, however, the FDA found that this equipment and its liquid chemical sterilant were adulterated, misbranded products *(93)*. As a consequence, this "system" (machine and sterilant cartridge) has been withdrawn from the market *(94)*. As of this writing, healthcare facilities have until August 2011 to seek out an alternative for this system (95,*96*), and the FDA has provided a list of currently available replacement equipment and chemicals *(80)*. Final FDA clearance to market new equipment and the PAA agent for a reprocessing system from Steris was granted in April 2010 (Steris System 1E) *(97)*. However, when the present content of the revised 510(k) summary of the device is compared to the FDA web page description of the system, the current status of this new PAA-based equipment is unclear, pending further action from the company and/or FDA *(97,98)*. A 510(k) is a written, premarket notification/submission to the FDA documenting the equivalence between a new product and a predicate device. Required documentation elements are annotated in 21 CFR Part 807, and include product labeling, product/device description, and a comparison of the new device to another legally marketed device, which is called a predicate. The threshold for market clearance is the demonstration of substantial equivalency of the new device to the predicate *(99)*.

MONITORING THE STERILIZATION PROCESS

As mentioned previously, the state of absolute sterility is difficult to prove and certainly cannot be measured or validated with post-process sampling and testing. It is common to define sterility in terms of the probability that a contami-

nating microorganism will survive a sterilization process. As mentioned previously, sterilization is defined as a microbial inactivation process in which the probability of any one microorganism (a bacterial endospore) surviving on a device is 10^{-6} or lower. This concept has been used to develop and monitor cycles for steam autoclaves, ethylene oxide sterilizers, hydrogen peroxide gas plasma sterilizers, ozone sterilizers, and radiation sterilization (used in industry). Since the survivor curve kinetics are log-linear for these physical, gaseous, or radiation sterilizing processes, the time needed to inactivate an additional six $\log_{10}$ of bacterial spores can be determined by extrapolation of the curve (see Fig. 81-1) (1). A physical, gaseous, or radiation-based sterilization cycle engineered based on this concept produces a great degree of overkill as well as a quantitative assurance of sterilization. In contrast, it is difficult to evaluate liquid chemical sterilization or disinfection processes using these criteria, in part, because the inactivation kinetics in these procedures are not log-linear. Additionally, biological indicators with bacterial endospores (i.e., BIs [discussed below]) used to validate sterilization processes need to come into contact with the sterilant while at the same time maintaining their hermetic integrity. Common proprietary BIs are packaged in containment, designed to allow sterilant penetration while the indicator microorganisms remain in place within the packaging. The indicator organisms can neither escape the "carrier" nor become contaminated from external sources. If such an indicator is used with a liquid chemical sterilization system, it is necessary to remove the filter paper carrier with the bacterial endospores from the hermetic packaging in order to effect contact with the liquid chemical. Under these circumstances, it is evident that a portion of the reduction in numbers of active spores on the carrier strip will be due, in part, to spore on the carrier strip removal or wash-off (100,*101*). This could easily give a user of such a system (naked indicator strip in an agitated liquid system) a false sense of potency of the process being "monitored."

There are three major categories of monitoring devices used for more traditional sterilization processes in healthcare facilities. These are BIs, CIs, and physical or parametric monitors. Of these, the BIs and the majority of CIs are placed in the sterilizer chamber appropriately among the load to react to the conditions within the chamber during the sterilization cycle. Physical or parametric monitors built into the sterilizer equipment are used to monitor and document cycle parameters such as time, temperature, pressure for steam sterilizers; time and temperature for dry-heat sterilizers; and time, sterilant concentration, temperature, and humidity for gaseous sterilizing equipment. Some CIs are designed to measure specific key functions of the sterilizer equipment. Air-removal indicators for test packs, for example, are CIs specifically used to determine effective air evacuation from the chamber of dynamic air-removal steam sterilizers prior to terminal reprocessing of devices and instruments. A more detailed discussion of each of the process indicators is found in Chapter 70. According to AAMI, each monitor or indicator device is essential to sterility assurance as each serves a different function in process monitoring (27).

Biological Indicators

BIs are classified by the FDA as Class II devices and are the preferred standard for monitoring the effectiveness of a sterilization cycle as a complete inactivation process. These viable microorganism indicators respond to time, temperature, and other operative parameters of the cycle. Their ability to withstand the sterilization process is also affected by other miscellaneous conditions such as superheat and the physical characteristics of the load (e.g., placement in the load and sterilant penetration of the load) (3). BIs verify that the conditions at the most occluded location within the load were adequate to kill a population of microorganisms resistant to the sterilization process and demonstrate the lethality of said process (26). BIs are generally contained within a "process challenge device" (PCD), which is designed to simulate the products being sterilized and to present a defined challenge to the sterilization process (26).

BIs are generally manufactured as filter paper strips impregnated with a standardized preparation of bacterial endospores, the numbers of which typically are 10^6 to 10^7. The selection of endospores depends on the type of sterilant used in the sterilization process. Box 81-3 lists the challenge bacterial endospore genus and species cleared by the FDA for use with the commonly used sterilants.

As mentioned previously, levels of spore resistance vary according to species and inactivating treatment. Virtually all spores resistant to moist heat are sensitive to dry heat. Conversely, those resistant to dry heat are sensitive to moist heat. Recalling the discussion of survivor curves and the kinetics of inactivation, sterilization cycles are engineered to be capable of inactivating 12 $\log_{10}$ of resistant challenge microorganisms. Since BIs will have approximately 10^6 bacterial spores on a carrier, it follows that a BI is, in reality, a *half-cycle* indicator (1). At the completion of the sterilization cycle, the BI is incubated and observed for growth or no growth compared to positive and negative controls (incubation temperatures are very important and must be exact according to the manufacturer's directions). If the BI shows growth, this indicates that the sterilization process may have been ineffective. For instance, if a spore (BI) indicator failure occurs, at worst, this result indicates a possibility that >50% of the potency of the sterilization cycle was not delivered to the BI. However, because sterilization processes are designed with significant overkill, the load from the cycle with the positive-growth BI may not have to be recalled. Other

BOX 81-3

Biological Indicator Microorganisms Used to Monitor Sterilization Processes in Healthcare Facilities

BI Microorganism	*Sterilant*
Geobacillus stearothermophilus	Moist heat (steam under pressure)
Bacillus atrophaeus	Dry heat
B. atrophaeus	Ethylene oxide
G. stearothermophilus	Ozone
G. stearothermophilus	Hydrogen peroxide gas plasma

process indicators and monitors need to be evaluated and considered (e.g., physical parameters such as temperature, time, and pressure; CIs). If these other indicators and monitors suggest that the sterilization cycle was operationally correct, a follow-up run with a BI in the sterilizer should be done using the same cycle and load parameters. If the BI in this follow-up run shows no growth, it is likely that the previous BI was inadvertently contaminated post–sterilization cycle, and the load can be released (17). If this follow-up BI reads positive for growth (i.e., a bacterial spore-former [the indicator microorganism]), the sterilizer should be taken out of service, repaired accordingly, and the subsequent dry run sterilizer cycles should be reevaluated with additional follow-up BIs (with appropriate challenge packs) (17). No growth in subsequent BIs from these dry runs signals that the equipment can be returned to service. Healthcare facilities should have clearly defined and regularly updated CSS standard operating procedures that address the action to be taken when a potential sterilizer failure occurs.

Some contemporary BIs will have an enzyme-based "early readout" capability in addition to a bacterial endospore response (27). This feature reduces the time required to obtain a load release decision. Manufacturer's instructions for this device should be followed precisely for proper interpretation of results. Additionally, it is important to periodically verify the accuracy of the enzyme reading by continuing to incubate the BI and by observing for growth or no growth (27).

Sterilizers should be monitored with the appropriate BIs at least on a weekly basis (17). If a sterilizer is used for several loads on a daily basis, it is advantageous to use a BI for the sterilizer each day. This will facilitate early discovery of sterilizer failure or procedural errors, thereby, minimizing subsequent load recall and patient surveillance (17,*102*). A BI should be included for every sterilizer load containing implantable devices, the release of which is dependent on the negative growth reading for the indicator (17).

Chemical Indicators

CIs are designed to display a chemical or physical change in the response to one or more of the physical conditions in the chamber during a sterilization process (27). For example, if a CI is designed to respond to temperature, the indicator will exhibit a visible change signifying that the target temperature had been reached at some point in the sterilization cycle. However, this may not be interpreted that the temperature remained at target for the duration of the exposure phase of the cycle. Nevertheless, the use of CIs provides additional information to complement the results of BIs and physical parametric monitoring. Proprietary CIs specific for each type of thermal or gaseous sterilizer have been cleared by the FDA.

AAMI defines six classes of CIs available to healthcare facilities (27,48,*103*). These are listed in Box 81-4.

Class 1 indicators are external CIs. That is, these are affixed to the outside of the pack. The purpose of this type of indicator is to differentiate processed packs and items from those that have not been processed. Class 1 CI reactions should not be interpreted as evidence of an adequate sterilization cycle but only that the packs or items have been exposed to the "trigger" temperature. A Class 1 CI should be affixed to each pack or item in the load. The exception to this approach occurs when the packaging for the medical devices has see-through areas that allow for visual inspection of any CIs inserted into the pack. Class 2 indicators (i.e., Bowie–Dick test pack indicator) are used for equipment control and evaluation of sterilizer performance (27,48,*103,104*). A Bowie–Dick test pack indicator, as mentioned previously, is used to monitor the effectiveness of the air-removal process in a dynamic air-removal steam sterilizer only. Classes 3, 4, 5, and 6 indicators are all designed to be inserted into a pack to demonstrate that the target parameter(s) (e.g., temperature) has been achieved. Class 3 CIs measure a single parameter of the sterilization process, most commonly temperature. There are specific Class 3 CIs for each target or specific temperature value (e.g., 121°C, 134°C, etc.) for the exposure phase of the sterilizer cycle. Class 4 CIs are designed to react to multiple variables of the sterilization cycle (e.g., time, temperature) *(104)*. Class 4 CIs will provide the sterilizer operator more information about the cycle performance compared to the information from a Class 3 indicator. Classes 5 and 6 CIs are the most recent additions to the chemical indicator product line and are used for pack control. Class 5 integrating CIs react to all critical variables of the sterilizing cycle. Class 5 CIs are the most accurate of the internal CIs when used in accordance with the manufacturer's instructions *(104)*. Class 6 emulating CIs are also used for pack control and react to all critical variables of the sterilizing cycle, but these devices must be specified for specific sterilization cycles *(104)*. Consequently, the CSS must have a different Class 6 emulating CI for each sterilizer time/temperature combination used *(104)*. Because

BOX 81-4

AAMI Classification for Chemical Indicators (CIs) (27,48,*103*)

Class 1—process indicators. Used with individual packs or items to indicate that the pack or item was exposed to a sterilizing cycle.

Class 2—specific test indicators. An example of this type of indicator is the Bowie–Dick type indicator that is used specifically to determine the efficacy of the air-removal process for dynamic air-removal steam sterilizers.

Class 3—single parameter indicators. Designed to react to one of the critical parameters of the sterilization process.

Class 4—multiparameter indicators. Designed to react to two or more of the critical parameters of the sterilization process.

Class 5—integrating indicators. Designed to react to all of the critical parameters over a specified range of sterilization cycles.

Class 6—emulating indicators. Designed to react to all of the critical variables of specified sterilization cycles, with stated values having been generated from the critical variables of the specified sterilization process.

the availability of Class 6 emulating CIs is a recent event in the US healthcare market, readers should consult ANSI/AAMI ST79:2010 for more detailed information regarding the use of this CI (27). The performance of Class 5 integrating CIs and Class 6 emulating CIs have been correlated to the performance of a BI when manufacturer instructions are followed. However, these indicators are not intended to replace or to be used to the exclusion of a BI. CI Classes 1–6 are available to monitor steam sterilization applications. CI classes appropriate for use with dry-heat sterilizers and ETO sterilizers are Classes 1, 3, 4, 5, and 6 (48,105). BIs and CIs cleared by the FDA specifically for use with ozone sterilizers and hydrogen peroxide gas plasma sterilizers are available; consult the sterilizer manufacturer's instructions/recommendations for the selection of these indicators (63).

The use of CIs can help to identify sterilizer equipment malfunction and is especially important if a given sterilizer run does not have a BI in the load. CIs are designed to show visible changes when the stated value or endpoint of the cycle variable being measured is reached. If a CI fails to display a visible change (i.e., a failure), the pack or item is set aside and an assessment is made as to the status of that pack. Other indicators (e.g., BI, physical monitors, other CIs placed elsewhere in the load) are considered in this determination, and if the other indicator results point to proper sterilization cycle performance, the pack in question may be released (17). If the results of BI assessment are not readily available, it may be prudent to quarantine the load in question until the BI results become available (105).

Process Challenge Devices

According to AAMI, a PCD assesses the performance of a sterilization process by providing a challenge to the process that is equal to or greater than the challenge posed by the most difficult item routinely processed (27). Depending on the type of load (i.e., one with implantable devices vs. one with no implantable devices), a PCD may contain (a) a BI; (b) a BI and a Class 5 integrator CI; (c) a BI and an enzyme-only indicator; (d) a Class 5 integrator; or (e) an enzyme-only indicator (27). For loads containing implants, the PCD must contain a BI at the minimum. For loads with no implantable devices, the PCD options are (a) a device with a BI only; (b) a BI plus a Class 5 integrator or an enzyme-only indicator; or (c) a Class 5 integrator or an enzyme-only indicator [a CI challenge test pack] (27).

PASTEURIZATION

Pasteurization is not a sterilization process and should not be considered as the terminal reprocessing step for critical medical instruments. Historically, the process has been used to reduce the numbers of pathogenic microorganisms in liquids while preserving product integrity. However, pasteurization is not sufficiently potent to inactivate bacterial endospores. The process typically involves heating of materials to approximately 60°C for 30 minutes, although other time/temperature combinations have also been used. Pasteurization as a microbial inactivation process has limited application in modern healthcare; its use in today's world is almost exclusively found in the food industry such as the production operations for dairy and other foods where quality would be compromised if the product was exposed to high heat. Examples of medical applications of pasteurization are some of the disinfecting processes employed in hemodialysis centers. For instance, some dialysis machines (e.g., Fresenius 2008 E, Fresenius 2008 H, Fresenius 2008 K, B Braun Dialog system, and Gambro Phoenix dialysis system) employ a heat disinfecting cycle that will heat the internal fluid pathways of the machine to approximately 83°C ± 0.8°C for ≤60 minutes. Some water systems (e.g., Gambro CWP and Mar Cor Purification System) will recirculate hot water throughout the distribution system and the storage tank. With the Gambro CWP, hot water of temperature between 85°C and 90°C is recirculated throughout the loop. Despite the fact that pasteurization does not inactivate bacterial endospores, hot water pasteurization in the past has been used as an alternative to high-level disinfection to reprocess respiratory therapy and anesthesia equipment (17,*106–111*). Pasteurization as a disinfecting process is achieved in this instance by exposing the cleaned devices to >70°C for 30 minutes *(106)*. Wet pasteurization at 70°C for 30 minutes with detergent cleaning has been used to reprocess semicritical devices such as rubber tubing and catheters, polyethylene tubing and catheters, thermometers, and some hinged instruments (17).

ACKNOWLEDGMENTS

We thank Matthew J. Arduino, DrPH, from the Division of Healthcare Quality Promotion, CDC, for information on heat disinfection processes used in dialysis centers, and Sheila Murphey, MD, from the Office of Device Evaluation, FDA, for information regarding regulatory developments re: liquid chemical sterilants.

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SECTION XII

Prevention of Infections Acquired by Patients in Healthcare Facilities Related to Design, Construction, Renovation, Demolition, and Ventilation Systems

CHAPTER 82

Elements of Design Aimed at Infection Prevention and Patient Safety in the Built Environment of the Healthcare Facility

Judene M. Bartley and Russell N. Olmsted

INTRODUCTION

The Institute of Medicine's consensus report, *Crossing the Quality Chasm: A New Health System for the 21st Century,* identified the following key domains aimed at improving the safety and quality of patient care:

- *Safe*: avoiding injuries to patients from the care that is intended to help them
- *Effective*: providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit
- *Patient-centered*: providing care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions
- *Timely*: reducing waits and sometimes harmful delays for both those who receive and those who give care
- *Efficient*: avoiding waste, including waste of equipment, supplies, ideas, and energy
- *Equitable*: providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status *(1)*

The built environment can both compromise and facilitate the achievement of many of these domains. Regarding the latter, one of the more critical devices in the built environment needed to prevent cross-transmission—the hand washing sink—was recently found to be a direct and indirect source of *Pseudomonas aeruginosa* infections among critically ill patients (2). Conversely, the emphasis on single occupancy patient rooms in national consensus guidelines (3) is supported by new epidemiologic evidence that finds up to an 11% increased risk of acquisition of important pathogens associated with multi-occupancy rooms and the number of roommates per day of hospitalization *(4)*. These domains, therefore, serve as important signposts for preventing healthcare-associated infections (HAIs) and improving patient safety.

Patient Safety, Yes, But What About Personnel?

Healthcare is likely the most complex and chaotic of all industries as its standardization is difficult given the unpredictability of patient responses to therapeutic interventions. Layered on top of this are factors such as the increasing acuity of patients, an aging population being served, increasing economic constraints, and challenges

and demands on care providers that require multitasking and almost continual interruptions. Gurses et al. *(5)* reported that critical care nurses at seven healthcare systems found workflow, supply access, and the built environment were among several obstacles that affect their ability to provide high quality, reliable care. In addition, nurses' work activities are interrupted at a high frequency of 10 times per hour, which illustrates the complexity of this work environment and underlies the reasons that errors are made *(6,7)*. To ignore the needs and function of direct care providers when designing the built environment is to invite potential for adverse patient outcomes *(8)*. In fact, studies have identified that equipment/supplies and facility issues are the two key issues that account for operational failures *(9)*. The 2010 Facility Guidelines Institute (FGI) guidelines emphasize the involvement of personnel who work in patient-care areas during planning and design. Infection prevention aspects of the work activity can also be addressed by the inclusion of direct care providers in the Infection Control and Risk Assessment (ICRA) management process. Details of ICRA are addressed elsewhere in this text (see Chapter 83).

Re-emerging Emphasis on the Role of the Environment and Cross-Transmission of Pathogens

In the 1970s, there was intense focus on the environment as a primary reservoir of pathogens. As a result, several interventions were promulgated, including delivery of disinfectants by fogging large areas or patient-care rooms, walk-off mats to "remove" contaminants prior to entering an operating room (OR), and routine environmental microbiologic sampling of the environment. Subsequent analysis and evidence failed to support these interventions as effective and the Centers for Disease Control and Prevention stated in its 2003 environmental infection control guideline:

> *… Although microbiologically contaminated surfaces can serve as reservoirs of potential pathogens, these surfaces generally are not directly associated with transmission of infections to either staff or patients … Disinfectant fogging is not recommended for general infection control in routine patient-care areas … (10)*

Fast forward to the 21st century, and one can find renewed interest and study of the role of the environment. Most of this has been driven by the ongoing challenges presented by multidrug-resistant organisms (MDROs) and the emergence of new strains of *Clostridium difficile* that have resulted in increasing incidence and are associated with considerable morbidity and mortality *(11–13)*. In addition, there have been several studies finding microorganisms persist in the environment and that admission to a room previously occupied by a patient either colonized or infected with an MDRO increases risk acquisition for the next patient (*14,*15,*16*). Coincident with studies of cross-transmission, disinfecting by use of whole-room, no-touch methods such as fogging or use of handheld ultraviolet germicidal irradiation (UVGI) devices have appeared in the literature as they undergo evaluation for efficacy and feasibility *(17,18)*. Therefore, the design of the environment is undergoing renewed scrutiny in terms of patient safety.

DESIGNING FOR PATIENT SAFETY AND INFECTION PREVENTION

The usual process involved in design and ultimate construction of healthcare facilities progresses in this order:

- Assessment of role and program
- Functional programming (e.g., engaging personnel to understand the patient-care processes and use this to assess design needs)
- Examination of adjacencies
- Development of schematic design
- Develop detailed design and mechanical engineering documents
- Contractor bid specifications/documents
- Construction

Reiling has identified two crucial aspects involving design (19,*20*). The first is to employ principles of human factors engineering—meaning how people interact with equipment and their environment. A clear illustration of the importance of this is the study of frequency of interruption of nurses during patient care and the potential for designs to mitigate or lessen these distractions *(6,7)*. The second is to incorporate principles of safety for patients and personnel into design. Key recommendations from these are provided in Table 82-1 (19).

TABLE 82-1

Principles of Safety for Design of the Environment

Design around latent conditions
- Noise reduction
- Scalability, adaptability, flexibility
- Visibility of patients to staff
- Patients involved with care
- Standardization
- Automate where possible
- Minimize fatigue
- Immediate accessibility of information, close to the point of service

Design around precarious events/active failures
- Operative/post-op complications/infections
- Events relating to medication errors
- Deaths of patients in restraints
- Inpatient suicides
- Transfusion-related events
- Correct tube–correct connector–correct hole
- Patient falls
- Deaths related to surgery at wrong site
- MRI hazards

(From Reiling JG. Creating a culture of patient safety through innovative hospital design. *Advances in patient safety: from research to implementation*. Vols 1–4, AHRQ Publication No. 050021-2. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Available at *http://www.ahrq.gov/qual/advances* [cited May 2010].)

Evidence-Based Design—and Infection: Is the Evidence Complete and Definitive?

The Center for Healthcare Design The Center for Healthcare Design (CHD) has coordinated a vast amount of work on defining and encouraging "evidence-based design" (EBD). The CHD defines EBD as "the deliberate attempt to base building decisions on the best available evidence with the goal of achieving the best possible outcomes for patients, families, and staff, while improving utilization of resources" *(21)*. EBD has been developing on a path that is parallel to emerging emphasis on evidence-based practice to prevent HAIs since the 1970s and has made impressive progress in its goal to improve patient outcomes (22). The CHD, formally established in 1993, functions as a major center of research, communication, and development of a body of knowledge while it seeks to sort out the best approach to identifying EBD. In its pursuit to ensure that basic principles are incorporated by healthcare design professionals, the CHD engaged top research design professionals and developed the "Evidence-Based Design Accreditation and Certification (EDAC): Introduction to Evidence-Based Design." The guide provides a comprehensive look at the EBD background, roots, and current developments, serving as a study guide to certify professionals in this field. Infection prevention professionals seeking to better understand many of the proposals that surface early in the ICRA design phase (e.g., patient safety based on IOM report, the Planetree and Pebble Projects, the influence of the military's health research, and more) would find this guide an excellent overview of EBD findings and one that also addresses issues beyond the scope of this chapter.

Sustainability As is noted later, more and more professional architects, interior designers, and engineers consider sustainability as critical to design, and IPs are increasingly faced with these proposals when participating in long-term design planning. From the design professionals' view, they are increasingly aware of the critical relationship between the environment and infection prevention and control issues, highlighting the importance of continued dialogue. Nowhere is this better demonstrated than in the consensus development work that occurs during the FGI standards review process, which includes infection prevention experts as well as an incredibly broad range of other disciplines ranging from engineering to interior design, all focused on development of the built environment to facilitate safer patient care and health outcomes.

HAI and the Environment In 2004, Ulrich et al. *(23)* published the results of their review of a substantial body of evidence on the impact of the environment on safety and quality. They found the environment has a significant impact on patients and others in healthcare facilities and that design that is based on solid evidence can improve safety and quality. However, studies of the efficacy of changes in the built environment in preventing HAIs remain incomplete. A systematic review of one aspect of design—single patient rooms—has reinforced that this gap continues to need more research (24).

The reasons for this include the multifactorial nature of HAIs, short lengths of stay that limit the ability to assess impact on HAIs, long incubation period between exposure and onset of infection (e.g., surgical site infection), and the need to use meaningful metrics of both processes and outcomes that are epidemiologically sound. By illustration, a well-designed study by Rupp et al. *(25)* involving hand hygiene and validated outcome metrics was not able to demonstrate a significant correlation between improved adherence with hand hygiene and reduction in HAIs. This need not discourage further research, but it is important that investigators use several measures of impact of environment-based interventions, assess the statistical power of their study, and avoid sole reliance on environmental microbiologic studies on which to make claims of efficacy.

A recent survey of key opinion leaders involved in design identified several critical issues going forward. These include addressing problems encountered during delivery of care, safety of care (e.g., need to prevent HAIs, medication errors, falls), patient satisfaction, and operational efficiency *(26)*. Of note, HAI was ranked by the survey respondents as the topic of most importance in terms of the need for improving the current state.

DESIGN LAYOUT TRENDS

Information Technology

The EHR and other devices such as wireless communication, newer methods for imaging and procedures, and wireless control of environmental conditions such as temperature control by the patient, are all elements of design in the 21st century *(27)*. Regulatory issues may set limits for new technology since regulations frequently lag in addressing newer, more efficient design innovations. Enforcement of the National Fire Protection Association Life Safety Code comes to mind as an example of the efforts needed to modify the codes for the installations of alcohol-based hand rub (ABHR) dispensers in the corridors. CMS will frequently offer interpretations of Conditions of Participation standards to resolve conflicts for issues not anticipated decades ago. For example, wall-mounted computers in the egress corridors were recently addressed by the CMS in light of regulations governing egress corridor width *(28)*.

Sustainability

Principles aimed at sustainability of the environment are also being used in over 80% of active projects based on a survey from 2008, and this is likely to continue *(27)*. These include enhanced efficiency of heating, ventilation and air-conditioning (HVAC) systems; building utilities (power and water); surface and furnishing treatments that lessen use of volatile organic compounds (VOC); the use of natural lighting; low-emission glass; and waste reclamation.

Assessment of Environmental Sustainability Leadership in Energy and Environmental Design (LEED) was developed by the U.S. Green Building Council that verifies a construction project is designed and built using environmental sustainability strategies. The certification process promotes accountability and greater attention to sustainability issues among contractors, building owners, and building occupants *(29)*. A comparable group, Green Globes (GG), developed by the Green Building Initiative has similar goals but, until recently, was primarily used for

commercial building and is now engaged in healthcare as well *(30)*. LEED and the GG systems are both environmental assessment methodologies that score buildings and award a ranking. These green building rating systems consist of a large set of questions relating to water efficiency, energy usage, construction materials, indoor air quality, and the building site. Details of the operational aspects have been published elsewhere (31,*32,33*). As noted above, as the EBD framework developed, the concept of sustainability has been incorporated as basic, and now all groups are attending more closely to environmental infection issues, as being just as critical for patient and worker safety.

Patient-Centered Care

Patient-centered care has emerged as the norm in acute care settings. As a result, hospitals have adapted the environment of care (EC) to accommodate increasing presence of family and other visitors, including lessening of restrictions in visiting hours.

Intensive Care Unit In light of this trend, the American College of Critical Care Medicine and the Society of Critical Medicine have published recommendations to support family involvement in the care of their critically ill loved ones (34). Many of these impact EC design and include the following:

- Open visitation but determined collaboratively between caregivers and family
- Single-bed rooms with space for families
- Opportunity to participate in patient-care rounds by clinic personnel

Neonatal Units Pediatric areas have not been as thoroughly studied as neonatal intensive care units (NICUs) *(30)*. NICUs, which have special challenges for sound and acoustic control, need to balance these with efforts aimed at infection prevention. NICUs have also undergone major transformations and, similarly, have focused on private rooms as well as space for family participation, remaining cognizant of HAI-reduction issues. Removing sources of loud noises, instituting quiet hours, educating staff and parents, putting in sound-absorbing ceiling tiles and flooring, and providing single patient rooms (as opposed to open wards) have been found to be effective in reducing noise levels, but these surfaces raise HAI-related questions. White's recommended standards for NICUs provide valuable and detailed information on both acoustics and floor covering balanced with HAI concerns (*21,*35,36).

Universal or Acuity Adaptable and Single-Occupancy Patient-Care Room

Transfers from one room to the next is disruptive to the patient, can result in hand-offs, and can increase the probability of errors or elevate the risk of HAI. Regarding the latter, frequent transfer of ventilator-dependent patients can increase the risk of ventilator-associated pneumonia *(37)*. To address these issues, the "universal" or "scalable acuity" room—defined here as the ability of the environment to accommodate a variety of patients, including those who are critically ill—is an emerging design element *(38)*. In addition, an emerging ICU practice involves not only emphasis on extubation from mechanical ventilation but also on early ambulation *(39)*. This latter care intervention will have implications for design as space will need to be expanded to permit ambulation in the room, as well as the number of personnel that will be needed to assist the patient, for example, physical therapy and nursing.

Even as the trend toward the acuity-adaptable room grew, the decentralization of nursing services became another factor influencing the design of the patient-care unit to ensure the close proximity of the nurse to the patient *(40)*. This desire for proximity of the caregiver to the patient resulted in a "racetrack" configuration—single occupancy rooms on the periphery of a common corridor with workstations (including viewing windows) in between every two rooms, increased attention to windows and use of natural lighting, and zones of space dedicated for personnel and family. Others, however, have suggested that for some units such as the ICUs, a central nursing station surrounded by private rooms permits easier visualization and response to rapid changes in patient status and should be a strong consideration for the physical design of critical care units (CCUs) *(41)*. Another aspect related to visualization is real time, rapid communication and collaboration between personnel to respond to unexpected changes in the patient's condition. Regardless, architectural design that enhances spatial separation of patients and facilitates communication can improve safety for patients and personnel.

Single-Occupancy Room

The FGI research committee commissioned a study led by Chaudhury et al. to assess the benefits of single-patient rooms as a design element (42). Chaudhury found reduction in the risk of cross-infection and greater flexibility in operation. The 2006 FGI guidelines review committee reached a consensus on requiring the single room as a minimum standard. However, it made provisions for the state plan reviews, accomplished by the authority having jurisdiction (AHJ), to consider two-bedded rooms dependent on the facility's programmatic needs. The Department of Defense independently supported the use of private rooms for its facility planning criteria at about the same time (22). More recent evidence has supported this direction in room design *(4,43,44)*. The upfront cost of building a single-patient room is higher compared to multi-bed rooms but benefits for the safety and comfort of the patient over the life of this room balance this initial investment. Detsky and Etchells *(45)* have also found this design enhances privacy/noise abatement, supports patient-centered care, results in fewer transfers, enhances flexibility with adaptable acuity, and offers spatial separation to mitigate cross-transmission of pathogens. Interestingly, some patient populations have expressed a preference for multi-bed rooms, whereas personnel favor single-patient room design (42,*46*). This highlights a need to involve patients in the design, if feasible.

Of note, the single-patient room has received ongoing scrutiny by others, especially in countries where multi-bed wards are more the norm. As highlighted earlier, others have called for more research on this design element (24). This design by itself is also not a panacea for infection prevention, as evidenced by the investigation by Hota et al. (2) of an outbreak described earlier in an ICU where all rooms

were single-patient occupancy. Overall, the single-patient room is likely to remain a significant design element, does provide some transmission limits, and continues to be a minimum requirement for new construction in the FGI's 2010 guidelines (3).

SPECIFIC ELEMENTS OF DESIGN FOR INFECTION PREVENTION

Hand Hygiene

Hand hygiene is the foundation of preventing cross-transmission of organisms and ultimately HAIs. Accessible, efficient, and effective use of hand hygiene by personnel is an essential element of care for which the infection preventionist/healthcare epidemiologist is the primary advocate.

Alcohol-Based Hand Rub ABHR is the cornerstone of both 2002 Centers for Disease Control and Prevention and 2009 World Health Organization (WHO) hand hygiene guidelines *(47,48)*. Functional programming—undertaken by architects in collaboration with direct care personnel, infection preventionists (IPs), and hospital epidemiologists (HEs)—is used to identify location, number, and design of ABHR dispensers. ABHR dispensers are not intended to supplant the inclusion of plumbed hand washing stations (HSs) for use by personnel.

Hand Washing Stations FGI guidelines for new construction recommend the minimum number of HSs for patient rooms as one in the toilet room and one in the patient room outside of the patient-care zone (e.g., beyond the area of a privacy curtain) to ensure healthcare personnel can carry out standard precautions. Having a sink in a patient/resident room and in the toilet room facilitates infection prevention by enabling hand washing as needed for standard precautions and addresses reluctance by personnel to use facilities dedicated to the patient's personal use. The IP/HE needs to work with facilities and patient-care staff to recommend the *location/height* of the HSs. FGI guidelines note that HSs placed outside the room in an anteroom or alcove are acceptable but cannot replace the HS in the patient room—again to support caregivers' needs for standard precautions. Hota et al. (2) described placement of sinks that were in close proximity of care delivery, but the sink design, a shallow basin depth with faucet directly over the drain, resulted in splashing of contaminants to adjacent surfaces and directly onto the patient. Therefore, IP/HE input is essential on the HS *selection* as well, noting that the HS design to reduce splashing requires sufficient depth with the spigot having a slight offset so that the water flow is not directed straight into the drain. Ideally, the flow should contact with the curve of the sink. Key aspects of FGI design requirements are listed in Table 82-2 (3).

Hands-Free Operation Nontouch design has been identified as a method to minimize recontamination of hands after completion of hand washing. There are several types of hands-free water activation for sinks: infrared-activated, touch-activated, and paddle/foot/knob activated. Long blade handles are intended to be used with the back of the hand to minimize contamination from soiled fingers, but are not optimally utilized. Current thinking has focused on automatic infrared activation of water flow. It has been discovered that the initial water out of a spigot *regardless of the type of activation* may contain higher bacteria levels

TABLE 82-2

Sink Design Features

Sink Design Features: Guideline for Design and Construction of Healthcare Facilities 2010	
Sinks in handwashing stations *shall* be designed with deep basins to prevent splashing; designed to prevent splashing to areas where direct patient care is provided, particularly those surfaces where sterile procedures are performed and medications are prepared	Basin: porcelain, stainless steel, or solid surface materials. If the basins are set into plastic laminate countertops, at a minimum, the substrate *shall* be marine-grade plywood (or equivalent) with an impervious seal
The number and location of handwashing stations *shall* be determined by the functional program and the ICRA	The water pressure at the fixture *shall* be regulated. (Pressure *should* be adjusted to reduce forceful discharge into the sink at maximum flow.)
Hand washing stations *shall* be convenient and accessible for healthcare personnel and other users	Design of sinks *shall* not permit storage beneath the sink basin
Sinks *shall* have well-fitted and sealed basins to prevent water leaks onto or into cabinetry and wall spaces	Faucets should not discharge directly above the drain as this causes splashing (i.e., water *should* be angled away from the drain)
Sensor-regulated water fixtures shall meet user need for temperature and length of time the water flows. Electronic faucets *shall* be capable of functioning during loss of normal power	Design of sinks *should* accommodate ADA requirements for clearance under the sink basin
Hand towels shall be dispensed so that users need touch only the towels and not the dispenser	Sink size and depth—ANSI standards *should* be considered for sink design

Note: Features using ***shall*** are requirements; features using ***should*** are appendix language for consideration.

depending on when the sink was last used. The bacteria levels drop drastically with flow after the stagnant water is flushed *(49)*. Collection or use of the initial water flow may increase bioload on hands and in contained water. Well-designed systems with manual temperature controls will encourage their use and reduce problems of bacterial load.

Aerators Lower water-flow rates reduce splashing risks, but aerators also assist in delivering a controlled flow of water and mitigate splashing; some aerators, not surprisingly, also have bacterial contamination occurring inside them. The study of ICU sink design, however, identifies that aerators are not the root cause of contamination; instead, in this case, it was splashing up from the heavily contaminated biofilm in the sink drain (2). The FGI guidelines do not prohibit their use in these fixtures.

Toilet Rooms and the Disposal of Human Waste in the ICU

The trend toward single-occupancy rooms and increased focus on patient privacy raised the issue of including attached toilet rooms in ICUs. This feature facilitates disposal of human waste but also requires additional space, fixtures, utilities, and energy. Also, patients in medical and surgical ICUs are often intubated and sedated, so they are less likely to use an attached bathroom. The level of acuity of other patients, such as those in cardiac ICUs, is different, and they are encouraged to ambulate. Historically, there were attempts to address this gap by providing Swivettes (Whitehall Mfg.) inside the ICU room. However, these devices were often unreliable, too low to the floor for use by patients and personnel, and there is a theoretical concern for the contamination of the environment when flushed. Barker and Jones *(50)*, using an *in vitro* study of the dispersal of *Serratia marcescens* and a bacteriophage during flushing of a toilet fixture, demonstrated significant release of these microorganisms over short ranges and contamination of the fixture. Finally, because of the risk of spills and contamination, patient-care personnel should not carry human waste for long distances to a soiled utility room flush sink.

Options There is an increasing effort to have patients ambulate sooner in other ICUs, not just in CCUs *(39)*. Infection preventionists/healthcare epidemiologists need to work with ICU personnel and environmental services professionals to determine the safest design for the patient *and* staff. Options include having an attached toilet room for emptying bedpans without leaving the patient room area or transporting waste material to the unit's utility room with a clinical/flushing rim sink. One of these is either a toilet room or a clinical (flushing rim) sink between two patient rooms. Current 2010 FGI guidelines require one of these options for major renovations or new constructions but clarify that a dedicated toilet room for airborne-infection isolation rooms (AIIRs) is required in all locations, including ICUs (3).

An alternative is a point-of-care, automated bedpan-cleaning/disinfection device. This equipment utilizes a reusable bedpan, wherein the bedpan is inserted into the washer/disinfecting equipment and the waste is discharged into the sanitary sewer followed by a cleaning and disinfection cycle. This design feature will require mechanical reengineering for current facilities but is a potential solution depending on the needs of care providers—whether in the patient room or the toilet/utility room as described.

Flooding Prevention Whether using a toilet, bedpan washers, or flushing rim sinks for the disposal of waste, inappropriate management of disposable cloths into the sanitary sewer systems can block water flow and result in the backup of a plumbing fixture or floor drains. Not only can this contaminate the environment but residual water damage to wallboards can also lead to mold contamination. Proper disposal into regular waste containers can avoid this situation and illustrates the important connection between the environment of care (EOC) and human occupants. Such decisions require joint input by the infection prevention program (IPC) team, addressing the need for procedures to avoid this type of consequence and preplanning contingencies if it does occur (51,*52*).

Surfaces and Furnishings

Multiple types of surfaces in all units require considerations for ease of cleaning, whether floor coverings or countertops around HSs. Some specific aspects include flooring (identify precise location of soft or hard surfaces); walls (coverings for inside or outside walls); headwall components; windows; doors; countertops; plumbing fixtures (i.e., sinks, faucets, handles, etc.); lighting (covered); electrical outlets; furnishings (e.g., bed, chairs, bedside tables); and computers, equipment, and supplies storage areas. This may include details as small as the type of drawer handles, considering whether they will be readily cleaned where actually touched. Choices should also consider the selection of latex-free construction materials for all items, sizes, dimensions, colors, finishes, securement, and seams. Counter space required for various activities should have countertops that are seamless, nonporous, and durable against multiple germicidal cleanings.

Ideally, surfaces are designed to include cleanability; problems can be avoided if surfaces near plumbing fixtures are smooth, nonporous, and water resistant. Operating and delivery rooms and isolation and sterile processing areas also need smooth finishes that are free of fissures or open joints and crevices that retain or permit passage of dirt particles (3,*53*).

Planning may include the consideration of light fixtures/covers that have flat surfaces for ease in wiping clean. Window ledges are dust-collecting horizontal spaces that can be eliminated with a minimal width of nonporous material. Seamless, sealed floors are required to be clean, not waxed, and have rounded corners and edges to aid in reducing the accumulation of debris from traffic, fluids, and dirt. Non-cloth furniture resists the absorption of moisture and stains, making cleaning more effective and efficient. Stainless steel surfaces, in particular, are both resilient and easily sanitized. Selection of surface materials, therefore, must balance use life, cleanability, cost, and maintenance (51,*54*). Interior designers and IPs have inquired about furniture design standards that would assist this process; some standards may be in development but have yet to be published.

Wall Surfaces The 2010 FGI guidelines continue to require that wall finishes be washable, noting that design for a healthy and productive indoor environment can be

accomplished through measures such as the use of low VOC finishes and reduced moisture entrapment, and cannot conflict with healthcare safety and infection control codes and standards. This aspect and related topics are discussed at length in the Association for Professionals in Infection Control and Epidemiology, Inc. (APIC) 2009 text on ventilation *(55)*.

Floor Coverings Selecting hard or soft floor covering materials poses major dilemmas for all facilities, considering material that is easily cleaned but also enhances patient comfort, noise, and safety. Newer floor coverings focusing on sustainability better address the balance of concerns with patient comfort (noise), patient safety (reduced slips, falls and injury), staff back injury (rolling beds, carts, stretchers), life cycle costing (maintenance and replacement), and cleaning (equipment and staff). However, studies on methods for assessing cleaning processes have highlighted the importance of selecting cleanable surfaces. All of these concerns are raised in the guidelines, requiring decisions by the ICRA panel.

Soft Coverings Carpeting has not been directly associated with HAIs *(56)*. Recent studies have found that although bacterial contamination per unit of carpet may be higher than for hard-surface floors, they have failed to implicate carpeting as the source of HAIs, though patient population needs and location are crucial components to factor into the final decision (*57*). Some studies suggest it is possible to strike the right balance of padding, low pile, and larger wheels to minimize the problem of mechanical friction and staff back injury; however, they should have an impermeable backing featuring heat- or chemically welded seams (36,*58,59*). One additional benefit from soft flooring materials such as carpeting is the mitigation of noise pressure levels that can disturb certain populations such as critically ill neonates (*21,*35,36).

Hard Flooring In terms of hard floors, there are many more selections today of resilient floor coverings, such as medical-grade rubber, that are easily cleaned, do not need waxing or stripping, and are environmentally friendly *(60)*. FGI guidelines support floor surfaces that can withstand frequent cleaning/heavy traffic and permit cleaning without the use of hazardous chemicals. In relation to ABHR, an area of concern to environmental services professionals involves spillage of ABHR onto floor coverings and potential for stains or need to remove any finish materials. IPs and HEs should investigate this issue early during planning and design with manufacturers of flooring.

Use of Antimicrobials for Surfaces and Finishes Given the notable increase in either the replacement or extensive renovation of healthcare facilities in the United States, there has been interest in designing an environment that promotes safety but also prevents cross-transmission of infectious agents. Current evidence demonstrating the efficacy of antimicrobials when applied or incorporated into or onto inanimate surfaces, patient-care equipment, fixtures, or finishes—including carpeting—specifically for prevention of HAI is lacking. The guidelines emphasize cleanability and do not support antimicrobial treatments including hard metal surfaces with similar claims. They do support privacy curtains/partitions that are washable or, preferably, wipeable fabrics with a smooth surface.

Given the current media attention to metals such as copper, a search for evidence demonstrating that copper surfaces have decreased actual HAIs (not just reduction of microbes on the surface) remains elusive. Investigation of other studies of MDROs using antimicrobial/disinfectant treatment provides evidence that recontamination of surfaces after treatment can still occur—in particular, soon after patients and personnel reoccupy the room (*44,*61,62).

General Soft Surfaces Current evidence is lacking that demonstrates the efficacy of antimicrobials applied to surfaces of patient-care equipment, fixtures, or furnishings—including soft carpeting in patient rooms—specifically for the prevention of HAIs. They can claim only that these treatments act as preservatives of the treated substrate submitted to the U.S. Environmental Protection Agency (EPA). Textiles such as carpeting or cubicle curtains with antimicrobial features including textiles developed to absorb sound have never been demonstrated to reduce infectious outcomes *(10,63)*.

Metal–Copper Surfaces Copper has recently been the focus of investigation as one possible solution to reducing reservoirs of environmental pathogens by using this preferentially for high-touch surfaces rather than the more common stainless steel *(64)*. For the first time, the EPA has approved a new label claim for copper and its alloys, as submitted by the Copper Development Association (CDA), but the approval has limitations. The label addresses only *reduction of microbes* (requiring 2 hours for a three-log reduction on surfaces and fixtures), and cannot make claims to reduce infection transmission or reduction in infection rates. Specifically, the EPA label states:

> *"The use of a copper alloy surface is a supplement to and not a substitute for standard infection control practices; users must continue to follow all current infection control practices, including those practices related to cleaning and disinfection of environmental surfaces. The copper alloy surface material has been shown to reduce microbial contamination, but it does not necessarily prevent cross-transmission."* (65)

The surfaces cannot be coated, waxed, or lacquered. Additional research is needed to provide evidence that a change to copper surfaces would decrease HAI rates, as opposed to CDA's numerous lab studies that kill bacteria. The laboratory results may be difficult to apply in natural settings. Other studies by Airey and Verran compared six copper alloys with other alloys using a model to simulate clinical care environments where disinfectants such as dilute sodium hypochlorite (bleach solution) are commonly used. There was a notable buildup of cells and soil on copper with signs of corrosion whereas stainless steel remained clean over the course of the 5-day study when deployed in a natural patient-care setting (61). The CDA is funding three hospital studies to look at HAI reduction, but results are not anticipated until late 2010.

Summary Manufacturers that do add fungicides or antimicrobials to their product may not make health claims, and such additives should not be a criterion when selecting floor coverings. The EPA's bulletin "Consumer Products Treated with Pesticides, August 2003" requires claims for treated articles or substances to use language such as, "This product contains a preservative (e.g., fungicide or insecticide) built-in or applied as a coating only to protect the product" *(66)*. Any pesticide-treated product that is not registered by the EPA cannot make public health claims. The EPA's policy is predicated on the fact that no scientific evidence exists that these products prevent the spread of germs and harmful microorganisms in humans. IPs/HEs need to use their critical thinking skills and assessment of the scientific literature when determining the efficacy and cost-effectiveness of such design elements when asked for their input into a construction project.

UTILITIES: VENTILATION DESIGN

Ventilation, Filters, and Filtration Requirements

General Planning General planning requires attention to ventilation mechanical systems referred to as "air handlers" or HVAC systems (including recommended ventilation and filtration specifications) and mechanical systems involving water supply and plumbing.

Ventilation Parameters Basic parameters for HVAC and water use have been discussed in Chapter 80. However, ventilation parameters found in the Table 7-1 of the American Society of Heating, Refrigerating, and Air-Conditioning Engineers (ASHRAE) Standard 170 (Chapter 6 of the FGI guidelines and single standard for ventilation guidance) have been updated with the recommended ranges (3) (see Chapters 80 and 81).

Filters and Filtration One necessary function of HVACs is air filtration, requiring the selection of filters by filtration efficiency for different spaces. Currently, efficiency is expressed as a Minimum Efficiency Reporting Value or MERV, as opposed to a percent. Table 6-1 in Standard 170 provides the recommended filters by MERV with a change to be published in the near future. HEPA filters are no longer labeled with a MERV designation since the efficiency testing is made on a different basis. The only space in the standard requiring a HEPA filter is the protective environment (PE) (initially labeled MERV 17); the approved correction is posted on ASHRAE's Addenda website and will be incorporated with the next publication of Standard 170 *(67)* (see Chapter 80).

Operating-Room HVAC

FGI OR Design The 2006 and 2010 editions of the FGI guidelines recommend ORs be designed so primary nonaspirating supply diffusers provide airflow that is *unidirectional* and moves vertically downward with *average velocity* 25 to 35 cfm/ft^2 (127 –178 L/s/m^2). Supply diffusers need to be concentrated to provide this airflow pattern over the patient and surgical team (68). The area of the primary supply diffuser needs to extend a minimum of 12 in. (305 mm) beyond the footprint of the surgical table on each side. The foundation is based on landmark studies using computational fluid dynamics (CFD) or airflow modeling to assess the dispersion of particles (which include contaminants such as microorganisms) in the OR. The power of CFD studies is that several variables can be modified, and the impact of each can be studied in detail as compared to challenges for this control in a real-world OR. The OR CFD analysis found a significant effect of the heat from both the patient and other devices creates a thermal plume that actually prevents deposition of particles into the surgical site. In addition, using this analytical tool, the study found that increasing the number of air changes per hour (ACH)—currently 20—did not improve protection of the site since deposition requires particles to be released close to the site (68).

Low Velocity Design and Maintaining Normothermia One of the important consequences of low-velocity, unidirectional airflow is not cooling the tissue, and therefore, maintaining normothermia—as opposed to the cooling from older high-velocity laminar air flow (LAF) systems *(69)*. This may explain the unexpected findings of Brandt et al. *(70)*, who saw an association of higher infection rates with LAF in orthopedic surgery. A critique of the Brandt study compared to the National Institutes of Health/FGI design is described elsewhere (71). Additional methods of ensuring normothermia include keeping the OR temperature closer to 70°F and using forced-air warmers (FAW). Questions have been raised in the United Kingdom concerning the impact of heat from other devices, including FAW on the airflow over the patient, but studies by Moretti and validated by Memarzadeh concluded that "… forced-air warming technology does not increase the risk of surgical wound infection." Furthermore, if the OR ventilation system is designed properly, contaminating particles from staff around the patient will not impinge on the surgical wound due to 'thermal plume' dynamics (72,73). Parameters of this design include maintaining positive pressure with respect to all adjoining spaces. Optimal location of return (exhaust) vents is spacing two low sidewall vents at opposite corners with the bottom of these grills installed approximately 8 inches (203 mm) above the floor.

Special Ventilation Areas and UVGI

AII and ORs UVGI has been available for decades as a supplemental means of disinfecting air and water as is useful for disinfecting dialysis water and biological safety cabinets. A recent National Institute for Occupational Safety and Health report summarized published evidence of its efficacy in tuberculosis (TB) control *(74)*. UVGI does have antimicrobial properties; the challenges, however, include allowing sufficient time and proximity to the surface or material that one intends for disinfection. For example, studies show that the added value of UVGI in a properly designed AIIR that is providing 12 ACH is *minimal (75)*. The exchange and mixing of filtered ventilation to an AIIR results in the dilution and removal of contaminants in an efficient and safe manner. A ceiling-mounted UVGI is less likely to inactivate organisms on surfaces near and around

the patient. Organisms transmitted by droplets do not have the aerobiological properties to be pulled up past the UVGI lamps for their inactivation. Experimental research has indicated that mechanical ventilation of up to four to six ACH does not have a significant effect on the effectiveness of upper-room UVGI systems; studies are needed to examine whether the mechanical ventilation of six ACH even *decreases* the effectiveness of upper-room UVGI systems. Memarzadeh et al. (76) conclude that UVGI does not appear to have a role in properly designed AIIR or the OR, where air changes are well above four to six ACH, with the improved low-velocity design described above and required by the 2010 FGI guidelines.

In Duct Applications UVGI lamps can be installed in various locations in an HVAC system. One possible location is inside the air-handling unit (AHU), typically in front of the cooling coils and drip pan. There are anecdotal reports that this configuration results in energy conservation and maintenance-cost savings, but more rigorous study is needed to reproduce and validate these claims. Some manufacturers of these systems have also made claims of a reduced incidence of HAIs with the use of UVGI in AHUs. To date, however, there is little, if any, supportive evidence in the peer-reviewed scientific literature. The available literature indicates claims of reduced HAIs from AHU-installed UVGI in healthcare facilities remain unfounded (76).

Alternative HVAC Designs

Displacement Ventilation Displacement ventilation (DV) has been under active investigation as an alternative to traditional mechanical or overhead ventilation (OHV) in healthcare facilities. DV and OHV have equivalent filtered air sources but distribute the air differently. OHV systems generally supply air from the ceiling, resulting in a mechanical mixing at relatively high velocity of all air inside a room. DV, by contrast, introduces air at low velocities and at a low level on the sidewalls of the room and has been used in commercial buildings. This design uses natural buoyancy and convective forces (created by heat sources such as people, lighting, equipment, etc.) to move contaminants and heat upward from the occupied zone to the return located in the ceiling. The driver for DV is reducing first, that is, capital costs and operating costs, improving energy expenditure, ensuring environmental comfort, ensuring ventilation effectiveness, and controlling airborne particulates.

A two-phase research study that utilized CFD modeling has been completed on the benefits of DV *(77)*. The results are being used in support of an amendment to ASHRAE's Standard 170, clarifying that the Standards do not preclude the use of DV as a design strategy for mechanical engineering HVAC design in healthcare *(78)*. Although two pilot tests have been conducted on patient rooms, practical applications or unintended consequences if used on a large scale remain a concern. For example, blocking the airflow into the room (obstructed vents) or heat gains from natural light could have negative effects. It is likely that DV will gain support over the next decade as it supports sustainability principles in energy conservation, but it remains under intense review.

Natural Ventilation Open windows or the use of outdoor air to change and condition indoor air has been considered for some occupancies. Except for a few temperate climates found in several regions in North America, the severe climatologic changes preclude the use of this in most facilities. Some evidence exists that demonstrates that natural ventilation (NV) can be used to promote the removal of airborne contaminants in buildings that lack traditional OHV systems *(79,80)*. This applies, most typically, to facilities located in under-resourced countries. The WHO has published a guideline on the control and prevention of TB in facilities discussing DV and NV *(81)*. Specifically, WHO recommends the choice of ventilation system be based on facility assessment and informed by local climatic, programmatic, and socioeconomic conditions. Simple NV can be optimized by maximizing the size of window openings, using high ceilings, and locating the windows on opposing walls for facilities in countries lacking the resources to operate mechanical ventilation systems. It is unlikely that NV will be utilized in US acute-care facilities as it compromises building envelope integrity, allowing the entry of nonfiltered air with outdoor air contaminants such as fungal spores.

Airborne Infection Isolation Room and Protective Environment

AIIRs and PEs are addressed in detail in other publications (e.g., APIC text) and will not be detailed in this review. Several recent design concerns are worth noting, however.

Room Sealing Recent studies of AIIR pressure relationships in a large number of hospitals in the United States found only 32% met the recommended negative pressure differential; 9% were actually found to have airflow out of the rooms *(82,83)*. A major factor for this suboptimal performance was unintended air leakage in the AIIRs studied. The complexities of *maintaining* air balances have been investigated, and findings reinforce the critical importance of tightly sealed rooms *(82,83)*. More recent work reinforces the importance of a tightly sealed room in the "bundle of elements" essential for AIIRs and PE rooms to truly protect patients, along with monitoring the room periodically for air leakage *(55,84)*.

Anteroom There have been concerns regarding whether one needs anterooms for AIIRs and PEs, and if so, what the alternatives may be for ventilation design. Several sources affirm that anterooms are not required for either AIIRs or PE rooms (3,51,*80,85*). However, a clarification has been added in the 2010 FGI guidelines by creating a new category—the Airborne Infection Isolation (AII)/PE—the only type of room that *requires* an anteroom with special ventilation. Units with PE rooms should have at least one AII/PE for the immunosuppressed patient with an airborne infection, that is, a patient who needs clean air coming into the room but requires the anteroom and toilet room to exhaust used, contaminated air from the room.

The ventilation tables and text of ASHRAE 170's Ventilation Table 7-1 delineates what the direction of the airflow should be and precisely where to conduct the pressure measurement *if* (whether required or not) an anteroom is present (3).

Summary Points

Proactive Planning and Design The IP/HE is a key member of planning and design of the built environment. Importantly, their input must occur as early as possible in the design/planning phase of a new project to avoid the incorporation of elements that are not supported by scientific evidence *and* to incorporate key environmental elements that are effective. Incorporation of the latter into design plans at later stages is inefficient and expensive.

Designing for Prevention of HAIs and Patient Safety This review highlighted several elements aimed at prevention of HAIs and other complications during care of patients. Key elements and emerging trends include the following:

- **EBD**: Use of evidence has and will continue to be important not only for preventing HAIs during procedures such as insertion of a central line but also for the environment in which care is provided. We have highlighted some instances where problems have been identified when EBD is not used. The IPs/HEs must be leaders in the application of this for infection prevention and control. Collaboration with other members of the design team is critical as IPC is not the sole domain of importance, and this collaboration needs to be sensitive to other issues. This likely will require the IP to be flexible and facile in maintaining infection prevention principles in an open-minded approach.
- **Single-Patient Room and Family-Centered Care**: The FGI has adopted single-patient room design as a key design element for a broad range of reasons. We see this trend as one with longevity, but as stated, flexibility may be needed based on input from patients and personnel in addressing the needs of some populations. Accumulating evidence points to this element as effective in preventing cross-transmission of pathogens that cause HAIs. Providers should also expect increasing involvement of family into the care delivery. This trend is also evidenced in requirements of providers from accreditation and regulatory authorities as well as consumer advocacy organizations.
- **HS and Hand Hygiene**: This has and will continue to be key subject matter expertise that the IP/HE brings to the design and planning team. New findings from the literature have identified the design of fixtures, basins, and surrounding surfaces as critical to the creation of an optimal HS (Table 82-2). The functional programming will identify strategies and locations for HSs but equally important are dispensers of ABHR. Both are critical elements of design for prevention.
- **Acuity Adaptable/Critical Care Units:** In the United States, the demographic trends of an aging population with a multitude of underlying chronic diseases will continue to drive the need for rooms that can be adapted to the patient's needs but also support critical care when needed. The latter includes medical gases, monitoring capabilities, patient lifting equipment, mechanical ventilation, etc., all without necessitating transfers in and out of several rooms.
- **Surfaces and Furnishings**: This is increasingly a key focal point for the IP/HE. The manufacture and subsequent marketing of complete "infection prevention solutions" that incorporate antimicrobials will escalate. It will be important for the IP/HE to apply their knowledge and wisdom in assessing the veracity of such claims and then apply a critique of these that will best serve the patient population. To date, there is ample evidence that the critical factors are thoroughness and frequency of cleaning, and not whether the surface incorporates an antimicrobial ingredient (86).
- **HVAC Systems:** Focus on energy consumption and environmental sustainability will continue to press for better design of HVAC systems. The IP/HE will need to emphasize, however, that dynamic flow and removal of contaminants remain a key goal of this element of the built environment. Optimal design of areas that require special ventilation parameters, OR/procedure rooms, AIIR, and PE will continue to be areas that the IP/HE address in their affiliate's ICRA. Good design and operation of these spaces are important to ensure these spaces provide optimal conditions throughout their use.

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CHAPTER 83

Prevention of Infections Related to Construction, Renovation, and Demolition in Healthcare Facilities

Judene M. Bartley and Russell N. Olmsted

Construction, renovation, and remediation of the built environment are a constant process in healthcare facilities. The former aspect, new construction, may be infrequent in any single facility, but the latter are typically encountered in all settings as the use of the built environment is much higher compared to other business occupancies, and the unique nature of care delivery requires extraordinary effort to provide comfortable and safe conditions. The focus of this chapter, therefore, is on planning for proper containment and protection of occupants during construction/renovation and remediation plus operational aspects that are related to the built environment. New concepts of design elements and the key roles that healthcare epidemiologists (HEs) and infection preventionists (IPs) play are reviewed elsewhere in this text (see Chapter 82).

PATIENT SAFETY INITIATIVES

A decade has passed since the Institute of Medicine's first report on patient safety in 1999 seized the nation's attention, focusing on the importance of the healthcare environment's effect on patient outcomes *(1)*. The Agency for Healthcare Research and Quality was charged with developing a plan to reduce adverse outcomes and improve the safety of workers and patients. This focus on medical safety continues to develop in healthcare organizations across the United States *(2)*. Care delivery processes occur in physical structures intended to be healing environments, enhancing patient's health outcomes. Coincident with the emphasis on patient safety, accreditation agencies such as The Joint Commission (TJC) continue to encourage and require facilities to ensure that the environment of care (EOC) in facilities does not serve as a reservoir for pathogens. Implicit in this emphasis on the EOC is preventive maintenance for critical utility systems that deliver ventilation and water to patient-care areas.

MICROBIAL HAZARDS ASSOCIATED WITH CONSTRUCTION AND RENOVATION

The physical environment in a healthcare facility may pose risks to occupants (e.g., patients, personnel, and visitors) if enhancements to the environment are carried out without a basic understanding of the potential for creating hazards and the associated morbidity and/or mortality. Physical hazards, infectious risks among them, may occur as the result of well-intentioned designs that may have unexpected consequences. For example, HEs and IPs need to balance proposals for a water feature, such as a water wall, with potential risks of disease from waterborne opportunistic infectious agents (e.g., *Legionella* species). Newer designs of ventilation systems aimed at sustainability and energy efficiency must be evaluated for risks of airborne contaminants. A clearer picture of infectious hazards associated with care delivery environments has emerged over the past decades. HEs and IPs increasingly recognize that such risks occur during construction, renovation, remediation, and preventive maintenance or from damage following natural or manmade disasters. Knowledge gained from disease outbreaks and successful interventions can be incorporated by architects and engineers to improve designs, resulting in truly healing environments. It is essential that architects, engineers, HEs, IPs, infectious diseases and safety specialists, and other stakeholders balance planning for construction and renovation with a thorough knowledge of infectious hazards, preventive techniques, and effective interventions to ensure the safest and most patient-friendly environment. Lessons are learned from prior outbreak investigations and related environmental issues. Experiences do provide information on mitigating risks and designing the EOC to prevent disease transmission as designs and materials are selected and approved in a process involving infection disease expertise *(3)* (see Chapter 82).

Airborne Microorganisms

Most studies that have associated airborne disease transmission with demolition, construction, or renovation have involved improper or ineffective environmental containment, incorrect ventilation design, or lack of planning prior to maintenance or remediation that allowed the exposure of highly immunocompromised populations, such as bone-marrow transplant patients, to opportunistic pathogens (e.g., *Aspergillus* species). Exposure to airborne infectious agents (e.g., fungi) can have a severe effect on the health of patients and healthcare personnel (HCP). The mechanisms of this exposure usually involve disruption and release of contaminants into the indoor air during the demolition of existing areas or removal of existing walls or surfaces in areas where there was an incidental encounter of prior water intrusion plus subsequent fungal contamination. Construction in these situations can result in a "burst" or release of fungal conidia into the surrounding air, which can then travel through the heating, ventilation, and air-conditioning (HVAC) system and result in the exposure of susceptible occupants. Insights gained from outbreak investigations involving construction/renovation activities have been used to mitigate the risks of healthcare-associated exposure. Effective interventions deployed during these outbreaks have been incorporated into recommendations for proactive planning and interventional strategies by guideline setting agencies (4,5). Selected examples of risk mitigation or prevention are summarized in this section to underscore the importance of specific design issues such as controlling the dissemination of particulates and airborne pathogens during demolition or remediation and ensuring that the design of HVAC or air-handler systems meet the needs for general and special patient-care areas (e.g., operating rooms [ORs], interventional cardiology/radiology units, airborne infection isolation rooms [AIIRs], protective environment [PE] rooms). Sources of airborne contaminants and infectious agents are closely related to water- and moisture-related conditions. Representative outbreaks are also discussed to illustrate the risk of exposure and cross-transmission of relevant infectious agents.

Construction and Dissemination of Airborne Microorganisms Air-quality management during construction is central to preventing the transmission of opportunistic microorganisms to susceptible patients, most notably highly immunosuppressed patients. Key publications of outbreaks related to the *Aspergillus* species and related fungi received increased attention in the 1970s and are summarized elsewhere *(6,7)* (see Chapter 57). The transmission of airborne infectious agents may originate from patient reservoirs, from laboratories, and from dust and soil introduced into the facilities during construction (8,9). The relationship between facility HVAC and airborne healthcare-associated infections (HAIs) is discussed elsewhere in this text (Chapter 84). Numerous studies have confirmed the process by which construction activity brings outdoor contaminants into a building normally "protected" by multiple systems. Key findings and interventions from investigations describing airborne microbial contamination associated with construction between 1976 and 2010 are summarized in Table 83-1 (*10–30*,31, *32–53*,54,*55–62*,63,*64,65*,66,*67*,68).

Soil and dust become vehicles for particulates, which carry microorganisms, leading to infection and disease in specific populations. This process has been described in several excellent studies *(23,24,69,70)*. Dust particles from excavation (aside from irritation from fumes and chemicals) become the vehicle for introducing opportunistic microorganisms into the HVAC systems *(33,71)*.

External Demolition and Implosions

Excavation has been cited as the major problem with external demolition and implosions *(72)*. Reports regarding the impact of large-scale demolition (e.g., implosion) have provided important information about whole-building HVAC and air pressurization (i.e., the importance of not permitting a whole building to become negative, resulting in outside air flowing into the building). Facility-associated cases of aspergillosis have been documented from temporal depressurization, in which contaminants were drawn into a facility adjacent to another building that was imploded (54,*73*,74) (see Chapter 84). Intrusion of contaminants during nearby building implosions produce high concentrations of dust, soil, and microbial contaminants in or on these substances; importantly, proper planning can reduce the risk from this increased burden of contaminants in outdoor air (*64,65*,68,*75,76*). Preemptive measures may include canceling elective surgery for patients at high risk, sealing windows and doors, adding extra filtering for air intake, and maintaining positive air pressure for patient-care areas where immunocompromised or other susceptible patient populations are located. Similarly, a fire in a nearby building may also have resulted in transmission of the *Aspergillus* species through open windows by imbedding spores in carpeting *(36)*.

Indoor Environment

Aspergillus species and *Rhizopus* are among the most important fungi introduced during construction and are characterized by an ability to grow in an indoor environment under favorable temperature and moisture conditions *(13,14,24)*. Other fungi that gain access through building penetrations include the *Penicillium* species, *Cladosporium* species, and similar airborne contaminants *(33,70,77)*. Reservoirs of these may also be created in the indoor environment from the undetected intrusion of water into walls or cabinetry in patient-care units.

Air Handlers

Many publications have addressed the importance of appropriate measures for the containment and protection of air-handling units (AHUs) during construction to reduce the risk of transmission of airborne pathogens such as the *Aspergillus* species to susceptible patients. Appropriate containment may include zonal use of portable high-efficiency particulate air (HEPA)–filtered air (used in negative air machines), provision of negative air pressure *(39,45,78,79)*, dedicated exhaust, and physical isolation of the construction area from patient-care areas *(24,32,40)*. Numerous patient outbreaks of bacterial and fungal infections associated with aerosols from contaminated ventilation ducts, grills, damaged barriers (e.g., bird screens, ventilation fans), and vacuum cleaners reinforce the importance of maintaining an intact air-handling system *(11,43,50)*.

TABLE 83-1

Airborne Microbial Contamination Associated with Construction—Selected Studies by Year and Microorganism

Year	*Author*	*Microorganism*	*Population/Location*	*Epidemiologic Factors*	*Remedial Measures or Preventive Measures*
1976	Aisner et al. *(10)*	*Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus* spp.	Hematology Solid tumor	False ceilings, moisture fireproofing materials	Solid, sealed ceiling
1976	Kyriakides et al. *(11)*	*A. fumigatus*.	Renal transplant	Ventilation contaminated with bird droppings	Replaced bird screen, repaired malfunctioning exhaust fan
1978	Arnow et al. *(12)*	***A. fumigatus***	Hematology	Building materials, wet	Replace water-damaged materials
1982	Lentino et al. *(13)*	*A. flavus*, *A. fumigatus*, *A. niger*, *A.* spp.	Hematology Renal transplant	Contaminated window AC units; road construction	Removal of window AC units (suggested)
1982	Sarubbi et al. *(14)*	*A. flavus*.	Medical–Surgical	Construction dust; non functioning air handler	Repair of defective air handler
1984	deSilva et al. *(15)*	Bacterial, multiple	Cardiac surgery	Ineffective operating room (OR) air handler; unacceptable surgical site infection	Increased air changes per hour (AC/H); improved filters; constant temp/ relative humidity (RH), increased positive pressure
1985	Anderson et al. *(16)*	*Varicella zoster*	Pediatrics	Isolation rooms without negative pressure	Negative pressure, no anterooms; no cases of nosocomial transmission
1985	Krasinski et al. *(17)*	*Penicillium, Zygomycetes Aspergillus* sp.	Newborn	Improperly functioning air handler	Barriers/negative pressure in construction area
1986	Opal et al. *(18)*	*A. flavus, A. fumigatus, A. niger, Aspergillus* spp.	Hematology, medical intensive care unit (ICU)	Construction/renovation activity; i neffective barriers and air handler	Physical sealed barriers; portable HEPA filter machines. Air handler treated
1987	Allo et al. *(19)*	*A. flavus*	Hematology; OR	Contaminated OR ventilation system	Cleaned ventilation system
1987	Ruutu et al. *(20)*	*A. fumigatus*	Hematology; bone marrow transplant (BMT)	Contaminated OR ventilation system	Cleaned ventilation system; ducts; filters changed, HEPA filter framing sealed
1987	Perraud et al. *(21)*	*A. fumigatus*	Hematology	False ceilings, acoustic insulation	Barriers; evacuate high-risk patients during renovation
1987	Sherertz et al. *(22)*	*A. flavus, A. fumigatus*	BMT	Efficiency of laminar airflow (LAF) HEPA filtration	Horizontal LAF HEPA filtration improved outcome
1987	Streifel et al. *(23)*	*Penicillium* spp.	BMT	Moisture; rotted wood released spores into room air	Replace with nonporous surfaces around sink
1987	Weems et al. *(24)*	*A.* spp. *Rhizopus;* *Mucorales* sp.	Hematology; renal transplant, BMT	Construction/demolition activity; excessive dust; improperly functioning air handler; open windows	Construction plans: HVAC; permanently sealed barriers against infiltration from windows
1989	Barnes et al. *(25)*	***A. fumigatus***	BMT	Construction	LAF units
1989	Hopkins et al. *(26)*	***A. fumigatus***	Renal transplant Hematology	Construction in centrally located radiology suite	Preventive measures in treatment areas, not pt. room
1990	Mehta *(27)*	***A. fumigatus*, *A.* ssp.**	Open heart surgery; OR	Ineffective air handler; bird nest adjacent to air intake; no preventive maintenance	Pigeons' nest removed; change of prefilters; use of HEPA filtration
1990	Fox et al. *(28)*	*Penicillium* sp. *Cladosporium* sp. *A.* ssp.	OR	Ventilation duct lined with contaminated fiberglass insulation	Decontamination of air handler ductwork; filter replacement

(*Continued*)

TABLE 83-1

Airborne Microbial Contamination Associated with Construction—Selected Studies by Year and Microorganism (*Continued*)

Year	*Author*	*Microorganism*	*Population/Location*	*Epidemiologic Factors*	*Remedial Measures or Preventive Measures*
1990	Jackson et al. *(29)*	***Sporothrix cyanescens***	Bronchoscopy suite	Renovation of suite pseudoepidemics from dust	Appropriate barriers and negative pressure
1991	Arnow et al. *(30)*	***A. flavus, A. fumigatus***	Hematology	Improperly sealed air filters	Air filters removed; water damage addressed
1991	Everett and Kipp (31)	**Bacterial, multiple**	Surgical patient	Inefficient OR ventilation system	Changes in OR air changes; OR temperature
1991	Humphreys et al. *(32)*	***A. fumigatus, A.* ssp.**	ICU	Perforated ceiling; fibrous insulation	Solid ceiling; proper insulation
1992	Abzug et al. *(33)*	**Mucorales Zygomycetes**	Pediatric Leukemia	Air intakes proximity to heliport	Modifications to helipad design and HEPA filters
1992	Hruszkewycz et al. *(34)*	***Penicillium* spp. *Aspergillus* sp.**	Laboratory pseudo-outbreak	Improper airflow during renovation near lab; false ceiling in work area	Sealed ceilings; proper use of lab hoods; appropriate air flow controls
1993	Flynn et al. *(35)*	*A. terreus*	ICU, BMT, hematology	Renovation adjacent to ICU affecting ventilation duct; false ceiling removal	Adjusted pressure relationships between ICU and renovation, including stairwell; elevators
1994	Gerson et al. *(36)*	***A. flavus, A. fumigatus***	BMT; leukemia	Open window; fire-contaminated carpet	Modifications of carpet cleaning/extraction procedures
1994	Iwen et al. *(37)*	*Aspergillus* sp. Mixed fungi	BMT unit Hematology	Improper airflow; suspected infiltration from windows	Sealed windows and balanced airflow; replaced HEPA filters
1995	Stroud et al. *(38)*	Multi–drug resistant *M. tuberculosis*	AIDS patients	Improper air changes and pressure relationships for isolation rooms	Adjusted ventilation according to CDC guideline for MTB prevention
1995	Alvarez et al. *(39)*	*Scedosporium prolificans*	Hematology unit	Internal renovation; ventilation system	Move patients to another floor level
1996	Bryce et al. *(40)*	*A. fumigatus, A. niger, A. terreus*	Med Surg ICU, burn unit patients	Renovation in central supply area, contaminated supplies used in ICU, burn patients	Sealed construction area with temporary vents; cleaning of supplies surfaces
1996	Cotterill et al. *(41)*	Methicillin-resistant *S. aureus*	ICU	Open window; improper air intake/exhaust	Windows closed; redesigned bed placement
1996	Fridkin et al. *(42)*	*Acremonium kiliense*	Ambulatory surgery	Poorly designed air handler; contaminated humidifier	Redesign; changed HEPA filters. Proper maintenance of pressure relationships
1996	Anderson et al. *(43)*	*A. flavus*, *A. fumigatus*, *A. niger*	BMT, pediatric oncology unit	Improper airflow from clinical waste disposal area; contaminated vacuum	Sealing of disposal room and ducts; use of HEPA-filter vacuum cleaners
1996	Leenders et al. *(44)*	*A. flavus*, *A. fumigatus*	Hematology	Environmental source not identified	Windows closed; new air handler
1996	Loo et al. *(45)*	*A. flavus*, *A. fumigatus*, *A. niger*	BMT, hematology unit	Construction; demolition; perforated ceiling tiles	Solid ceiling, HEPA machines; use of copper 8 quinolinolate
1996	Philpot-Howard *(46)*	*A.* ssp. and other filamentous fungi	Hematology patients	Construction; ventilation parameters	Preventive maintenance of air supply; use of barrier
1996	Pittet et al. *(47)*	*Aspergillus* sp.	COPD	Insufficient air filter replacement	Monitor filter function; replaced filters
1997	Dearborn et al. *(48)*	***Stachybotrys atra***	Infants	Residential water damage; potential release of toxin	Decontamination with diluted bleach

1998	Tabbara al Jabarti *(49)*	***A. fumigatus***	Cataract; OR ocular surgery	Hospital construction	Proper maintenance of physical structure
1998	Kumari et al. *(50)*	Methicillin-resistant *S. Aureus*	Orthopedic patients	Ventilation grills	Air handler cleaned, maintained proper pressure relationships
1999	Cornet et al. *(51)*	***A.* ssp.**	Hematology	Renovation and dust production	Use of portable HEPA filters versus LAF HEPA
1999	Garrett et al. *(52)*	*A.* ssp.	Rheumatology patients	Construction not sealed off; improper pressure relationships and air changes	Adjusted ventilation according to CDC guidelines (tuberculosis)
1999	Laurel et al. *(53)*	*A. niger*	Laboratory Pseudo outbreak	Construction; installation of ventilation duct adjacent to biological safety cabinet	Cleaning, prefilter; HEPA filter changes, construction protocols for laboratory
2000	Thio et al. (54)	*A. flavus.*	BMT Hematology	Pressure relationship of units to whole hospital; negative pressure	HEPA; readjust pressure relationships to ensure hospital as a whole slightly positive
2001	Burwen et al. *(55)*	*A. flavus*	Hematology–oncology	Distance from renovation; construction activity	Screen and use HEPA-filtered air; applicable CDC guidelines
2001	Lai *(56)*	*A. niger, A.* ssp.	BMT patient wards	Construction adjacent to BMT unit	BMT site tightly sealed; high-risk patients to avoid site during construction
2001	Oren et al. *(57)*	*A. flavus, A.* ssp.	Leukemia, BMT patients	Construction; natural ventilation	Ward with air filtration using HEPA filters
2001	Pegues et al. *(58)*	*A.* ssp.	Heart–lung transplant	Renovation; dust production	Removal of carpeting; replacement of ceiling tiles
2002	Hahn et al. *(59)*	*A flavus, A niger*	Hematology–oncology	Contaminated insulation in affected unit and nurses station	Installation of HEPA filters
2002	Kistemann et al. *(60)*	*A.* ssp.	COPD and corticosteroids	Reconstruction, pigeon droppings, water damage from leakage	Clean up of area; maintenance/precautions to reduce exposure to patients
2002	Raad et al. *(61)*	*A. fumigatus, A. flavus terreus, A.* ssp	Hematology	Construction dust outside of protected BMT area	High efficiency masks on patients during transport
2005	Adler et al. *(62)*	*Bacillus* sp.	NICU	Construction during relocation of the NICU	Case–control study identified association retrospectively
2006	Vonberg and Gastmeier (63)	*A. fumigatus, A flavus*	Hematology	Construction or demolition work	Reduce exposure of hematological patients to construction
2007	Nihtinen et al. *(64)*	*A. fumigatus*	Stem cell transplant unit	Heavily contaminated air outside at construction site	HEPA filters prevented fungal colonization
2009	Brenier-Pinchart et al. *(65)*	Filamentous fungi	Hematology wards	Outdoor and indoor risks identified; outdoor air higher load of fungal flora	HEPA filtration; more influence on protecting rooms plus cleaning
2009	Kidd et al. (66)	*A fumigatus*	ICU	ICU ventilation likely; definitive source not identified using typing	Cleaning/sealing all points of leakage: lights, vents, ceiling tiles.
2010	Jensen et al. *(67)*	*A.* spp.	OR; postop rooms	Postop environment showed high counts of conidia	Room air cleaning
2010	Fournel et al. (68)	*A.* spp.	Three high-risk patient units	Air contamination—extensive testing outside and indoors	Protective measures more effective than air cleaning in minimizing impact

Room Design and Location Room design must consider the location of supply air and exhaust vents as critical factors to interrupt the risk of transmitting airborne contaminants *(33,41)*. Negative air pressure in pediatric oncology units, for example, was shown to reduce the spread of varicella-zoster virus (VZV) among workers and patients *(16)*. Lower bloodstream-infection and mortality rates were reported for burn patients in enclosed intensive care unit (ICU) beds than for patients in open wards *(80)*. Multiple outbreaks related to *Mycobacterium tuberculosis* were terminated with properly designed and improved maintenance of negative air pressure (AII) rooms *(81)*.

The Surgical Suite Environment The OR environment has been studied extensively in an attempt to reduce infectious risks in patients undergoing clean surgical procedures such as orthopedic joint replacement. Other invasive procedures are increasingly being performed in a variety of locations such as procedure rooms, which mirror the desired conditions in an OR, and so the scope of this setting needs to extend beyond the surgical suite *(67)*.

The literature on reductions in surgical site infection (SSI) rates, primarily found in total joint arthroplasty, is reviewed elsewhere *(82–84)*. The focus for this chapter relates to contamination of the OR during construction and renovation from airborne fungi and other pathogens (*27,28*,31,*85,86*,87,*88–92*). A summary of the general issues and interventions to mitigate these problems have been reported elsewhere (8,9,*28,89,93*) (see Chapter 84). Multiple interventions in ORs have led to improvements in performance and outcome involving surgical patients. Many of these emphasize optimizing air quality and exchange. As a result, current standards include increased outside air and total air exchanges per hour, improved air filtration efficiency, proper humidification, and filter location in air handlers serving ORs (4,*15*,31,*42*). Major studies by Lidwell *(94,95)* focused on the use of ultraclean (laminar airflow [LAF]) HEPA-filtered air in clean orthopedic surgical procedures. These studies, together with other multisite studies (87,*96*), led to a better understanding of the independent contribution of ultraclean air in reducing clean SSIs; its effect is comparable to the use of preoperative prophylactic antibiotics. Although LAF using HEPA filtration has been considered for specific procedures such as orthopedic surgery, given the major resultant morbidity and mortality if the replaced joint becomes infected, definitive evidence on the efficacy of elaborate LAF in the prevention of SSIs has been lacking. The Centers for Disease Control and Prevention (CDC) 2003 guidelines, assessing available scientific literature, concluded: "No recommendation is offered for performing orthopedic implant operations in rooms supplied with laminar airflow …" (97). Brandt et al. recently published a multihospital study in Germany that suggested an *increased* risk of SSI was associated with ORs using LAF compared to standard turbulent-air ORs (*98*). Details of specific HVAC design at the participating hospitals are lacking in this investigation; however, these systems were older, vertical, high-velocity LAFs and are not comparable to the current design required in the United States in the 2006 Facility Guidelines Institute (FGI) guidelines (99) and the latest 2010 FGI guidelines (4) that use a low-velocity unidirectional airflow (100). For complete information on this design, see Chapter 82.

Waterborne Microorganisms

Water can be a reservoir of pathogens that can cause waterborne diseases but can also harbor other microbes (e.g., *Fusarium* spp. and *Aspergillus* spp.) that may propagate in the environment. Those at greatest risk are immunocompromised patients, and many outbreak investigations have identified potable water systems and storage tanks, showerheads, and ice machines as sources of waterborne pathogens *(101–104)*. Table 83-2 summarizes findings from investigations of clusters of infection caused by waterborne pathogens (*103,105–113*,114, *115–122*,123,124,*125*,126). *Legionella* species, for example, have been implicated in patient infections acquired through the inhalation of aerosols spread from contaminated storage tanks, shower heads, and equipment that used tap water, such as water baths, stagnant water on the roof (124), decorative water fountains (126), and/or entire water systems (114,*127–131*). A review of healthcare-associated waterborne infections excluding those caused by *Legionella* species revealed 43 outbreaks with associated deaths of almost 1,400 per year and called for the provision of sterile rather than potable water for high-risk patients during hospitalization *(132)*. Maintenance of potable water quality depends on good design, preventive maintenance, and conduits that support dynamic movement in a continuous fashion. Problems arise when portions of water-delivery systems are capped, permitting water to stagnate, and both biofilm and concentrations of microbes increase to high levels. Surveillance for HAIs related to water reservoirs, therefore, is an important component of the design and operation of this major utility. One study assessed the risk of bacterial pathogens in drinking water in an attempt to determine if dose–response relationships could be developed, and whether or not potable water poses a public health hazard *(133)*. The results included a ranking of water-associated microorganisms from studies reported primarily from medical centers. Although the purpose of the study was not directly related to construction, the review does confirm the expected frequency of opportunistic microorganisms causing serious infections associated with water. These opportunistic microorganisms are of concern because of their potential for direct or indirect transmission from taps and sinks or through the inhalation of aerosols generated from construction activities affecting patients and construction workers (124). One recent outbreak of *Pseudomonas aeruginosa* in an ICU and transplant unit resulted in serious morbidity and mortality due to water from sink drains contaminating patients and clean supplies *(125)*. See Chapter 82 for complete details of how sink modifications ended the outbreak. Even contaminated condensation from window air-conditioning units when combined with other work practices can lead to invasive infections such as the *Acinetobacter* species bloodstream infections in high-risk pediatric populations *(134)*.

Moisture and Fungi Excessive moisture around pipes and insulation, condensation in drain pans, and flooding from broken pipes can lead to extensive environmental fungal contamination. Such contamination has been associated, for example, with water-soaked cabinets in

TABLE 83-2

Water-Associated Contamination Associated with Construction Selected Studies by Year and Microorganism

Year	*Author*	*Microorganism*	*Population*	*Epidemiologic Factors*	*Remedial or Preventive Measures*
1981	Crane et al. *(103)*	*Pseudomonas paucimobilis*	Intensive Care Unit (ICU)	Contaminated tap water	Thermal decontamination of water system; revised procedures for tap water use for equipment
1981	Cordes et al. *(105)*	*Legionella pneumophila* serogroup 6	Hospital patient rooms	Contaminated water supply; shower heads	Decontamination shower heads
1986	Panwalker and Fuhse *(106)*	*Mycobacterium gordonae*	Hospital	Contaminated ice machines	Disinfection; preventive maintenance
1991	Burns et al. *(107)*	*Mycobacterium fortuitum*	Alcoholism rehab unit	Ward showers; tap supply	Disconnected and disinfected showers
1993	Hlady et al. *(108)*	*L. pn* ser. 1	Hotel	Decorative water fountain	Proper heat and maintenance
1993	Sniadeck et al. *(109)*	*Mycobacterium xenopi*	Hospital rooms	Water supply (pseudo-outbreak)	Maintain temperature (>120°F [49°C; preferably 54°C])
1994	Prodinger et al. *(110)*	*L. pn* ser. 1	Renal allograft	Water distribution system	Replaced central water supply with individual electric water heaters in each room
1995	Bangsborg et al. *(111)*	*L. pn* ser. 1 and 6	Heart–lung transplant	ICU kitchen ice machine	Disinfection of machine; preventive maintenance
1997	Graman et al. *(112)*	*L. pn* ser. 6	Vent patients	Ice machine	Replace supply line and treatment of water system
1997	Patterson et al. *(113)*	*Legionella pn, bozemanii, gormanii*	General hospital	Water storage and distribution systems	Maintain hot water above 58°C
1998	Kool et al. (114)	*L. pn, L.* ssp.	Transplant center	Water system	Hyperchlorination
1999	Biurrun et al. *(115)*	*L. pn.* ser. 6.	General hospital	Water distribution system	Copper–silver ionization and continuous chlorination system
1999	Weber et al. *(116)*	***S. maltophilia***	Surgical ICU	Potable water- aerators	Removal or routine disinfection
2000	Kappstein et al. *(117)*	*Acinetobacter junii*	Pediatric oncology	Contaminated aerators	Remove, use aerators with radially/ vertically arranged lamellae
2000	Knirsch et al. *(118)*	*Legionella micdadei*	Solid organ transplant	Hot water sources	Treat hot water supply
2000	Stout et al. *(119)*	*L. pn* ser. 1	LTC residents	Water distribution system	Install copper–silver ionization system
2000	Borau et al. *(120)*	*L. pn* ser. 6	ICU patients	Hot water system	Elevate hot water temperature
2002	Grove et al. *(121)*	*Legionella longbeachae*	ICU patients	Cooling tower; pigeon's nest 1–2 cm from vent; demolition	Removal of nest; PM cooling towers
2002	Darelid et al. *(122)*	*L. pn* ser.1	General hospital	Water distribution system	Maintain water temperature 55°C.
2009	Hota et al. (123)	*Pseudomonas aeruginosa*	ICU; Transplant unit	Biofilm inside drain; design of hand washing stations	HW stations redesigned to prevent splashing
2009	CCDR (124)	*L. pn* ser.1	Hospital workers; patients	Potential for condensing tower; stagnant water in kitchen roof	Water treatment; removal of dead legs; intensified surveillance; educate workers
2009	Rao et al. *(125)*	*Phialemonium curvatum*	Hospital hemodialysis center	Product water-source of bloodstream infection	Remediation of water distribution system and discontinuing use of waste handling option ports
2009	Palmore et al. (126)	*L. pn* ser.1	Radiation Oncology Center	Decorative fountain	Cases occurred even with filter and ozone generator. Unacceptable risk to maintain a fountain

medication rooms *(23,62)*. Static water systems can provide a reservoir of microorganisms in the healthcare environment by supporting their growth. Nonsterile water used for invasive patient-related procedures can result in direct or indirect transmission of microorganisms to patients *(103,109,135)*. Bloodstream infections due to the mold *Phialemonium curvatum* were identified in a hospital hemodialysis unit in which the product water was determined to be the source. Resolution required discontinuing the use of waste-handling option ports *(125)*. A report of fungal endophthalmitis from *Acremonium kiliense* following cataract surgery in an ambulatory surgery setting demonstrated the process by which contaminated humidifier water functioned as a reservoir for an infectious agent, eventually spreading through the airborne route by way of the ventilation system *(42)*. Typically, healthcare-associated transmission of fungi is airborne; however, there is emerging evidence that potable water in health facilities may also be a significant reservoir, suggesting that prompt disinfection of high water-use areas such as showers is an important measure to prevent exposure to fungal pathogens *(136)*.

Legionella Species Annually, there are estimates of between 8,000 and 18,000 hospitalizations for legionellosis *(137,138)*. However, reported hospital outbreaks predominate in the literature because of the fatal effects on susceptible patient populations; they have helped characterize *Legionella* and identify key risk factors from affected individuals *(139–142)*. Although each reported outbreak of legionellosis improved the epidemiologic understanding of this pathogen, endemic, sporadic cases (representing most of the observed cases) still evade full understanding. The mode of transmission implicates not only cooling towers, potable water reservoirs, and distribution systems *(140–144)* but also water-related equipment such as medication nebulizers *(145)* and potable water used for nasogastric feeding *(104)*. An investigation by the National Institutes of Health recently reported an outbreak associated with a decorative fountain in its radiation oncology center (126).

Legionella species from nearby environmental water sources enter hospital water systems, multiply in cooling towers and evaporative condensers, and/or contaminate the potable water system. Because infection develops after inhaling airborne water droplets containing *Legionella* species, any opportunity for contaminated water to aerosolize is of concern during construction and renovation. Major construction has been associated with numerous healthcare-associated outbreaks or clusters *(127)*. Potential mechanisms include the release of this microorganism from vibration or significant changes in water pressure. These disturbances loosen corrosion and disturb biofilms, thereby releasing *Legionella* species into water system pipes. Excavation permits the microorganism to be released from the soil; the microorganisms eventually enter cooling towers, air intakes, or water systems, leading to direct inhalation from water sources (146). Summaries of outbreaks have been described in the CDC guidelines and other government and private recommendations for detection and treatment (146,*147–151*) (see also Chapter 36).

CHANGES IN HEALTHCARE DELIVERY AND IMPACT ON CONSTRUCTION TRENDS

Construction Costs

Annual construction and design surveys in the United States indicate a continued major expenditure on healthcare construction and renovation. Changes in patient acuity, aging, and reduced capital funds have affected construction expenditures in a number of ways. Recent trends show dollars are spent primarily on inpatient specialty beds (e.g., cardiac and cancer) along with increasing demands for assisted-living and skilled nursing centers. A December 2009 survey of construction for hospitals, nursing homes, and outpatient facilities in 2009 totaled $61.1 billion for new construction and $25.8 billion for renovation (152). The distribution of projects continues the usual pattern of 70/30, that is, 72% of the projects involved renovation and 28% were new construction or replacements. These investments represent actual drops and delays due to the faltering economy in 2008 to 2009 that profoundly affected construction. The good news is that new construction and renovation also reflect new attention to infection prevention following FGI guidelines' (99) requirements and the inclusion of in-room sinks being among the five top features included in hospital design.

The increasing age of US healthcare facilities generates a constant need for repair and remediation work (cabling, room additions). These processes increase the risks of environmental contamination, affecting air and water quality. Natural and manmade disasters during construction (e.g., flooding) add extra opportunities for contaminating healthcare delivery sites. New concerns for protecting buildings from airborne contaminants from the intentional release of biologic agents or unintended manmade disasters have focused additional attention on the building envelope, ventilation management, and isolation room capacity *(153,154)*.

Costs of Healthcare-Associated Disease

Outbreak investigations documenting health outcomes resulting from contamination are associated with multiple healthcare settings but focus primarily on hospitals. Although the actual percentage of HAIs directly related to construction is unknown, one can consider costs in terms of one significant airborne infectious agent: *Aspergillus* species. Aspergillosis can be either community-acquired or healthcare-associated, but it is difficult to always distinguish between them. The total cost impact is enormous. For example, in considering aspergillosis alone for 1 year (1996), costs were estimated at $633.1 million. Although the number of aspergillosis-related hospitalizations are a small percentage of total hospitalizations, the average length of stay attributable to treating this disease is 17.3 days, costing an average $62,426 (95% confidence interval $52,670–$72,181) based on 176,272 hospital days (95% confidence interval 147,163–206,275 days) *(155)*. The case fatality rate for aspergillosis averages 58%, but for bone-marrow transplant recipients, it reaches 86.7% *(156)* (see Chapter 59). A better assessment of risks and their mitigation can enable architects to design

and plan for patient-friendly and safer facilities. Although there has been improvement with more recent improved therapies, prevention from environmental exposure remains critical to reducing these rates and cost (63,*157*).

DESIGNING FOR DISEASE PREVENTION AND HEALTH PROMOTION

Healthcare Study Design

This section focuses on the design and construction of healthcare environments that plan to reduce the risks of adverse outcomes learned from past experience and that emphasize infection prevention and control (IPC) during new construction and renovation (external and internal). Suggestions and recommendations to prevent and control infectious risks are based on published investigations occurring most frequently in hospitals; these recommendations may need tailoring for other healthcare delivery sites. Design professionals are increasingly interested in identifying individual variables that affect patient outcomes and worker productivity, forming a growing science around the relationship between the built environment and quality of care *(157)*. The *built* or physical environment is defined as any aspect of the environment that is constructed by design experts such as architects or designers. More attention is being given to designing facilities that are cost-effective, efficient, and functional for staff while cultivating a caring, healing environment for patients (see Chapter 82, Infection Control Elements in Design).

Current and Future Design and Materials

Because of the paucity of scientific evidence, HEs and IPs must rely on fundamental principles such as the epidemiology of infectious diseases to determine what interventions are most likely to be effective in preventing infection. Evidence from prevention of HAIs through the use of antimicrobial-impregnated medical devices is leading to the incorporation of an antimicrobial surface or polymer treatments to minimize environmental reservoirs of potential pathogens *(158,159)*. Because of the focus on the prevention of HAIs, many manufacturers are developing and marketing surface treatments that claim to be antimicrobial or self-disinfecting surfaces (e.g., copper) and oxidizing agents bound to surfaces utilizing normal light wavelengths or ultraviolet light *(160,161)*. Although none of these have yet demonstrated a reduction in HAIs and have limited results from laboratory studies, they are designed for healthcare settings to lessen the risk of cross-transmission. Other architectural and utility system features under study include ventilation systems that provide 100% exhaust, design of microbial-resistant building materials (e.g., glass mat faced gypsum board), the use of ultraviolet germicidal irradiation to prevent the biofouling of AHUs, and design features that minimize the buildup of biofilms in potable water systems *(162,163)*.

A number of engineering studies directed at determining ideal ventilation for patient rooms *(164)* or AIIRs *(165)* have provided a foundation for design recommendations *(166)*. Additional studies of areas needing special ventilation such as the OR suite have and will continue to drive changes in specific parameters for consensus guidelines. The National Institutes of Health computer modeling study of efficacy of OR HVAC design found that increasing the number of air changes per hour was not as important as air velocity, and as noted earlier, unidirectional airflow at the surgical site was more important than the location (high or low) of exhaust ducts (100) (see Chapter 82).

Floor covering materials such as carpeting have been studied extensively, and although it may be colonized with a variety of pathogens (e.g., *Clostridium difficile*), no direct link to patient infections has yet been found *(36,167,168)*. Accordingly, carpet in patient-care areas should be chosen with respect to aesthetics and cleanability and not because of risk to patients. Surface treatments or incorporation of antimicrobial products into the surface matrix to inhibit microbial growth are available commercially. However, most efficacy studies involve *in vitro* investigations; to date, there are no professional peer-reviewed publications to support HAI reduction related to antimicrobial treatment of environmental surfaces including patient-care equipment, fixtures or furnishings, and carpeting. There is evidence that antimicrobials can reduce the incidence of HAIs when incorporated into or onto devices that are placed in the patient (e.g., central venous catheters). Antimicrobial-treated environmental surfaces or products are submitted to the U.S. Environmental Protection Agency (EPA) by the manufacturer as preservatives of the treated substrate, and any claims of disease prevention that have come under scrutiny by the EPA are lacking supportive scientific evidence. Specifically, textiles such as carpeting or cubicle curtains with antimicrobial features, including textiles developed to absorb sound, have never been demonstrated to reduce infections in patients *(169)*.

REGULATORY AND ACCREDITATION AGENCIES' GUIDELINES AND STANDARDS THAT IMPACT CONSTRUCTION

Agencies with Impact on Design and Physical Environment

Standards and guidelines issued or enforced by the following agencies have had major impact on the physical structure of healthcare settings. There are many agencies and professional associations that have a direct impact or provide resources to plan, design, and better construct facilities; some of note include the following:

1. FGI: "2010 Guidelines for Design and Construction of Healthcare Facilities"—minimum standards for most states (4)
2. Centers for Medicare & Medicaid Services (CMS): "Hospital Conditions of Participation (COP)"—for Medicare & Medicaid *(170)*
3. TJC: "Comprehensive Accreditation Manual for Hospitals: The Official Handbook" *(171)*
4. CDC/Healthcare Infection Control Practices Advisory Committee: "Guidelines for Environmental Infection

Control for Healthcare Facilities" (97) and numerous other guidelines *(5,148,172–174)*

5. Other agencies
   - Occupational Safety and Health Administration (OSHA): tuberculosis, construction, bloodborne pathogens, and legionellosis *(149,175,176)*
   - National Institute of Occupational Safety and Health (NIOSH): HVAC, sharps containers, air sampling, testing, filtration *(153,177–179)*
   - State and local standards—for example, enforcement of national consensus guidelines by state-based "authorities having jurisdiction," who are professionals from a variety of backgrounds who review and approve plans for construction in healthcare facilities *(180)*
6. Professional organizations with resources and/or standards
   - Association for Professionals in Infection Control and Epidemiology (APIC): chapter on construction (8,9), and the infection control risk assessment (ICRA) (8,9,*181,182*) (www.APIC.org)
   - American Society of Healthcare Engineering (ASHE): contractor certificate program including ICRA; monographs (www.ASHE.org)
   - American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE): basic design research; design handbooks and American National Standards Institute ANSI/ASHRAE/ASHE Standard 170-2008, Ventilation of Health Care Facilities in the 2010 FGI guidelines (4) (www.ashrae.org)
   - The Center for Health Design supports research and development of science to support evidence-based design (www.healthdesign.org).
   - Green Guide for Health Care issues practice guidance for healthy and sustainable design, construction, and operation of healthcare facilities (www.gghc.org).
   - U.S. Green Building Council developed "Leadership in Energy & Environmental Design"; develops consensus-based standards for design and construction of sustainable or green buildings, oversees Leadership in Energy & Environmental Design certification, and offers education and training (www.usgbc.com).

Relationship between FGI Guidelines and Regulations

Facility Guidelines Institute The original *General Standards of 1947* used as regulations for the Hill–Burton program have evolved into today's *Guidelines for Design and Construction of Hospital and Healthcare Facilities*, *2010* under the guidance of the FGI founded in 1998 to ensure a process to keep the guidelines current (4). The American Institute of Architects was the publisher, a role now carried out by ASHE and the American Hospital Association press. The change to "FGI Guidelines" also highlights the multidisciplinary aspect of the >100-member "Healthcare Guidelines Review Committee" (HGRC)—the group that carries out the revision through consensus. The HGRC steering committee has always included at least one infection prevention expert representative. The 2010 guidelines expanded on the planning process of the ICRA, which first appeared in the 1996 to 1997 guidelines, developed further into the 2001 and 2006 editions and is now well-integrated into the complete "Planning, Designing, and Construction" section of the 2010 guidelines. As a consensus guideline, it relies heavily on input from groups such as ASHE and ASHRAE, increasingly from clinicians and organizations such as APIC and the Society for Healthcare Epidemiology of America (SHEA), and it references published guidelines from the CDC. The guidelines include ventilation requirements for negative air pressure rooms as specified in the 2005 CDC "Guidelines for Preventing the Transmission of *M. tuberculosis*" *(5)* and the design and ventilation recommendations in the 2004 "Guidelines for Preventing Health-Care-Associated Pneumonia, 2003" as well as the CDC/Healthcare Infection Control Practices Advisory Committee guidelines for environmental infection control in healthcare facilities. The combined effect of these guidelines has set in motion an increased opportunity for long-range and ongoing involvement of infection-prevention programs in planning for construction and major renovation. The current 2010 edition of the guidelines continues to improve the scope and importance of the ICRA and is viewed as a core element. The role of HEs and IPs in implementing the ICRA is multifaceted and is needed for long-range strategic planning and operational project initiatives and for ongoing maintenance activities.

Centers for Medicare & Medicaid Services Changes related to facility design aimed at reducing infectious risks are evident in many of the revised standards. CMS requirements are consistent with the FGI guidelines, although CMS uses additional physical plant standards to enforce the Hospital COP and Life Safety Codes (LSC). In addition to CMS, more than 42 states adopted the FGI guidelines as minimum design standards or adapted them with state-specific regulations governing physical plant and safety issues, transforming the guidelines to regulatory status. A large proportion of the FGI HGRC members are state and federal "authorities having jurisdiction" who review and enforce design plans as agents of CMS.

The Joint Commission Facilities accredited by TJC must consider the EOC standards because these impact LSCs and utility management standards for all facilities. TJC added specific standards for design and construction that reflect the FGI guidelines requirement for a risk assessment. These are primarily found in the EOC standards and elements in EC.02.05.01, which address the evaluation of ventilation and water for pathogenic biological agents, as well as referring specifically to the guidelines and EC 02.06.05, addressing demolition, renovation, and new construction. For example:
2010 Standard: EC.02.06.05

> *When planning for demolition, construction, or renovation, the hospital conducts a preconstruction risk assessment for air-quality requirements, infection control, utility requirements, noise, vibration, and other hazards that affect care, treatment, and services. Note: See LS.01.02.01 for information on fire safety procedures to implement during construction or renovation…the hospital takes action based on its assessment to minimize risks during demolition, construction, or renovation. (171).*

Centers for Disease Control and Prevention The CDC guideline for environmental infection control supports

many key guidelines and recommendations and provides strength-ranked recommendations based on peer-reviewed scientific evidence (97).

INFECTION CONTROL RISK ASSESSMENT—DESIGN AND CONSTRUCTION ASPECTS

Concept—The Infection Control Risk Assessment

Infection Control Risk Assessment—Construction Projects The FGI guidelines recognize that renovation and new construction in existing facilities can create conditions that may be hazardous to occupants. The 1996 to 1997 edition of the guidelines required construction and major renovation assessments during project planning related to specific risks. The current 2010 guidelines lend stronger weight to IPC input at the *initial stages* of planning and design of a project by requiring documentation of an ICRA (4). The ICRA is considered a process requiring documentation of *continued involvement* of IPC throughout specific projects. ICRA is a determination of the potential risk of transmission of various agents, particularly biologic, in the facility but expands far beyond determining optimal numbers of isolation rooms or the location of handwashing stations. Instead, ICRA supports design of the EOC toward systems that prevent transmission of infection and ensures a safe environment for patients, personnel, and visitors. For example, an important component of ICRA is determining locations and installation of dedicated exhausts when the cleaning and disinfection of medical equipment is anticipated. In 2006 and with additional clarifications in 2010, the guidelines clarified activities associated during *design planning*, *construction planning*, and actual *preparation for the construction* project referred to as "infection control risk mitigation recommendations" (ICRMR), addressing specific measures during a construction project. Specifically, the ICRA is now summarized as follows:

> *The ICRA shall be conducted by a panel with expertise in IPC, risk management, facility design, construction, ventilation, safety, and epidemiology. The panel shall provide documentation of the risk assessment together with updated mitigation recommendations throughout planning, design, and construction and commissioning. The owner shall also provide monitoring of the effectiveness of the applied ICRMR during the course of the project. The owner shall ensure that construction-related ICRMR- and ICRA-generated design recommendations are incorporated into project requirements.*

ICRA elements related to *building design features* include the following:

1. Numbers, location, and types of AII and PE rooms
2. Location of special ventilation and filtration of HVAC units serving such areas as emergency department waiting and intake areas
3. Air handling and ventilation needs in surgical services, AII and PE rooms, laboratories, local exhaust systems for hazardous agents/chemicals, and other areas with special needs
4. Water systems to limit *Legionella* spp. and other waterborne opportunistic pathogens
5. Location, design, and accessibility of hand-hygiene products and equipment (e.g., hand washing stations)
6. Furnishings and surfaces

ICRA elements related to *building site areas affected by construction* include the following:

1. Impact of disrupting essential services to patients and employees
2. Determination of the specific hazards and protection levels for each hazard
3. Location of patients based on susceptibility to infection and definition of risks to each patient
4. Impact of potential outages or emergencies and protection of patients during planned or unplanned outages, movement of debris, traffic flow, cleanup, and testing and certification
5. Assessment of external and internal construction activities
6. Location of known hazards

ICRMR Preparation for Actual Construction
The ICRA panel must also address the following:

1. Patient placement and relocation
2. Standards for barriers and other protective measures required to protect adjacent areas and susceptible patients from airborne contaminants
3. Temporary provisions or phasing for the construction or modification of heating, ventilating, air conditioning, and water supply systems
4. Protection of occupied patient areas from demolition
5. Measures to be taken to train healthcare facility staff, visitors, and construction personnel on the maintenance of interim life safety and ICRMR

Finally, the guidelines specifically require not only the "installation of infection control measures" but also "continuous monitoring for effectives throughout the project." This may be done by "in-house IPC, safety, or construction coordinator personnel" or "independent outside consultants." This major issue must be determined in the initial stages by the ICRA panel. In any case, "provisions for monitoring shall include written procedures for emergency suspension of work and protective measures indicating the responsibilities and limitations of each party (owner, designer, constructor, and monitor)."

There is no single best way for carrying out an ICRA or documenting the outcome that must be communicated to the architects and construction companies. Suggestions and examples for practical approaches may be found in the APIC's Construction SOAR and the third Edition Construction and Renovation Toolkit (8,9,*181*).

ICRA and Long-Range Planning and Design Although the ICRA as described by the guidelines is basic, it is equally important to step back and consider the long-range planning that goes into the overall master facility plan and the critical need for early and continuous input from IPC. Although the language of the ICRA clearly calls for input

during planning, it is applied most frequently to specific projects, which is the focus of this chapter. APIC published a strategy in 2000 for assessing healthcare facilities for infectious risks during construction in the APIC SOAR on construction and renovation and recommended an ICRA similar to that later required by FGI guidelines and the CDC 2003 environmental infection control (IC) guidelines. However, the tactics begin with developing a *construction and renovation policy (CRP), a multidisciplinary team, and a process to implement the policy* (9). See Chapter 82 for more on the ICRA and long-range planning.

Once a system is in place providing for oversight, the application of the guidelines fit into each specific project. The guidelines require documentation of an ICRA for each *specific* project; they are not retrospective and apply only to new construction or major renovation. However, the approaches may be applied to smaller repair or preventive maintenance projects as appropriate. Thus, development of a broad-based CRP is an efficient and effective method to address basic principles that affect all projects, using the CRP as a reference point for the facility. Recommended resources for a CRP include the FGI guidelines, the CDC environmental IC guidelines, the APIC SOAR and relevant chapters in the APIC Text, guidelines from Health Canada on the prevention of *Aspergillus* and *Legionella*, and construction guidelines from the Canadian Standards Association.

Infection Control Risk Assessment—Overview for Planning and Design

Teams Multidisciplinary planning committees vary in size, although all resources agree that an assessment panel must include professionals with expertise in IPC, risk management, facility design, construction, ventilation, safety, and epidemiology. The panel is most effective if it includes an administrator and major stakeholders such as environmental services and the patient-care manager most affected by the construction or renovation. If a CRP is developed and approved, it becomes the basis of the ICRA for major or minor processes. A key first step is the identification of a multidisciplinary planning group involving design professionals, engineers, risk and safety officials, IPC and epidemiology professionals, the IPC committee (or committee charged with development and review of the IPC policy), and administrators representing special program needs.

Construction and Renovation Policy A comprehensive CRP requiring IPC input is the fundamental strategy that ensures timely notification of the IP (or person with IPC responsibilities) for early program planning. Once established, the IP should be made aware of planned projects as a matter of routine. This, in turn, ensures that an IPC evaluation of the project will be provided from concept to completion as is now required by the ICRA. The evaluation should include the design of the EOC, construction preparation and demolition, intraconstruction operations and maintenance, project completion with postconstruction cleanup, and monitoring. The ICRA documentation process fits future projects from small to complex (8,9,*181*).

Construction and Renovation Policy Elements The policy should address overall planning, designing, and monitoring processes, anticipating that future projects will vary in degree of complexity. It should ensure that input is required in all phases (i.e., structural design and specific practices to protect occupants during the preconstruction, intraconstruction, and postconstruction phases).

Basic issues include the authority and responsibility for establishing internal and subcontractor coordination of each stage of the project. The policy should be submitted for approval by the facility's board of trustees and reviewed and approved periodically (e.g., annually). Specific elements that should be included in the policy include the authority and responsibility for establishing internal and subcontractor coordination of (a) construction preparation and demolition, (b) intraconstruction operations and maintenance, (c) project completion and postconstruction cleanup, and (d) monitoring.

A comprehensive policy is the basis of *individual project* ICRAs and should include the ICRA elements listed earlier for prior to and during construction and potential remediation needs and educational needs of HCP as well as construction workers.

Integration of the CRP and ICRA Once approved, a CRP becomes the "driver" to ensure appropriate and continuous input from IPC into (a) the structural design processes to identify appropriate and timely IPC practices and (b) specific projects during each construction phase, focusing on patient and worker protection from construction activity.

Infection Control Risk Assessment

Budget Issues Healthcare epidemiology and infection prevention control (HEIPC) staff participation is critical in the initial planning and approval meetings during the programming or design phase. Issues frequently addressed include budget, space constraints including storage and equipment cleaning areas, AHUs, handwashing facilities, appropriate finishes, specific products with infectious implications, and applicable regulations. HEIPC staff should be prepared to support their position and recommendations with published citations whenever feasible, especially when a recommendation is not budget neutral (8,9,*93*). HEIPC staff frequently work with consultants during the planning phase of specific projects, including architectural and construction companies in a "partnering" process. Consulting an environmental expert might also be necessary if the size and complexity of construction provides considerable risk to highly susceptible patients because of location, prolonged time of construction, work conducted over continuous shifts, and likelihood of air handlers sustaining frequent interruptions. These variables increase risks to patients and personnel and may require environmental testing. If appropriate, budgets for environmental consultants and anticipated testing or environmental monitoring must be considered at the earliest stage of planning. Major design components that must be addressed include design to support IPC practice and design, number, and type of isolation rooms (i.e., AIIR or PE).

Special Environments—AIIR and PE New Construction or Renovation FGI guidelines outline the design characteristics for AIIR, and continue to not require anterooms. Anterooms may be useful for supplies and

accommodating personal protection equipment but are not needed to maintain negative air pressure of the room with respect to the adjacent corridor. The 2010 guidelines are clearer about what should be in place and the direction of the airflow *if* an anteroom is installed. The guidelines do not support dual-purpose positive and negative ventilation (i.e., rooms "switched" from negative to positive air pressure) because of concerns over reliability and maintenance of intended pressurization relationships. AIIR in new construction or renovation require a negative airflow of 12 air exchanges per hour. Although audible alarms may be used to monitor AIIR, current guidelines for new construction require permanently installed *visual* mechanisms to constantly monitor the direction of airflow (4). AIIRs also require self-closing doors and tight sealing of the room. If the air cannot be exhausted directly to the outside, it must be filtered through HEPA filters before it is recirculated through the areas' air handler system.

PEs are not required by the guidelines because they are dependent on the program of the organization. The 2010 guidelines are clearer about what the requirements are, especially when planning for a PE design (4). These designs are consistent with CDC guidelines regarding tuberculosis and pneumonia *(5,148)*. One condition that requires an anteroom to achieve proper airflow (i.e., a highly immunosuppressed patient who is infected with an airborne infectious agent like VZV requires positive pressure in the room to protect from other airborne infectious agents such as *Aspergillus* and also requires the removal of the air to ensure the protection of caregivers from VZV). The guidelines offer two designs to accomplish the pressure relationships, both requiring an anteroom.

Ventilation and Mechanical Systems and Basic Infrastructure Planning requires attention to key systems such as HVAC, including recommended ventilation and filtration specifications and mechanical systems involving water supply and plumbing. Key parameters for HVAC include filtration efficiency expressed today as a Minimum Efficiency Reporting Value or MERV as opposed to a percentage, air exchanges, pressurization relationships, humidity, and temperature. Recommended ranges for each of these are outlined in detail in the guidelines and elsewhere in this text (4) (see Chapter 84).

Rooms and Storage Supporting Infection Control Practice The guidelines require specific areas such as utility rooms (soiled and clean), instrument processing, holding, and workrooms. Storage of movable and modular equipment is critical from both a life safety and cleanliness viewpoint. The public perception of clutter is frequently associated with contamination and is seen as an IPC problem. Stretchers, wheelchairs, intravenous poles, and other large patient-care equipment are generally shared among units. Adequate space is needed to store, remove, clean, and maintain the items in an orderly fashion and reduce damage to surfaces, and they must be located away from normal traffic (4). In addition, CMS and state-based enforcement agencies emphasize clear, unobstructed corridors in healthcare facilities.

Design and Surfaces Ideally, surfaces are designed to include cleanability; problems can be avoided if surfaces near plumbing fixtures are smooth, nonporous, and water resistant. Operating and delivery rooms and isolation and sterile processing areas also need smooth finishes that are free of fissures or open joints and crevices that retain or permit the passage of dirt particles (4,*180,181*). Selection of surface materials, therefore, must balance use life, cleanability, cost, and maintenance.

Selection of Building Materials The construction materials vary for flooring (identify precise location of carpet or vinyl); walls; headwall components; windows; doors; countertops; plumbing fixtures (i.e., sinks, faucets, handles, etc.); lighting; electrical outlets; furnishings (e.g., bed, chairs, bedside tables); and computers, equipment, and supplies storage areas. Choices should consider selection of latex-free construction materials for all items, sizes, dimensions, colors, finishes, securement, and seams. Counter space required for various activities should have countertops that are seamless, nonporous, and durable against multiple germicidal cleanings.

IPC aspects associated with construction materials must be included along with those of local fire marshal requirements and state and local mandated codes and standards. General IPC considerations include nonporous surfaces that are easily cleaned with EPA-registered germicides. They should also consider hands-free, foot-pedal, or sensor-activated faucets; lids; handles; dispensers; and controls to the extent feasible. HEIPC staff should evaluate materials that withstand harsh chemical contact without corrosion, staining, or disruption of function and durability. Modifications that reduce soil and debris reservoirs include seamless design, rounded corners, sealed seams, wall bumpers, handrails, and electronic door openers. Drawers and containers for storage should be constructed from seamless, molded materials with rounded corners to prevent cracks, crevices, or folded edges that attract soil and are difficult to clean *(183,184)* (see Chapter 82).

Furnishings, Fixtures, and Equipment *Furniture* Modular furniture that is not easily moved should be installed on raised platforms or suspended in some manner to achieve a minimum 6- to 12-in. clearance from the floor to allow pull out for cleaning or to allow cleaning underneath. Attention must be paid to storage units with electrical or computer connections. Upholstered furniture should be managed like carpeting (including disposal) in the event of major soaking and contamination as a result of floods, leaks, or sewage. If furniture is affected by only steam moisture, it can be dried. Hardwood with intact laminate can be cleaned and disinfected with dilute bleach. Laminated furniture that has exposed particle board beneath the surface or other furniture composed of pressed wood or chipboard supports fungal contamination and growth when wet and should be discarded if it becomes soaked (9,*71*).

Hand Washing Stations and Hand Cleaning Agent Dispenser Placement Design and placement of handwashing stations becomes more critical with the additional consideration of waterless alcohol-based hand rubs (ABHRs) and has an impact in the event of plumbing disruptions or lack of preventive maintenance.

Number and Design The guidelines for new construction recommend the minimum number of handwashing facilities for hospital patient rooms as one in the toilet room and one in the patient room beyond the privacy curtain to ensure that HCP can carry out Standard Precautions. Having a sink in a patient or resident room and in the toilet room supports essential IPC practices. IPC plays a critical role in recommending the proper placement of hand wash facilities. In addition, IPC support for a sink standard of minimum dimensions may prevent the installation of small "cup" sinks that challenge proper hand washing *(180)*. The guidelines describe permissible types of controls for hand washing facilities in various areas.

Placement Improper placement can add to the environmental reservoir of contaminants. Sinks must be convenient and accessible, but nearby surfaces should also be nonporous to resist fungal growth *(71,180)*. One source recommends a minimum distance of 15 ft from all inpatient beds or bassinets and 25 ft from outpatient chairs, stretchers, and treatment areas to ensure access *(180)*. Hand washing facilities should also be situated to avoid splashing (suggesting at least 36 in. from patients or clean supplies) or equipped with a splash guard to avoid splash contamination *(180)*. CDC hand hygiene guidelines *(185)* make a strong recommendation for the addition of waterless alcohol-based hand antiseptic agents as part of a facility's overall hand-hygiene program. Dispenser location has emerged as one of the critical issues to address for this class of products. For example, the CDC guideline recommends that these not be placed near the hand washing stations to reduce confusion between them and antimicrobial soap used with water. Since the publication of these guidelines, there has been an increase in the adoption of waterless ABHR by US healthcare facilities.

The concern about a potential fire hazard with the placement and storage of dispensers of alcohol-based formulations of hand sanitizers prompted a multiyear collaboration to address all the conflicts in LSCs among groups such as the National Fire Safety Association and the International Code Council, which develops the *International Fire Code*. The codes are enforced by regulators such as CMS and accrediting groups such as TJC. By 2007, all groups had completed their changes, and CMS and TJC now specify the proper conditions for placement and storage of ABHR dispensers for rooms and exit corridors *(186)*. Perceptions that waterless hand hygiene products will supplant the need for hand washing stations are also unfounded. Both traditional washing with soap and water and the waterless products are needed, especially in the management of clusters or outbreaks of new strains of *C. difficile* such as BI/NAP1/027, and the ICRA process should ensure adequate provision for hand hygiene by patients, visitors, and personnel in new construction and renovation *(187)*.

Sink Cabinets Areas beneath sinks should not be considered storage areas because of their proximity to sanitary sewer connections and risk of leaks or water damage. Clean or sterile patient items should not be placed beneath sanitary sewer pipe connections or stored with soiled items; cleaning materials such as reagents or chemicals are examples of the types of materials acceptable for storage under sinks, from TJC's interpretation posted on their website under Standards in 2009, noting that state and local jurisdictions may be more stringent *(171)*. Facilities may develop design standards excluding storage space beneath sinks, thus preventing misuse and the need for cleaning. As noted earlier, cabinet construction materials need to be nonporous to resist fungal growth.

Aerators Aerated sink faucets located near patients, particularly in ICUs, have been considered a potential risk because of their ability to enhance the growth of waterborne microorganisms. The faucet aerator has been identified as a reservoir and possible source of infection within the hospital. Rutala *(188)* noted that the most convincing evidence for the role of faucet aerators is provided by Fierer et al. In this study, premature infants became infected with *P. aeruginosa* from delivery room resuscitation equipment contaminated by a faucet aerator. Rutala concluded that the degree of importance of aerators as reservoirs for healthcare-associated pathogens remains unknown. Because *Legionella* species grow well in the sediment formed in aerators, Freije et al. *(151)* recommend aerator removal. More recently, the Hota report provides evidence of infection due to splashing from the contaminated sink drain (123). The interventions used to end the outbreak demonstrate that drains are the true reservoir, and splashing is the primary route of transmission. In fact, aerators used in proper sink design may actually assist in reducing splashing from the drain (4). Proper sink design and dimensions can reduce splashing and risks of general contamination, while eliminating concerns for aerators completely (see Chapter 82, Design).

Flush Sinks, Hoppers, and Toilets **Clinical sinks** are required in soiled utility rooms for the disposal of body fluids and liquids but warrant similar considerations for moisture and contamination. Clinical or "flushing rim" sinks remove contaminated fluids in a manner similar to toilets and are not intended as utility or instrument-cleaning sinks. Splashguards are valuable, but inclusion may depend on sink design and use. If staff members are not routinely required to use face protectors, a splashguard should be required.

Toilets and Disposal of Human Waste There is no safe, aesthetic management of stool and other human waste in bedpans; system design should provide for emptying bedpans without leaving the patient room or for minimal travel distance to clinical/flushing rim sinks in treatment areas.

Intensive Care Units Removal of human waste is especiallychallenging when caring for critically ill patients. One option is to equip all patient rooms with attached bathrooms, but a toilet room for each patient has been seen as a space issue since most patients needing this care are not ambulatory. Prior to 2010, toilet rooms were not required in ICUs, except in coronary care units, because patients are usually too ill to use them. In the 2010 edition, each ICU room must now have direct access to an enclosed toilet room ***or*** a soiled utility room for the disposal of bodily waste. The standard requires at minimum a toilet room and toilet equipped with a bedpan washer or a soiled utility room with a flushing clinical sink located between every two ICU rooms. All rooms in the ICU must have a

dedicated toilet room (i.e., not shared with an adjacent room) (4,*183,187*) (see Chapter 82, Design).

Whirlpool and Spa-like Bathing Facilities Various types of bathing facilities are now available for mothers in birthing rooms and, as an additional amenity, for some patient-care rooms. Recommendations for cleaning have been compared with hydrotherapy tanks and equipment-cleaning procedures (9). However, plumbing for a traditional whirlpool bath circulates water through piping and jets that are inaccessible to mechanical cleaning. Potential risks for cross-transmission of contaminants is, therefore, possible, especially if used during labor, given the likelihood of introducing blood or other body fluids, which can be trapped in the pipe system. Pipeless whirlpool baths are commercially available, and cleanability using an *in vitro* testing protocol has been verified by the National Sanitation Foundation (Sanijet Corp., Coppell, TX; *www.sanijet.com*). Controlled trials comparing traditional to pipeless whirlpool baths are lacking, and the evidence demonstrating disease transmission from these systems is anecdotal. Communication with state regulators, cleaning and disinfecting the tub and jets with specific spa-cleaning products and proper draining and flushing sequences are essential when considering installation (9). Recommendations for use and disinfection should be consistent with the American Physical Therapy Association recommendations for tanks and equipment. The CDC guidelines for environmental infection control provide a full description of the issues (97).

Eyewash Stations OSHA directs proper use and placement of eyewash stations with distance determined by the pH of the involved chemicals. Source water in stationary eyewash stations may stand unused in the incoming pipes at room temperature for long periods, providing a reservoir for potential pathogens *(188)*. After a report of *Acanthamoeba* in eyewash stations, OSHA issued a bulletin recommending cleaning and disinfection methods. The schedule follows the American National Standards Institute Z358-1981 recommendations for flushing the system for 3 minutes each week *(135)*.

Decorative Water Fountains, Water Walls, and 2006 and 2010 Guidelines Updates As organizations recognize the importance of care delivery sites as therapeutic environments, they need HE and IP input when considering where to install features such as fish tanks, decorative water fountains, water walls, or other water features. In balancing the risk of adding a potential reservoir of waterborne opportunistic pathogens, CDC recommends facilities avoid placing them in patient-care areas *(181)*. The FGI guidelines address conditions and maintenance issues if they are included (4). Use of water as an architectural element has also been associated with disease transmission in which preventive maintenance (filters, ozone generators) did not prevent *Legionella* growth (126,*188,189*).

Ice Machines Ice availability for human consumption and medical nursing treatment may be located in the nutritional area or a clean room. Since contamination frequently occurs with ice because of inadequate machine maintenance or during collection and handling of ice, an ice delivery method should be designed to minimize contamination. When ice-making equipment is accessible to patients or visitors, it should be self-dispensing to avoid touch contamination. The IP should ensure that the ice machine is designed to deliver ice without permitting the receptacle and human hands from coming in contact with the dispensing port. The drainage tray should permit routine cleaning and disinfection and eliminate any standing water source. Direct access and storage bins with ice scoops should be avoided *(190)*. If a wall collection and removal system is planned, then construction materials and mechanisms would need to address IPC aspects of containment and confinement with risk-reduction cleaning capabilities.

Sharps Containers Dispenser Placement The location of disposal containers should consider ease of visibility to avoid overfilling and should be within easy horizontal reach of the user. Systems should have secure locking and enable easy replacement. When containers are fixed to a wall, the vertical height should allow the worker to view the opening or access the container. NIOSH recommendations suggest ergonomic considerations for installation heights or creative approaches for specialty areas *(178)*. Sufficient temporary storage space for filled containers must be in design planning *(176)*. If a mobile cart mechanism is used, construction materials for the carts and containers must be fluid-resistant, have appropriate biohazard signage, be puncture-proof, and have a secure closure *(176)*. Sharps containers and needle boxes are currently wall-mounted in close proximity to the point of use; the containers are usually replaced when two-thirds full *(178)*. Location, placement on the wall, and so forth must consider use such as residents' needs for medication, the main medication preparation area, and treatment rooms. Although this may be addressed in furnishings, it is appropriate to consider it with waste management. CMS also addresses proper storage and containment of waste in dumpsters and the management of the loading dock (e.g., free of debris and covered receptacles) *(170)*.

ICRA for Construction and Renovation Projects—Process

Overview An effective CRP supports long-range planning, as discussed previously, and provides guidance for individual construction projects, large or small. An ICRA for a specific construction project ensures appropriate planning for major new construction that also involves excavation and/or demolition or basic steps for simpler renovation projects. The ICRA team reviews the plan with considerable attention to detail by making inquiries to clarify understanding before a sign-off is completed. HEIPC staff assess the plans, paying particular attention to the specific requirements cited for the building improvement. HEIPC staff should focus on both the general and specific design aspects that influence and/or impact desired IPC practices. If IPC input does not occur in the beginning phase, there may be problems later with the infrastructure systems, such as air, water, traffic, and disruptions that impact residents. For example, air quality may be compromised because of infrequent filter changes, leading to aerosolized fungi released from dust during the demolition phase (8,9)

(see Chapter 84). Water may become contaminated with microbes when numerous dead-end pipe junctions contain stagnant water or when old piping is disrupted in replacement phases. Problems also occur when chlorine and/or temperature interventions to control *Legionella* are not maintained. A recent report documents that plumbing in even newly constructed nursing homes was readily colonized with *Legionella (119)*.

Patients The ICRA team assesses the inherent susceptibility of the patient (e.g., degree of immunosuppression as in a bone-marrow transplant patient) and the risk associated with the degree of invasiveness for procedures (e.g., patient undergoing surgery). The degree of dust and moisture is also assessed according to the size of the project, the length of time of the project, and the frequency of shifts. After the assessment is made, a determination of the impact on the populations and the impact on areas adjacent to the construction site is made. Figure 83-1 describes one widely used process using a matrix that matches levels of patient risk with levels of anticipated construction dust *(182)*.

The risk score determines needed interventions based on the following:

- Construction activity—project complexity in terms of dust generation and duration of activity
- Patients—assessment of the population at risk and location in terms of invasive procedures
- The matrix grid format immediately leads to identifying the following:
- Number and types of necessary controls and IPC interventions
- Signatures of all parties, thus providing accountability for the mutually agreed-on plan (9,*181*)

The process is made efficient by incorporating the precautions that can be determined using a decision-support matrix and a checklist in the form of a permit with signatures. Submission of an IC permit is an additional step and a useful method that is designed to assess the complexity of the project as a matrix of risk groups (i.e., patients versus the degree of contamination in the environment) (Fig. 83-1). The Precautions, internal and/or external, include determining appropriate protection of occupants from problems due to demolition, ventilation, and water management following planned or unplanned power outages, movement of debris, traffic flow, cleanup, and acceptance of the final renovation from the constructor. Whether or not this matrix method is used, there are key issues that should still occur:

- Routine submission of scheduled project lists from facility management to IPC, enabling the IPC staff to be proactively aware of projects and to anticipate IPC needs
- Submission of an "IC permit" or "project approval signature block" before the beginning of projects, beyond required project lists (9,*181*). Formats may range from simple checklists to questionnaires designed to assist staff members in assessing risks and identifying prevention strategies

Worker and Contractor Expectations Contracting companies receiving the documentation that describes steps to take to protect patients must also consider management of contractor employees for security and IPC purposes. Requirements for contract workers must be spelled out in project manual specifications documents. Expectations include control methods such as badges (photos), point of entrance or access to the construction site, or entrance to the hospital. Check-in and checkout procedures, specific areas for donning and removing protective garb, and eating and toilet facilities should be identified well before the project begins. Health requirements and educational issues vary by project but should be included in principle as items that must be determined by mutual agreement between the owner (healthcare organization) and the construction company or companies.

Obtaining the cooperation of contractors is critical to ensure that the hired work crew observes appropriate behavior when entering a hospital site. Provision of training and education by IPs and healthcare professionals to contractors and subcontractors is the first step in creating a stronger sense of partnership. Training should include information on hygiene, traffic patterns, availability of protective wear (e.g., shoe covers and cover gowns), and other dust containment recommendations. Tendering documents should include all expected necessary containment recommendations. These recommendations may include that dust on clothing and boots be removed before entering the healthcare facility; that entrance to high-risk patient and staff traffic areas be avoided; that cover gowns and booties be made available for workers; and that workers be provided with portable toilets for their use only and with potable water to wash, preferably outside of occupied healthcare facility grounds. These precautions help limit the amount of dust that is introduced into the healthcare facility. A partnership with contractors helps ensure greater respect for IPC concerns among construction workers and raises the level of IPC awareness regarding the different phases of the project, particularly high dust-generating activities (e.g., demolition of a targeted building) (74). Select aspects that should be in place for contractors and subcontractors include the following:

1. Proof of liability and worker's compensation insurance
2. Training on owner (facility) safety and IPC policies and any other federal, state, and local authority having jurisdictional requirements
3. Identification of hazardous chemicals planned for use and material safety data sheets (MSDS) provided to owner
4. Spill response plans outlined for hazardous chemicals
5. Personal protective equipment (PPE) available and notice of anticipated generation of hazardous waste
6. Location and access to owner emergency care services
7. Assessment and documentation of interim life safety measures
8. Evacuation and fire safety response plans confirmed
9. Plans for worksite dust containment reinforced and attention to wall or floor penetrations

Infection Control Risk Assessment Matrix of Precautions For Construction & Renovation

Step One:
Using the following table, identify the Type of Construction Project Activity (Type A–D)

TYPE A	**Inspection and Non-Invasive Activities.** Includes, but is not limited to: ▪ removal of ceiling tiles for visual inspection only, e.g., limited to 1 tile per 50 square feet ▪ painting (but not sanding) ▪ wall coverings, electrical trim work, minor plumbing, and activities which do not generate dust or require cutting of walls or access to ceilings other than for visual inspection.
TYPE B	**Small scale, short duration activities which create minimal dust** Includes, but is not limited to: ▪ installation of telephone and computer cabling ▪ access to chase spaces ▪ cutting of walls or ceiling where dust migration can be controlled.
TYPE C	**Work that generates a moderate to high level of dust or requires demolition or removal of any fixed building components or assemblies** Includes, but is not limited to: ▪ sanding of walls for painting or wall covering ▪ removal of floor coverings, ceiling tiles and casework ▪ new wall construction ▪ minor duct work or electrical work above ceilings ▪ major cabling activities ▪ any activity which cannot be completed within a single workshift.
TYPE D	**Major demolition and construction projects** Includes, but is not limited to: ▪ activities which require consecutive work shifts ▪ requires heavy demolition or removal of a complete cabling system ▪ new construction.

Step 1 _____

FIGURE 83-1 ICRA matrix of precautions for construction and renovation and infection control construction permit. *(Figure continued on following pages.)*
(Forms modified and provided courtesy of Bartley J, ECSI Inc, Beverly Hills, MI 2002, updated/revised 2009. Steps 1–3 adapted with permission from Kennedy V, Barnard B, St Luke's Episcopal Hospital, Houston, TX; and Fine C, CA. Steps 1–3 Adapted with permission V Kennedy, B Barnard, St Luke Episcopal Hospital, Houston, TX; Fine C, CA. Steps 4–14 Adapted with permission Fairview University Medical Center, Minneapolis, MN. Forms modified/updated and provided courtesy of Judene Bartley, ECSI Inc. Beverly Hills, MI 2002. Jbartley@ameritech.net. Updated 2009. Steps 4–14 adapted with permission from Fairview University Medical Center, MN.)

Step Two:

Using the following table, ***identify*** **the Patient Risk Groups** that will be affected.
If more than one risk group will be affected, select the higher risk group:

Low Risk	Medium Risk	High Risk	Highest Risk
▪ Office areas	▪ Cardiology ▪ Echocardiography ▪ Endoscopy ▪ Nuclear Medicine ▪ Physical Therapy ▪ Radiology/MRI ▪ Respiratory Therapy	▪ CCU ▪ Emergency Room ▪ Labor & Delivery ▪ Laboratories (specimen) ▪ Medical units ▪ Newborn Nursery ▪ Outpatient Surgery ▪ Pediatrics ▪ Pharmacy ▪ Post Anesthesia Care Unit ▪ Surgical Units	▪ Any area caring for immunocompromised patients ▪ Burn Unit ▪ Cardiac Cath Lab ▪ Central Sterile Supply ▪ Intensive Care Units ▪ Negative pressure isolation rooms ▪ Oncology ▪ Operating rooms including C-section rooms

Step 2_____

Step Three: Match the

Patient Risk Group (***Low, Medium, High, Highest***) with the planned **…**

Construction Project Type (***A, B, C, D***) on the following matrix, to find the **…**

Class of Precautions (***I, II, III or IV***) or level of infection control activities required.

Class I–IV Precautions are delineated on the following page.

IC Matrix — Class of Precautions: Construction Project by Patient Risk

	Construction Project Type			
Patient Risk Group	**TYPE A**	**TYPE B**	**TYPE C**	**TYPE D**
LOW Risk Group	**I**	**II**	**II**	**III/IV**
MEDIUM Risk Group	**I**	**II**	**III**	**IV**
HIGH Risk Group	**I**	**II**	**III/IV**	**IV**
HIGHEST Risk Group	**II**	**III/IV**	**III/IV**	**IV**

Note: Infection Prevention & Control approval will be required when the Construction Activity and Risk Level indicate that **Class III** or **Class IV** control procedures are necessary.

Step 3_____

Description of Required Infection Control Precautions by Class

	During Construction Project	Upon Completion of Project
CLASS I	1. Execute work by methods to minimize raising dust from construction operations. 2. Immediately replace a ceiling tile displaced for visual inspection	1. Clean work area upon completion of task.
CLASS II	1. Provide active means to prevent airborne dust from dispersing into atmosphere. 2. Water mist work surfaces to control dust while cutting. 3. Seal unused doors with duct tape. 4. Block off and seal air vents. 5. Place dust mat at entrance and exit of work area 6. Remove or isolate HVAC system in areas where work is being performed.	1. Wipe work surfaces with cleaner/disinfectant. 2. Contain construction waste before transport in tightly covered containers. 3. Wet mop and/or vacuum with HEPA filtered vacuum before leaving work area. 4. Upon completion, restore HVAC system where workwas performed
CLASS III	1. Remove or isolate HVAC system in area where work is being done to prevent contamination of duct system. 2. Complete all critical barriers i.e. sheetrock, plywood, plastic, to seal area from non work area or implement control cube method (cart with plastic covering and sealed connection to work site with HEPA vacuum for vacuuming prior to exit) before construction begins. 3. Maintain negative air pressure within work site utilizing HEPA equipped air filtration units. 4. Contain construction waste before transport in tightly covered containers. 5. Cover transport receptacles or carts. Tape covering unless solid lid.	1. Do not remove barriers from work area until completed project is inspected by the owner's Safety Department and Infection Prevention & Control Department and thoroughly cleaned by the owner's Environmental Services Department. 2. Remove barrier materials carefully to minimize spreading of dirt and debris associated with construction. 3. Vacuum work area with HEPA-filtered vacuums. 4. Wet mop area with cleaner/disinfectant. 5. Upon completion restore HVAC system where work was performed
CLASS IV	1. Isolate HVAC system in area where work is being done to prevent contamination of duct system. 2. Complete all critical barriers, i.e., sheetrock, plywood, plastic, to seal area from non work area or implement control cube method (cart with plastic covering and sealed connection to work site with HEPA vacuum for vacuuming prior to exit) before construction begins. 3. Maintain negative air pressure within work site utilizing HEPA-equipped air filtration units. 4. Seal holes, pipes, conduits, and punctures. 5. Construct anteroom and require all personnel to pass through this room so they can be vacuumed using a HEPA vacuum cleaner before leaving work site or they can wear cloth or paper coveralls that are removed each time they leave the work site. 6. All personnel entering work site are required to wear shoe covers. Shoe covers must be changed each time the worker exits the work area.	1. Do not remove barriers from work area until completed project is inspected by the owner's Safety Department and Infection Prevention & Control Department and thoroughly cleaned by the owner's Environmental Services Dept. 2. Remove barrier material carefully to minimize spreading of dirt and debris associated with construction. 3. Contain construction waste before transport in tightly covered containers. 4. Cover transport receptacles or carts. Tape covering unless solid lid. 5. Vacuum work area with HEPA-filtered vacuums. 6. Wet mop area with cleaner/disinfectant. 7. Upon completion restore HVAC system where work was performed.

Step 4. Identify the areas surrounding the project area, assessing potential impact

Unit Below	Unit Above	Lateral	Lateral	Behind	Front
Risk Group	Risk Group	Risk Group	Risk Group	Risk Group	Risk Group

Step 5. Identify specific site of activity, e.g., patient rooms, medication room, etc.

_____

Step 6. Identify issues related to: ventilation, plumbing, electrical in terms of the occurrence of probable outages.

_____

Step 7. Identify containment measures, using prior assessment. What types of barriers? (e.g., solids wall barriers); Will HEPA filtration be required?

_____

(Note: Renovation/construction area shall be isolated from the occupied areas during construction and shall be negative with respect to surrounding areas)

Step 8. Consider potential risk of water damage. Is there a risk due to compromising structural integrity? (e.g., wall, ceiling, roof)

Step 9. Work hours: Can or will the work be done during non-patient care hours?

Step 10. Do plans allow for adequate number of isolation/negative airflow rooms?

Step 11. Do the plans allow for the required number & type of handwashing sinks?

Step 12. Does the infection prevention & control staff agree with the minimum number of sinks for this project? (Verify against FGI Design and Construction Guidelines for types and area)

Step 13. Does the infection prevention & control staff agree with the plans relative to clean and soiled utility rooms?

Step 14. Plan to discuss the following containment issues with the project team. E.g., traffic flow, housekeeping, debris removal (how and when)

_____

_____

_____

Appendix:

Identify and communicate the responsibility for project monitoring that includes infection prevention & control concerns and risks. The ICRA may be modified throughout the project. Revisions must be communicated to the Project Manager.

Infection Control Construction Permit

	Permit No:
Location of Construction:	Project Start Date:
Project Coordinator:	Estimated Duration:
Contractor Performing Work	Permit Expiration Date:
Supervisor:	Telephone:

YES	NO	CONSTRUCTION ACTIVITY	YES	NO	INFECTION CONTROL RISK GROUP
		TYPE A: Inspection, non-invasive activity			GROUP 1: Low Risk
		TYPE B: Small scale, short duration, moderate to high levels			GROUP 2: Medium Risk
		TYPE C: Activity generates moderate to high levels of dust, requires greater 1 work shift for completion			GROUP 3: Medium/High Risk
		TYPE D: Major duration and construction activities Requiring consecutive work shifts			GROUP 4: Highest Risk

CLASS I	1. Execute work by methods to minimize raising dust from construction operations. 2. Immediately replace any ceiling tile displaced for visual inspection.	3. Minor Demolition for Remodeling
CLASS II	1. Provides active means to prevent air-borne dust from dispersing into atmosphere 2. Water mist work surfaces to control dust while cutting. 3. Seal unused doors with duct tape. 4. Block off and seal air vents. 5. Wipe surfaces with cleaner/disinfectant.	6. Contain construction waste before transport in tightly covered containers. 7. Wet mop and/or vacuum with HEPA filtered vacuum before leaving work area. 8. Place dust mat at entrance and exit of work area. 9. Isolate HVAC system in areas where work is being performed; restore when work completed.
CLASS III **Date** **Initial**	1. Obtain infection control permit before construction begins. 2. Isolate HVAC system in area where work is being done to prevent contamination of the duct system. 3. Complete all critical barriers or implement control cube method before construction begins. 4. Maintain negative air pressure within work site utilizing HEPA-equipped air filtration units. 5. Do not remove barriers from work area until complete project is checked by Infection Prevention & Control and thoroughly cleaned by Environmental Services.	6. Vacuum work with HEPA-filtered vacuums. 7. Wet mop with cleaner/disinfectant 8. Remove barrier materials carefully to minimize spreading of dirt and debris associated with construction. 9. Contain construction waste before transport in tightly covered containers. 10. Cover transport receptacles or carts. Tape covers. 11. Upon completion, restore HVAC system where work was performed.
CLASS IV **Date** **Initial**	1. Obtain infection control permit before construction begins. 2. Isolate HVAC system in area where work is being done to prevent contamination of duct system. 3. Complete all critical barriers or implement control cube method before construction beg ins. 4. Maintain negative air pressure within work site utilizing HEPA-equipped air filtration units. 5. Seal holes, pipes, conduits, and punctures appropriately. 6. Construct anteroom and require all personnel to pass through this room so they can be vacuumed using a HEPA vacuum cleaner before leaving work site or they can wear cloth or paper coveralls that are removed each time they leave the work site.	7. All personnel entering work site are required to wear shoe cover 8. Do not remove barriers from work area until completed project is checked by Infection Prevention & Control and thoroughly cleaned by Environmental Services. 9. Vacuum work area with HEPA-filtered vacuums. 10. Wet mop with cleaner/disinfectant. 11. Remove barrier materials carefully to minimize spreading of dirt and debris associated with construction. 12. Contain construction waste before transport in tightly covered containers. 13. Cover transport receptacles or carts. Tape covers. 14. Upon completion restore HVAC system where work was performed

Additional Requirements:

Date Initials	_____Exceptions/Additions to this permit Date Initials are noted by attached memoranda
Permit Request By:	Permit Authorized By:
Date:	Date:

PRECONSTRUCTION

Project Management ICRA Team Sets the Stage

Worker Risk Assessment and Education

Health, Training, and Education Health risk evaluations for potential exposures depend on the type of construction planned. Facility staff overseeing or working with outside contractors should assist in determining potential environmental risks for facility workers or contractors. Policies should include provisions for training and by whom (facility or contractor). Training must be appropriate to the task (e.g., staff entering air systems for preventive maintenance, such as changing filters, should be alerted to the potential for airborne dust containing spores of microorganisms and arrange to first turn off fans and don a mask). Staff members working in sanitary or septic sewage systems, drainage pipes, and so forth should be alerted to the risks of moisture and fungal contamination (8,9,*89,148,172,173,188*). Agreements should be developed appropriate to the project regarding provisions for pertinent health protection, vaccinations, tuberculosis assessment, and purified protein derivative skin testing, or related education before workers begin construction. Requirements vary with the degree of environmental risk and proximity to the patient population.

As agreements are completed, they should provide evidence that workers have received appropriate health protection, as noted previously, and should include the following information:

- Facility exposure control plan(s) for IPC, hazardous chemicals, and life safety
- How to seek help and report exposures (e.g., first-aid location and initial steps to report exposures)
- Use of particulate respirators and/or other PPE
- Risk prevention for unexpected safety issues, such as noxious fumes, asbestos, and so forth (9,*148,172–174*) (see Chapter 84).
- The facility should be satisfied that provisions have been made for effective IPC education designed to address facility-specific needs related to potential infectious risk exposures, as described previously (9,97,*148,172–174*)

Preparation for Demolition and Construction The project teams provide ongoing planning and monitoring during area preparation and throughout the demolition, construction, cleanup, preparation for return to service, and final project review (4,8,*171*). Before construction begins, the focus of preparations should be on isolation of the construction or renovation area. Some sources categorize projects in terms of minor or major risk based on the level of needed barriers; checklists are developed accordingly (9).

External Excavation Precautions External excavation is ideally conducted during off-hours so that air handlers can be adjusted; the goal is to protect the intake as much as possible. Small projects require similar planning and vary by degree, but preparation still requires early communication with facility management. Specific educational needs (e.g., OSHA), regulations, and health issues for patients and workers need to be addressed. A final customized checklist should be appended to the CRP (9).

Inspection of the Worksite Daily inspections should be made, particularly at the start of a project. Recording inspections and observations is recommended. The inspection should look at major areas, including the following:

- Dust containment barriers at the source are appropriate
- The frequency in wetting excavated soil or demolished building, truck, and equipment path is adequate
- Doors, windows, and other ports of entry located near the project are sealed or barred from use
- Construction worker behavior, such as removing dust and observing good hygiene before entering healthcare grounds, is acceptable
- Waste is kept to a minimum
- Materials delivered and stored outside for later installation are properly protected (e.g., shrink-wrapped covering)

It is recommended that an inspection worksheet or checklist be created, with daily inspections and observations recorded, and copies should be given to the designated individuals who can correct the situation when necessary. The worksheet should include key precautions to observe and a follow-up segment. These worksheets act as a means of communication, and if a problem arises, they become evidence that due diligence was exercised by IPs and other healthcare professionals (74).

Additional Consideration for External Construction Beyond Internal Issues Increased potential for contaminating dust and debris on air-intake filters may result in decreased filtration, allowing airborne spread of microorganisms via the ventilation system. HVACs may be disrupted and nonfunctional during certain periods of construction. Medical vacuum systems and water supply may be affected similarly. Finally, contamination of patient rooms, supplies, equipment, and areas patients may visit (e.g., procedure rooms) may occur.

Many interventions can decrease the risk during external excavation or construction. The steps begin with identifying the location of air intakes with respect to the location of high-risk patients. The team may consider the following:

- **Filter changes:** The frequency of changing the prefilters should be increased. When admission is necessary, high-risk patients should be located in areas as remote from the construction area as possible.
- **Cleaning:** Areas adjacent to construction activity should be cleaned with increased frequency.
- **Air-handler changes:** Beyond the barrier checklist outlined earlier, the team may have to consider closing down dampers temporarily in areas adjacent to construction to reduce the circulation of contaminated air or fumes.
- **Power disruptions:** When power is reestablished after a power interruption, and dampers and fans resume operation, dust released during this process may contain and transmit infectious agents to patients and staff. Policies or protocols should address issues such as communication, operating the HVAC for a specified time to run air out of the ducts, and immediate cleaning before putting the area (e.g., OR) back into service. Long-range follow-up includes preventive maintenance and cleaning of ducts near dampers to reduce the dust load; it also includes surveillance of airborne infectious agents or hospital-acquired infections

- **Verification of air-handler status:** It must be ensured that the hospital systems can provide the proper air exchange rates and pressure relationships in crucial areas near construction activity; it must be ensured that air is not being circulated from construction areas into other hospital areas.
- **Cleaning of air handler:** Facility engineers should be contacted about special maintenance and cleaning of the ventilation system likely to be affected by construction. After completion of construction, it must be ensured that the ventilation systems are balanced to design specifications and that scheduled maintenance is determined.
- **Final cleaning:** The new area must be thoroughly cleaned before installing furnishings, privacy curtains, and clean supplies and before patient admission.

Interruptions of Normal Water Service Special infection risks and hazards are associated with the disruption of normal water service utility during construction or renovation, requiring long-range planning. These hazards include (a) lack of potable water for drinking, food preparation, and ice; (b) lack of water for hand washing and bathing; and (c) lack of water for flushing toilets, clinical sinks, decontamination, sterilization, food service needs, and support services (e.g., laboratory). Anticipating and planning preventive and control interventions can minimize risks; the following should be considered:

- Schedule interruptions for low-activity times when feasible
- Plan and arrange for volume of potable water for drinking and food preparation
- Plan and arrange for supplies for patient care and cleaning
- Provide disposable towelettes or waterless alternatives for hand washing for patients and personnel

Internal Issues

Type and Extent of Construction Project complexity varies with time, numbers of workers, whether contractors work continuous shifts, scope and degree of activity (high or low dust generation), and proximity to patients with varying degrees of risk for infection.

Internal Renovations Internal projects require much additional planning compared to external construction. Patient areas or units that cannot be closed or that are adjacent to a major renovation require special planning (e.g., OR additions adjacent to an active surgical suite). These situations may justify environmental monitoring beyond visual inspection to detect increased airborne contamination and to plan interventions (4,*5*,8,9,*18,89*,97).

General Issues

Patient Location during Construction There should be no flow-through traffic in the area, meaning routing patterns for staff traffic and visitor access traffic must be planned and designated, and signage must be posted for ease in compliance. Adherence to existing codes and standards for the size of corridors and doorways remains in effect. Visitors or residents investigating progress during construction may place themselves and construction workers at risk. This requires considerable monitoring by staff to ensure a safe environment surrounding the renovation and/or construction.

Risk Factors Managing infectious risks during construction means collaboration among all personnel. These risks include dust and debris compromising the environment, airborne microbes carried to immunocompromised residents, an unbalanced ventilation system affecting air quality, water contamination, accumulated and multiple waste reservoirs, and ineffective dustproof barriers to name a few. Depending on the location of the construction and the proximity to resident-care areas, residents may have to be relocated to a safer unit. Meticulous maintenance of physical barriers and utility systems (i.e., air, water, etc.) are required as risk-reduction efforts. Airborne debris of particulate matter may carry microbes that contaminate the air and are especially hazardous to residents who may inhale the debris and develop respiratory infections and/or complications. Control of airflow patterns (e.g., clean to dirty); interruption of utility, building, and equipment services; and communication requirements should be specified in the project bid proposal to ensure construction-specification compliance.

Environmental Control and Containment

Containment Isolating the construction site by physical dust-control partitions requires floor to deck (solid compartment separation between floors above dropped ceiling) walls made of airtight fire-rated barriers, usually consisting of drywall or plywood with caulked seams or heavy-duty plastic with sealed seams and gasketed doorframes. The airflow should be from "clean to dirty," requiring some method to ensure isolation of the area from patients (4). Site access points are controlled entries for those authorized to enter. These egress paths are located where minimal debris can be transferred from the construction site to the cleaner areas of the facility. Personnel authorized for entry are commonly identified by badge and protective gear, such as hard hats. Emphasis is placed on dust control, which is a constant challenge during the project; diligent cleaning efforts are critical. Dust collection mats with an adhesive surface can also assist with minimizing the migration of dust and debris carried by construction personnel. These mats typically have several layers that can be removed as needed when the exposed surface becomes loaded with dust. Daily cleaning by gathering gross debris for disposal is necessary before damp mopping the area as a dust-control mechanism. Containment is further practiced when a debris exit path is marked and a delivery point of materials and supplies is designated.

Containment Also Includes HVAC Systems Measures such as sealing of grills or vents against construction debris; frequent changing of filters within the ventilation ducts; ensuring that the window seals are leak-proof and airtight; and if chutes are used to remove demolition materials, monitoring for negative pressure and ensuring that the chutes are closed when nonoperational or during duct cleaning are all important aspects to address.

Noise and Vibration The potential for vibration or disturbances to dislodge dust collected above suspended or false ceilings and the effect of vibration on contamination of plumbing should be recognized. Noise and vibration also may be disturbing or harmful to certain patient

populations (e.g., premature neonates, cardiac or stroke patients, pediatric or psychiatric patients).

Water During construction, unintentional water contamination of porous, acoustical ceiling tiles and/or fireproofing and filter materials may occur. Prompt removal of damaged, moisture-laden materials reduces the potential for fungal spore release (9,*71*,97,*183*).

Dust and Debris Control—Barrier Systems As noted, the area should be isolated, as the project requires. Small, short-duration projects generating minimal dust may use fire-rated plastic sheeting but should be sealed at full ceiling height with at least 2-ft overlapping flaps for access to entry. Any project that produces moderate to high levels of dust requires rigid, dust-proof, and fire-rated barrier walls (e.g., drywall) with caulked seams for a tight seal. Large, dusty projects need an entry vestibule for clothing changes and tool storage. The entry area should have gasketed door frames; tight seals should be maintained at the full perimeter of walls and wall penetrations in order to ensure the pressure differential and airflow into the construction site (4). An interim plastic dust barrier may be required to protect the area while the rigid impervious barrier is being constructed. Cleaning is required at the completion of the barrier construction; plans should also describe a terminal barrier removal process that minimizes dust dispersal (9,*71*).

Ventilation

Air System Flow It should be determined whether the construction area uses fresh (outside) or recirculated air; filters should be added or return vents covered as needed with filter material or plastic. Air must flow from clean to dirty areas (4,8,9) (see Chapter 84).

Negative Air Pressure The air within the construction area must be negative with respect to surrounding areas and with no disruption of air systems of adjacent areas. Constant negative pressure within the zone should be monitored with an alarmed device, which must be maintained and monitored by construction personnel. Exhaust from construction air should be directed outside or exhaust vents in the construction area should be sealed to prevent recirculation if possible. If there is no outside exhaust, rather than tying into a recirculated air system, it is acceptable to run exhaust air through a negative air machine and into the corridor. Exhausting air into the duct work even with use of HEPA filters, risks overpressurizing the duct work and risks contamination of adjacent areas. Necessary interruptions (e.g., fire drills) should be planned for to minimize risk (4,9,*71*). Portable HEPA filtration devices can also aid in the capture of particulates that might be aerosolized during the demolition of drywall, removal of flooring materials, and so forth. Such devices can also facilitate the creation of negative pressure. Other variables to address include the following:

- The status of sealed penetrations and intact ceilings should be verified in adjacent areas.
- Air exchange rates and pressure relationships: It should be verified that the facility can maintain proper rates in critical areas near construction activity, ensure air is recirculated using HEPA filtration from the construction area to internal areas, and provide accountability for and frequency of testing air pressures throughout the project (8,9,*71*).
- Vibration or disturbances: Drilling and other sources of vibration have potential to dislodge dust collected above suspended or false ceilings; vibrations loosen corrosion within water pipes as well. Plans should require vacuuming of affected areas and flushing debris from water systems before reoccupancy (8,*24,130,151*).
- Specification of temperature and humidity ranges: Determine limits as appropriate (4,9 *93,171*).
- Monitoring: Consideration must include risks of malfunction or complete loss of utilities. Both visual cues and particulate air monitoring may be used. The type and frequency of monitoring, evaluation of results, and follow-up action by designated parties are essential to planning (8,9,*71*).

Traffic Control

Control The safety approach to traffic control is signage that identifies construction areas and restricts entry to authorized construction personnel who have appropriate protective equipment. The IPC perspective is to divert nonessential traffic (e.g., patients, HCP, or visitors) from the site, thereby, reducing the risk of exposure to or dissemination of airborne pathogens carried by dust. If intersection of patient-care areas and construction is unavoidable, the route should be designed to minimize risks of exposure to infectious agents even if they have donned personal protective attire (masks). Visitors are guided to the most direct but safest route to visit residents. Because visitors are potential reservoirs of infectious agents transmissible to susceptible residents, they should be assessed for symptoms of communicable infectious diseases whether construction projects are in progress or not. Designated entry and exit procedures must be defined. Egress paths should be free of debris, designated elevators should be used during scheduled times, and only authorized personnel should be allowed to enter the construction zone. Signage should direct pedestrian traffic away from the construction area and materials (8,9,*24,71*).

Debris Management: Windows, Chutes

Debris Used materials should be removed in carts with tightly fitted covers, using designated traffic routes. Medical waste containers (sharps or other medical regulated waste) must be removed by the facility before the start of the project. Efforts should be made to minimize the use of elevators with transport during the lowest period of activity. Debris should be removed daily and at times specified by agreements. If chutes are used to direct debris outside, HEPA-filtered negative-air machines should be used, and the chute opening should be sealed when not in use. Filters should be bagged and sealed before being transported out of the construction area (8,9,*24,71*).

Exterior Windows Windows should be sealed to minimize infiltration from excavation debris.

Patient Equipment—Contamination of Patient Rooms, Supplies, and Equipment

Worksite Attire Contractor personnel clothing should be free of loose soil and debris before leaving the construction area. If protective apparel is not worn, a HEPA-filtered vacuum should be used to remove dust from clothing before leaving the barricade. PPE (e.g., face shields, gloves, respirators) is worn as appropriate. Contractors entering invasive procedure areas should be provided with disposable jumpsuits and head and shoe coverings. Protective clothing should be removed before exiting the work area. Tools and equipment should be damp-wiped before entry and exit from the work areas (8,9,*71*).

Barriers Areas around construction should be monitored to maintain protection of in-use patient-care areas, as described. Patient doors adjacent to the construction area should be kept closed, with appropriate traffic control (8,9).

Storage Sites should be designated for new and damaged construction materials (9).

Contractor Cleaning The construction zone should be maintained in a clean manner by contractors and swept or HEPA-vacuumed daily or more frequently, as needed, to minimize dust. Adjacent areas should be damp-mopped daily or more frequently, as needed. Walk-off mats may minimize tracking of heavy dirt and dust from construction areas (8,9).

Facility Cleaning Contracts should clearly specify responsibilities and expectations for routine and terminal cleaning before opening the newly renovated or construction zone (8,9).

Site Cleanliness Monitoring the area proximal to the barriers surrounding the project site is usually delegated to the housekeeping and support service. Frequent cleaning is basic to maintaining dust control. Project-site cleaning is an ongoing activity that should be viewed as a critical success factor in reducing risk. A question may be raised concerning the need for air testing of particulate matter to determine site cleanliness. A more productive approach is a preventive one, that is, to establish routine cleaning frequencies at the same rate that a facility might institute *if* air testing demonstrated that dust levels were high.

The IPC and safety aspects of maintaining a clean work area include reduced clutter and fall hazards, diminished exposure to airborne debris that may cause infectious or allergic responses, and enhanced visibility to perform the work at hand. CMS is also concerned with providing an environment that is free from hazards (e.g., wet floors not identified with signage or blocked access) *(170)*. Similar concerns arise throughout construction or renovation projects and require vigilance on everyone's part to maintain safety and control dust.

Standard housekeeping IPC practices are followed. Housekeeping equipment should be designated for this area. Fresh germicidal solutions are used and changed often. Chemically treated dust cloths and mop heads should not be shaken and are laundered daily. Vacuum and suction machines are equipped with high-efficiency filters and changed frequently for maximum benefit in controlling airborne dispersal of dust and microorganisms. Frequency of filter changes is workload-dependent and based on filter efficiency and performance effectiveness *(191)*.

INTRACONSTRUCTION PHASE AND THE ROLE OF A HEALTHCARE EPIDEMIOLOGY AND INFECTION PREVENTION AND CONTROL PROGRAM

Communication

Once renovation or construction has begun, the IP should be available to provide maintenance and operational input. Frequency of input or meetings depends on the scope of the project. Specific concerns must be customized in each project and include IPC practices, education, and monitoring. The IP is vital in educating and supporting staff in managing their area under construction (e.g., educating staff members on how to monitor their own performance as much as possible). In more complex projects, the IP may assist directly or make provisions for items already outlined. A number of areas involving specific IP involvement are discussed later.

Environmental Rounds

An efficient method to integrate key IPC and life safety issues is the use of rounds, using simple checklists based on the items addressed previously *(181)*. IPs can advise or participate in rounds, which should be scheduled as often as necessary and include a variety of observable "indicators" such as barriers (doors, signage), air handling (windows closed), project area (debris, cleaning), traffic control, and dress code. It may be necessary on occasion to schedule rounds after normal hours or on weekends if that is when construction or renovation is scheduled (8,9,*24,71*).

Environmental Monitoring Activities during Construction There are currently no recommendations for routine environmental culturing during construction. Enhanced targeted patient surveillance (e.g., respiratory illnesses consistent with aspergillosis or legionellosis) near construction areas should be part of the ICRA. Other control measures previously discussed must be continuously monitored. However, when an outbreak associated with construction is suspected or identified, water or air sampling may be indicated. It is vitally important to establish a hypothesis with clear and measurable goals. Culturing or sampling procedures should be defined before initiation (e.g., asbestos, fungal, or total particulates). Sampling procedures relative to the suspected agent(s) and sources should be used. The investigator must be cognizant of the many pitfalls associated with the interpretation of environmental data *(179)*. Therefore, as part of the investigation planning, it is important to establish parameters for interpreting collected data.

Outcome or Process Measures Projects may be approached as performance improvement initiatives using outcome measures (e.g., SSI rates) or process measures

(measuring compliance) using visual observations, airborne particulate monitors, satisfaction surveys, and so forth (9,*18*,97).

Impact on Special Areas

Patients requiring AIIRs need close monitoring to ensure that negative-pressure relationships are maintained, particularly when there is potential for disruption of pressure relationships (8,9,*32,192*). Intake areas such as emergency departments need planning to triage potentially infectious patients (4,*5*,97). If highly susceptible patients cannot be relocated, indicators should be identified to trigger planned intervention (8,9,*18,24,71*). Immunosuppressed populations in bone-marrow transplantation units or protected environments, ICUs, and so forth require special planning. The goal is to minimize patient exposure to major construction activity; therefore, nonemergency admissions should be avoided during periods of major excavation. If delaying admissions is not an option, patients should be located in areas as remote as possible from construction activity (8,9).

Patient Location and Transport

Healthcare providers should plan patient care activities to minimize exposure to construction sites. At least one study found that critically ill, ventilator-dependent patients transported from the ICU for diagnostic or therapeutic procedures was an independent risk factor for development of ventilator-associated pneumonia (9). To decrease exposure for patients during construction activities the following should be considered:

- Provide treatment in the patient's room
- Transport via an alternate route
- Schedule transport or procedures during periods with minimal construction activity
- Minimize waiting and procedure times near construction zones
- Mask patient or provide other barriers (e.g., covering open wounds) based on patient's clinical status

Emergent Issues—Interruption of Utility Services

Utility services may be interrupted during any type of construction. Infectious agents may contaminate air-handling units, medical vacuum, and water systems after planned or unplanned power disruptions. HEIPC can provide input into emergency preparedness to reduce the potential risks of contamination. Response plans should include assessment of the population at risk and cleanup should focus on steps to prevent, detect, and reduce risk from infectious hazards. For example, as power is reestablished after an interruption, dampers and fans of AHUs resume operation. Dust and particulate matter released during this process may transmit allergenic or infectious agents such as *Aspergillus* species to patients and staff (8,9,*17,24,71,135*). Therefore, IPC policies for areas in which invasive procedures are performed should require sufficient time to clear the air of potential contaminants before resuming the use of the room(s). Ventilation time should be based on the number of air changes per hour required by the area. The NIOSH chart for removal efficiency of airborne contaminants may provide guidance, but its use should be tempered by its assumptions *(5,160)*. In the event of major contamination of patient care areas, plans should specify responsibilities for these decisions and for intensified cleaning, environmental surveillance of airborne infectious agents, and restriction of water use until testing or flushing determines safe use.

POSTCONSTRUCTION

Postconstruction and Cleanup

Project Checklists Check-off lists of expected practices identified at the beginning of the project should be reviewed for items agreed on before the area is returned to full service or patient occupancy. A useful tool during review is the contractor's "punch list" to ensure that missed details have been addressed, such as installations of soap dispensers or designated types of hand washing and sink controls (8,9,*181*).

Owner Preinspection before Move-in Suggested checkpoints for inspections include validating air systems by verifying air balances and pressures, checking electrical current of wall outlets, testing suction capability of wall units, assessing oxygen and gas delivery ports for ease in delivery and control accuracy, checking illumination sources, flushing water systems, rechecking that sinks are in place and functioning properly, determining if aerators are absent, testing whether soap and towel dispensers are full and functional and whether sharps containers are properly placed.

Postconstruction Agreements

Cleanup agreements (e.g., cleaning, air balancing, filter changes, flushing of water systems, etc.) and other utility service checks and cleaning must be established in the early planning phase, as discussed previously. These include the following at minimum:

- Contractor cleaning to include area clearance, cleaning, and decontamination and wipe-down
- Cleaning after removal of partitions around construction area, minimizing dust production
- Facility-based routine and terminal cleaning before returning area to service
- Provision of timeframes for facility review (e.g., 2 weeks) after completion of the project to ensure that all issues were addressed properly
- Systematic review of outcomes in the facility's designated review process, whether by contract or committee structure. Items may range from sealed cabling and electrical penetrations and ceiling tile replacements to the completed punch list
- Cleaning and replacement of filters and other equipment if affected by major or minor disruptions or conditions that could have contaminated the air or water supply (9,*23,62*,63,*71*)

Steps before Occupancy

Checklists specific to the project should be developed for a walkthrough just before occupancy. Core IPC issues for inclusion are listed later as applicable. The designated team should do the following:

General Checks: Conducted as part of an operational project team. The facility's punch list is invaluable to assess and ensure items are completed before occupancy

- Airflow, pressures, filters, location of air intakes and vents
- Drains to the sanitary sewer system are connected and functioning
- Check whether surfaces in procedure and service areas are appropriate for use (e.g., smooth, nonporous, water-resistant)
- Verify that air balancing has been completed according to specifications
- Test whether air flows into negative-pressure rooms or out of positive-pressure room

Two weeks prior to opening:

- Use processing packs to check steam, gas sterilizers
- Verify correct water temperatures
- Complete written schedules and procedures for routine maintenance of equipment, cooling towers, and suction machines (central and portable); establish documentation
- Determine transportation systems
- Walk through the facility with local health department representative and facility management personnel to ensure compliance with local and state codes

One Week before Moving into New Facility:

- Evaluate HVAC supplying special areas, such as ORs and interventional cardiology rooms. Objective evidence should be requested from contractor that HVAC is providing air exchanges and filtration as designed, before owner acceptance. Assess methods for determining effectiveness of particulate matter removal
- Evaluate laminar air hoods for effective operation; ensure functioning according to manufacturer specifications. Ensure a maintenance contract has been arranged and testing has been accomplished
- Open all faucets simultaneously to test drain effectiveness
- Verify that sinks in critical patient-care areas have properly functioning fixtures
- Ensure that hand hygiene products are in dispensers and that dispensers function properly and are convenient to users, including hand-drying supplies
- Check floor drains, and ensure that traps have water seals to prevent sewer gases from entering rooms
- Ensure that contractors have completed their own cleaning and disinfecting; ensure housekeeping department has completed facility follow-up cleaning
- Ensure registered pest control and management is functioning and checked
- Be prepared to intensify surveillance for HAIs and monitoring of IPC practice

In conclusion, the role of HEIPC in construction and renovation remains a challenging and exciting one and is the ultimate demonstration of its multidisciplinary nature. Interaction and integration of efforts with other disciplines is consistent with the underlying foundation of HEIPC—disease prevention for patients, HCP, and visitors.

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CHAPTER 84

Design and Maintenance of Hospital Ventilation Systems and the Prevention of Airborne Healthcare-Associated Infections

Andrew J. Streifel

A building ventilation system is expected to supply air at a comfortable temperature and humidity level (1–3). In the hospital setting, heating, ventilation, and air-conditioning (HVAC) systems must often provide specially conditioned air to protect the health of patients and staff. Certain patients (e.g., bone marrow transplant [BMT] recipients) are particularly vulnerable to infection from airborne pathogens *(4)*. Others, such as tuberculosis patients, are potential sources of airborne infection, which may put those around them at risk. To design a proper hospital ventilation system, one must be familiar with both the physical and biologic characteristics of airborne agents causing healthcare-associated infections. Knowledge of ventilation strategies and equipment used to reduce the potential for airborne transmission of disease requires an understanding of airborne particle management for contamination control *(5)*.

The science of aerobiology began with Louis Pasteur's discoveries in the middle of the 19th century. By this time, investigators had made great strides in characterizing airborne flora and fauna and in developing methods for accurate quantitative sampling of these populations. During the 1930s, William Wells published on the infectious capacity of droplets and droplet nuclei. He also studied the air-sterilizing properties of ultraviolet (UV) light. By the 1960s, investigators were reporting on the airborne transmission of a variety of infections, including tuberculosis, influenza, smallpox, and measles. From particle science and fluid dynamics has evolved the study of bioaerosols, which quantitatively describes the generation and dispersal mechanisms that dictate the behavior of airborne microorganisms *(6)*. By applying an understanding of these biologic and physical principles, the hospital can provide a ventilation system that can help protect against the spread of healthcare-associated or occupationally acquired airborne infection. Although these principles are well known, the challenge on a global scale is for the world's medical facilities to keep up with the advances in medicine. These advances are producing mainstream treatments for life-threatening diseases such as leukemia or solid organ failure. Medical schools can deliver trained personnel to utilize advanced medical treatments, but the buildings where patients are being treated cannot keep up with the demands for specialized treatment areas.

BIOAEROSOLS AND INFECTION

For an object to remain airborne, it must be small enough so that the viscosity of the air impedes its fall in response to gravity. Lewis Stokes *(7)* developed an equation that predicts the falling velocity of a particle as a function of its diameter. Stokes's law for determining the sedimentation velocity (V_s) of particles from 1 to 100 μm in diameter is as follows:

$$V = (2gr^2)(d1 - d2)/9\mu$$

where V is the velocity of fall (cm sec^{-1}), g is the acceleration of gravity (cm sec^{-2}), r is the "equivalent" radius of particle (cm), $d1$ = density of particle (g cm^{-3}), $d2$ = density of medium (g cm^{-3}), and μ = viscosity of medium (dyne sec cm^{-2}).

Gregory published a table of experimentally observed falling velocities for a number of microorganisms. It can be readily observed that many particles ranging in size from 1 to 5 μm have falling velocities in still air on the order of 1 yard an hour. Many spores, such as those of *Aspergillus fumigatus*, have roughened surfaces that tend to further enhance their buoyancy. Such particles can stay airborne almost indefinitely and can ride on air currents for thousands of miles from their point of origin *(7)* (Table 84-1).

The removal of these infectious particles is essential for ventilation efficacy. Newer concepts provide an understanding of the age of air (AOA) as a direct measure of ventilation performance. The principles concerning AOA (or the movement of particles around and eventually out of the rooms) are important for airborne infectious disease management.

Often, the focus for indoor air complaints is the inference that infections are caused by poor ventilation. We do, of course, want to ensure that ventilation is moving air approximately at design specification, because we also know that stagnant air and infectious aerosols prolong exposure potential and disease depending on

TABLE 84-1

ASHRAE Filtration Standard 52.2

Minimum Efficiency Rating Values (MERV)	*Average % Dust Removal Efficiency*	*Particle Size Range (μm)*	*Applications*	*Filter Type*
16	99.97	≤0.3	Clean rooms	HEPA
15	95	0.3–1.0	Hospitals	Cartridge
14	90	0.3–1.0	Hospitals	Cartridge pocket filter
1–13	<20–85	0.3 to >10.0	Industrial protection	All kinds

circumstances. This excuse of poor ventilation as a cause of healthcare-associated infection is a continuing challenge, and determining the AOA will be useful for proving or disproving ventilation issues (8). It is important to realize that if such small particles were entrained in a patient's respiratory airstream, they would be of the size most likely to elude the cilial and mucosal defenses of the upper respiratory tract and to deposit in the alveoli of the deep lung (Fig. 84-1). Since the early 1970s, investigators have enhanced the understanding of the respiratory fate of small particles as a function of their Stokes diameter.

Quantitative information about particles is as reliable as the measuring instrumentation. By knowing the airborne spore concentration in a given air body and the tidal volume of the lung, one can estimate the probability of inhaling a certain quantity of pathogenic material. Riley and Nardell *(9)* used the concept of infectious dose in the form of quanta to predict the probability of infection from the release of infectious particles. Using ventilation for infection control, one can achieve protection, to a degree, before reaching a point of diminishing returns *(10)*, especially for agents such as *Mycobacterium tuberculosis*.

Reliable assessment of biologic risks from airborne pathogens is difficult because of the variables that are intrinsic to living systems. Two *Aspergillus* spores or influenza virus particles may have widely differing potentials for causing infection, depending on such factors as viability of the spores or particles and the health status of the person inhaling them. To determine control strategies for such agents, it is first necessary to estimate what constitutes an infective dose and then to determine what sort of ventilation control system will reduce concentrations of the suspected pathogen to a safe or noninfective level *(11)*. The movement of the air is an important aspect of ventilation efficacy because particles <5 μm behave similarly to a gas. We can test such aspects of ventilation to find the optimal factors, such as air velocity, for ensuring air cleansing. Marshall utilizes the AOA concept for demonstrating ventilation efficacy in BMT rooms. This analysis of the air in various locations in the room will demonstrate the well-ventilated versus the poorly ventilated areas. The poorly ventilated areas have higher AOA readings, and hence, higher concentrations of infectious particles.

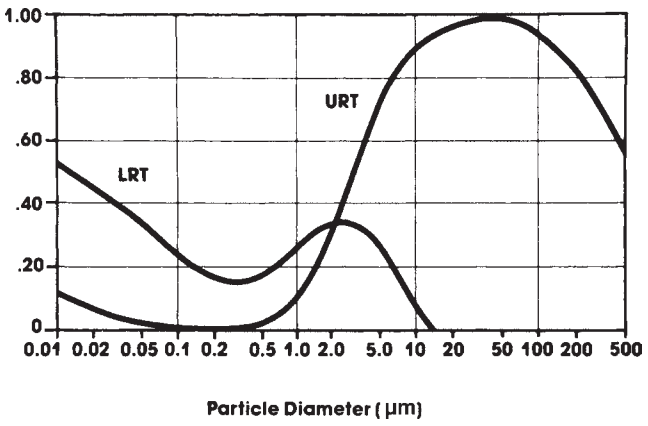

FIGURE 84-1 Upper and lower respiratory tract (URT and LRT) deposition of idealized spherical particles as a function of diameter. (From Rhame FS, Mazzarella M, Streifel AJ, et al. Evaluation of commercial air filters for fungal spore removal efficiency. Third International Conference on Healthcare-Associated Infections. Atlanta, GA, 1990, with permission.)

GENERAL VENTILATION PRINCIPLES

Although air is a gaseous mixture containing nitrogen, oxygen, carbon dioxide, and a number of trace elements, it behaves in accordance with the principles of fluid dynamics. In descriptions of ventilation systems, air is treated as though it were a liquid flowing through the system. Air moves in response to pressure. For liquids, the most common source of pressure is gravity. For gases, the most common source of pressure is temperature. The global system of air movement is powered by the rays of the sun. In a building HVAC system, pressure is provided by fans and blowers that push or pull air through the building. The most basic rule of airflow in a duct system is that air in must equal air out (12). For any two points in a closed duct, $A_1V_1 = A_2V_2$, where A_1 is the cross-sectional area (measured in square feet) and V_1 is the air velocity (in feet per minute). A_1V_1 gives the airflow in cubic feet per minute (cfm). This equation indicates that if the ducts contract (reducing A), air speed, V, must increase proportionally to maintain the same cfm flow rate.

The basic rule of air pressure is $TP = VP - SP$, where TP is the total pressure in the system, VP is the velocity pressure, and SP is the static pressure. Velocity pressure is measured in the direction of airflow and is directly proportional to V, the speed of the moving air. Velocity pressure is always positive. Static pressure is the pressure a body of air exerts on its container, and it can be measured in all directions. Static pressure may be either positive or

negative. It is pressure that tends to either burst (positive pressure) or collapse (negative pressure) the duct. If a body of air increases in speed, the velocity pressure increases, whereas the static pressure drops.

TP, the total pressure, may be either positive or negative and is the sum of the static and velocity pressure. As a body of air moves through a duct system in response to pressure generated by a fan, the total pressure in the system decreases because of frictional losses between the moving air body and the walls of its container, the duct system. This concept is illustrated by a third equation, $TP_1 = TP_2 - H_L$, which states that, for a body of air moving from point 1 to point 2, the total pressures at the two points differ by the frictional losses (H_L) caused by the intervening run of duct.

These three rules provide the conceptual framework within which ventilation systems are designed. In a simple recirculating model, the fan creates sufficient positive pressure to force air through the supply ductwork and sufficient negative pressure to draw the air out of the rooms into the return ductwork and back to the fan, completing the circuit. The pressure generated by the fan must be sufficient to overcome the energy losses created by friction between the moving air and the duct system through which it travels. The ductwork blows air into the various rooms through supply openings. The air circulates in the room and then moves toward return openings that draw air back into the return duct system with negative pressure (suction). With consideration for "ceiling real estate," the careful placement of supply and return/exhaust ducts in a room will help optimize the efficacy of particle removal.

The supply and return openings in the room illustrate an important difference between positive and negative pressure ventilation. An individual with healthy lungs can easily blow out a candle at arm's length. The same healthy lungs could not generate enough negative pressure, or suction, to cause the flame to even flicker (13). The supply duct is comparable to blowing out the candle, whereas the exhaust is attempting to suck it out. We refer to the strong directional flow of positively pressured supply air as "throw," whereas the negatively pressured exhaust duct has a "capture velocity" (Fig. 84-2). The control of such a ventilation system is facilitated by a sealed room. A tight seal on the room allows air to enter and escape only through the ducted openings, thus avoiding room surface air leakage problems. Such measures help to maintain consistent control of the ventilation (14,15). An additional advantage of a tight room seal is to control sound transmission. Important to hospital patient rights is the concept of the Health Insurance Portability and Accountability Act (HIPAA), which ensures patient privacy. Air is the medium for sound transmission, and the tight seal of a room enhances privacy as well as ensuring ventilation efficacy. To what standard of seal should we adhere? The standard for a weathertight house promotes a leakage rate per square foot of surface area in a house at 2.5 in^2/ft^2. This weathertight standard of leakage can apply to hospitals but should be expressed as the leakage volume of air at a specified pressure such as 0.1 cfm/ft^2 of surface in a patient room (15). By establishing this leak rate, it assures that the "make-up" air for the exhaust will, in fact, come from the supply rather than "holes" in the room. Many leak holes can provide sufficient air volumes to negate the effect of the offset between exhaust and supply air volumes. This can create confusion, because low pressure differentials can result in fluctuating airflow directions: for example, a room flipping from negative to positive airflow in and out of the room. Such confusion has spurred exposure investigations concerned with the lack of consistent airflow monitoring on infectious patients with diseases such as tuberculosis or disseminating varicella zoster.

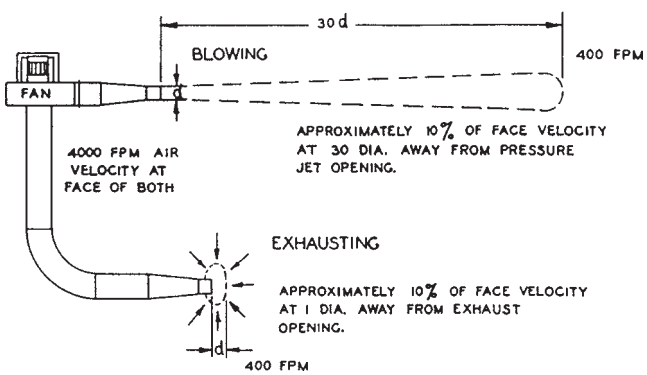

FIGURE 84-2 Basic difference between flow and pressure openings.

HOSPITAL VENTILATION SYSTEMS

In designing an HVAC system for any occupied building, one must properly size ducts and fans to provide the proper air pressures and duct velocities to meet the ventilation requirements of the entire building. Properly sized heating and cooling equipment and noise reduction enter into the total calculations, as does some sort of filtration or air-cleaning system. As air recirculates in a building, it builds up an increasing load of gaseous contaminants that are not readily removed by filtration. It is necessary to exhaust a certain percentage of this stale air and replace it with fresh outdoor air to ensure occupant health and comfort *(16)*. A wide variety of systems have been used to meet these criteria. A few of the more common types with an eye toward the needs of the hospital environment are considered below.

Energy management is a formidable challenge for building management in the future. Hospitals have among the highest utility costs per square foot of any industry. Strategies for controlling ventilation costs in climates where heating and cooling are extreme have shifted to energy-saving concepts. Displacement ventilation is one such concept *(17)*. Air is delivered from the bottom (low part of room) and, as the air is warmed, will rise to be extracted from the room. What we use today is contrary to physical forces: forcing air down when the natural tendency is for air to rise. Although energy savings are immense when allowing air to be discharged into a room at a higher temperature, the lack of space and/or design in most patient rooms does not allow for its large-scale implementation yet.

Central Air-Conditioning System

This system brings in fresh outdoor air and mixes it with recirculated air. This air mixture is filtered and conditioned for temperature and humidity according to institutional

requirements and then distributed to all building locations. This system is favored for its low cost and simplicity. In a large hospital, the major drawback of centrally conditioned air is the difficulty in adapting it to the specific requirements of local areas, which may have differing heating and cooling needs. This is a particular problem in cold climates in which rooms along the exterior shell require warmer air than rooms in the core. Large central supply ducts, which reduce noise by slowing airflow, require large amounts of space. Efforts to create local or zone conditions with additional equipment, such as extra heating and cooling coils or booster fans, rapidly increase costs and are often only partially effective.

Dual Duct System

This system has a central system that separately produces two air streams, one hot and the other cold, which are then parallel-ducted throughout the building. Each room is provided with a mixing box in which the two air streams are blended. This allows individual thermostats and volume controls for each room. Although more expensive and difficult to install, this system can provide a number of microclimates without much add-on equipment. The principle drawbacks are the degree of care required in installing the system and the sound baffling required to reduce the noise created by faster airflows within the smaller ductwork. Other variations in the air-handling system may be unique to a regional climate condition that design engineers have considered in the ventilation specifications. This may be a factor for consideration when humidifying or dehumidifying the air.

The control of water in the air-handling system is paramount for controlling potential allergens and pathogens associated with the growth of microorganisms on fibrous insulation *(18,19)*. There can be considerable air-handling system variation when designing for the climate. All designs, however, require careful maintenance and operational considerations for infection control. For example, a local fan coil system has often been used in hospital areas requiring supplemental cooling. Such climate control is often provided with local systems that recirculate ambient air and provide dehumidification and cooling. Such systems, although engineered for temperature control, do not accommodate air-purification control. The fan coil drain pans, if not properly maintained, become reservoirs for local fungal contamination *(20)*. Air conditioners may also be reservoirs for fungal growth or accumulation *(21,22)*. Such systems should be discouraged for areas in which immunocompromised patients are hospitalized. Recent outbreak investigations have demonstrated prolific mold growth on cold ducted systems, either on filters or associated with mixing boxes.

Filtration

Hospital HVAC systems are often required to perform additional tasks related to the prevention of healthcare-associated infections. By appropriate use of air-filtration technology, a hospital air-handling system can deliver air that is virtually particle-free to areas where such a level of protection is needed. The problem presented by such a rigorous filtration system is the energy cost involved. Most filters scrub the air by trapping particles in dense pleated media using impaction and interception for particles >1 μm and diffusion or electrostatic attraction for particles <1 μm. Dense filters impede the flow of air and cause a loss of system pressure. To maintain effective air velocities in the ductwork, a more powerful fan must be installed to overcome this pressure drop across the filter (23).

Filters are rated by their percentage of efficiency. A number of different test methods are used to rate air filters *(24,25)*. Most common are the dioctyl phthalate (DOP) and dust spot tests. The DOP test challenges an air filter with an aerosol 0.3 μm in diameter. A light-scattering instrument downstream measures the penetration of the filter by these particles. A filter that can arrest 99.97% of the DOP particles is referred to as a high-efficiency particulate air (HEPA) filter. This method actually counts particles as a measurement of efficiency.

The dust spot test is used to rate less rigorous filters. This test uses atmospheric air or a defined dust as the challenge. Air upstream and downstream from the tested filter is drawn through filter paper. The samples are then compared for opacity using a photometer. Although not quantitative in evaluating particle reduction, this test measures the ability of a filter to reduce the dirt load of an air stream. Kuehn *(26)* and Rhame et al. *(27)* have shown that dust spot methods can measure high-efficiency removal of particles.

Effective hospital filtration systems that have been evaluated for air cleaning demonstrate the removal of particles at the 90% efficiency level for the removal of particles >0.5μm in diameter. Often filter system failure is associated with defective filter housing rather than filter media failure. Outdoor air is initially filtered through 20% to 40% efficient media, mixed with recirculating air, and sent through a 90% dust spot–efficient filter. These 90% filters have been demonstrated to provide nearly 100% efficiency in removing particles 1 to 5 μm in diameter with a lower pressure drop than when the 99.97% HEPA filters are used. Modern filters designed with larger surface areas can provide high-filter efficiency while maintaining relatively low pressure drops compared with previous versions of the HEPA filter. Distributing such clean air throughout the system provides an additional layer of safety to all occupants at risk for airborne pathogens. Then, where required, rooms or zones can be HEPA-filtered for a higher degree of protection. Modern filtration technology is creating minimal pressure drop filters featuring enhanced fiber electrostatic qualities and increased surface area of the filter. Although reduced resistance pressure while maintaining high-filter efficiency is beneficial for cost savings, careful consideration for proven long-term efficiency is necessary to prevent problems such as filter failure due to a shielded charge on synthetic filter fibers (Raynor et al. *[28]*). High-efficiency filter innovation certainly helps provide sufficient air volume to assist in maintaining essential air quality parameters in hospitals (which often become deficient in air-volume delivery and exhaust as the building ages). Such systems reduce risks created by opening and shutting doors and from transporting vulnerable patients for procedures that cannot be performed in specially protected areas. Filtration and room air exchanges continue to dominate priorities for air quality (29,*30*) in prevention of aspergillosis. However, the combination of appropriate ventilation parameters (filtration, air exchanges, and especially pressure management) helps to ensure control of the many sources of opportunistic filamentous fungal infections plaguing the immunocompromised host (31).

AREAS REQUIRING SPECIAL VENTILATION

Certain areas in the hospital have special ventilation systems as described in the HVAC handbook (2) and Facilities Guidelines Institute's Guidelines for Design and Construction of Health Care Facilities (3), and now the ASHRAE Standard 170: Ventilation for Health Care Facilities (1). Air systems have been designed to meet these specific needs, most commonly, operating rooms, positive-pressure protective environments, negative-pressure isolation units, and local air control flow life islands (Table 84-2). Each of these situations has specific ventilation requirements related to the prevention of healthcare-associated infection or occupational exposure to airborne infectious diseases or medicated aerosols or gases. All operate on the underlying principle that clean air should move from less contaminated to more contaminated areas (clean to dirty airflow). To more clearly illustrate the principles involved, a specific patient, pathogen, or procedure is discussed here for each type of situation.

Protective Environments

Operating Room Surgery is by nature a process requiring invasive procedures that expose host tissues to the outside environment, creating the potential for exposure to external agents, such as bacteria and fungi. Therefore, in the operating room, the surgical site and instrument table should be considered the cleanest area, and infection control efforts should be directed toward providing protection through appropriate ventilation control.

Surgical site infection is a well-documented surgical complication *(32)*. Procedural practices including aseptic technique and prophylactic antibiotics provide the first line of defense, but it has been shown that removing bacteria and fungi from operating room air helps to minimize infection *(33,34)*. Microorganisms shed by humans are the most common airborne agents in a correctly designed operating room with appropriate air filtration *(35)*. Large volumes of air filtered through high-efficiency filters should be provided from panels in the operating room ceiling over the surgical site. The downward force of air from the ceiling supply diffuser provides a focused ventilated area around the surgical site that is constantly washed by a high-volume flow of clean air. Such airflow moves particles away from the operating table toward the air returns at the margins of the room. It is important that this directional airflow of filtered air is delivered in such a manner that infectious particles shed by the operating team are swept away toward the return ducts and not trapped and recirculated within the vicinity of the procedure. The more objects there are that interrupt the airflow pattern, the greater the turbulence will be. Special clean room laminar flow ventilation with HEPA filtration has been used in orthopedic cases to prevent the consequences of surgical site infections. A vertical flow system designed to provide a downward flow of air over the surgical site actually increases the air exchanges in the cleanest zone (*36,*37). Air delivery from a horizontal direction does not provide an extra benefit, because personnel and equipment in the way of the directed airflow cause turbulence and potential trajectory of problematic particles toward the surgical site. Vertical flow is preferred over horizontal airflow for space management and infection control considerations. Memarzadeh and Manning (38) performed computational fluid dynamic studies that reinforced the empirical findings of Lidwell (37) that a vertical flow with velocity from 30 to 35 linear feet per minute (lfpm) (0.15–0.18 m/s) could be achieved at the surgical site. If air supply can provide a laminar flow regimen albeit at a lower velocity than the official definition of laminar flow of 90 lfpm (0.45 m/s), control of the shed particles over the surgical site is realistic. In addition, AOA evaluations help establish (independent of test and balance report) the degree of ventilation efficacy. This can be conducted to check air transit times of any common gas, such as carbon dioxide, from which we can ascertain the time that it takes for a particle (<5 μm) to move from the source to the extractor vents in the respective rooms. Readings of 3 to 5 ft/s indicate satisfactory air movement (8).

Pressure management in the protective operating room environment is designated by a positive airflow out of the cleanest area of the operating room suites. This designation

TABLE 84-2

Summary of Special-Ventilation Hospital Areas

	Infectious Disease Isolation Room	*Compromised Host Ventilation*	*Operating Room*
Air pressure	Negative	Positive[a]	Positive
Room air changes	≥6 renovation ≥12 new construction	≥12	20
Sealed	Yes	Yes	Yes
Room leakage	(0.1 cfm/ft^2)	(0.1 cfm/ft^2)	(0.1 cfm/ft^2)
Directed airflow[b]	Clean-to-dirty (employee clean)	Clean-to-dirty (patient clean)	Displacement flow in surgical site critical
Filtration supply	90% (dust-spot ASHRAE 52–76)	99.97%[c]	90%
Recalculation	No	Yes	Yes

[a]Minimized infiltration for ventilation control.
[b]Clean-to-dirty (negative) to infectious patient (positive) away from compromised patient.
[c]Fungal filter at point of use—high-efficiency particulate air (HEPA) 99.97% @ 0.3-μm particles.
ASHRAE, American Society for Heating, Refrigerating, and Air-Conditioning Engineers.

does not give guidance for what is necessary to provide that pressurization. Murray et al. (14) have suggested that a differential air volume (supply vs. exhaust or return) exceeding 10% to 15% provides the required airflow. This concept works best in a high airflow volume environment like an operating room or in BMT rooms, which also require higher airflow volumes. Such suggestions have not been validated. Consistent management of pressure is a problem when windows are operable or doors are left open. Using an anteroom or door closure is an essential component for room-pressure management. Operating rooms have multiple doors, and if any of those doors are open, the pressure differential is eliminated until the door is closed. Procedural practice for operating rooms should include closed doors, except for egress, while the surgical site is open.

Investigations have shown value in properly clothing the operating room team for maximum contamination control. The surgical team is a potential reservoir of infection. The average person sheds approximately 10^7 particles of sloughed skin per day *(39,40)*. During an hour-long surgical procedure, each individual in the operating theater may shed 10^6 particles. Each one of these particles may be carrying bacteria that can infect a surgical site. However, in the properly ventilated operating room, such shedding should not pose an infection risk to patients. For operative procedures involving insertion of a prosthetic device and for which ultraclean air may be desired, shedding can be greatly reduced by providing surgical personnel with negatively pressurized evacuated gowns.

Opportunistic environmental microbes such as *Clostridium perfringens* or *Aspergillus* spores should be minimized in an operating room setting. These soil microorganisms are readily filtered from incoming air if filters are installed and maintained properly. Such microorganisms would be expected in air-supply systems that have leaks or tears in the filters. A lack of maintenance is also a problem, because it allows a reservoir of microbial growth in the air-delivery system. Such inadequate maintenance or installation must be avoided in the critical surgical areas.

Shed microbes from human attendants must be controlled with directed airflow and barrier protection. The use of masks for personnel and patient protection is one such control. However, Tunevall and Jorbeck *(41)* raised the issue that masks do not affect the presence of microbes in a surgical setting. This is a naïve notion given unexpected sneezing, coughing, and normal surgery room conversation creating droplets that are capable of falling into the wound. The range of microbial recovery from air sampling suggests that the use of barriers prevents the inadvertent shedding of microbes from exposed areas such as the mouth or hair. Barriers have also been shown to prevent contamination of drapes and the surgical site. Even with aseptic technique and appropriate ventilation, the exposed skin from both the patient and attendants becomes an important source for microbial exposure in the surgical setting *(42)*. Unclean floors from tracked dirt and accumulated debris could become an internal source for *C. perfringens* or other soil microorganisms *(43)* if disturbed. Human source microbes can be controlled with aseptic technique *(44)* and barrier protection *(45)*. A forced air ventilation system enhances the cleanliness of the critical surgery area. The ventilation system is essential for protecting the surgical site using particle displacement dynamics of properly directed purified air movement. The AOA concept has also been used to evaluate operating rooms thought to have ventilation problems. It is instructive to demonstrate that when extractor vents are blocked, the removal of contaminants is impeded. With the measurement of air movement in ft/second, we can demonstrate slow inadequate ventilation and dissipation rates in highly ventilated areas.

The patient is also a potential source for infecting the personnel in the operating room setting. The generation of aerosols during the use of cautery and lasers is a matter of concern. Information on the transmission of infectious agents by these procedures is minimal; however, scavenging devices are being used to minimize the presence of obnoxious odors or aerosols in the operating room setting. For example, such local exhaust and filtration systems can be used to capture problematic aerosols generated during the removal of extrapulmonary tuberculosis lesions.

Positive-Pressure Room (Protective Environments)

Oncology and Solid Organ Transplant Patients. Modern medical technology has provided methods for transplanting immunologically dissimilar tissue between donor and recipient. The immunosuppressive treatment necessary to prevent rejection of the transplanted organ or tissue puts the host at risk for opportunistic infections. Environmental pathogens causing legionellosis or aspergillosis are common (4,46,47) and must be controlled in a critical hospital setting. These environmental microorganisms pose little threat to the healthy individual protected by normal humoral and cellular immune defenses.

A. fumigatus is a common soil fungus. Its spores range in diameter from 2 to 3.5 μm and are commonly recovered from outdoor air samples. This airborne fungus is cosmopolitan and is commonly recovered when using a volumetric air sampler. This thermotolerant fungus poses a particular risk as a healthcare-associated pathogen because of its ability to reach the alveoli in the lung and its ability to thrive at 37°C. On inhalation by the granulocytopenic patient, these spores can cause a form of pneumonia that is difficult to diagnose and treat. Peterson et al. *(48)* noted that 17 of 19 patients with aspergillosis died in a series of 60 BMT patients. Opportunistic filamentous fungal infections seem to be less responsive to conventional antibiotic therapy. Providing spore-free air through filtration, ventilation, and local activity control is the best method for preventing infections transmitted by fungal spores *(49)*. Because some patients remain immunocompromised for up to several months, it is also necessary to minimize airborne environmental contamination by microbes in the environment of convalescent transplantation and oncology patients.

The basic ventilation approach in such facilities is to provide positive-pressure ventilation wherein the amount of HEPA-filtered supply air exceeds the amount of air exhausted by at least 10%. The offset should be approximately 125 cfm between the supply and exhaust/return to provide a substantial difference for ensuring a consistent pressure differential in the special ventilation rooms. This difference should be able to establish a pressure differential >0.01 in water gauge (2.5 Pa). By delivering air at a rate of between 6 and 10 air changes per hour, depending on heating and cooling requirements, and by using supply and

return air that ensures thorough mixing, the room can be kept relatively spore-free *(50)*. Supply air diffusers should be located in the ceiling and positioned to throw air down far enough into the room to ensure particle displacement and mixing. In the protected ventilation environment, the filtered air should flow from the vulnerable patient toward the corridor. Such clean to dirty airflow provides air movement that should prevent inhalation of common airborne fungal spores by the patient.

Bone-Marrow Transplantation Unit Simple positive pressure ventilation may not provide sufficient protection for the extremely vulnerable patient. Patients requiring BMTs are often housed in laminar airflow (LAF) rooms *(46)*. Such rooms are designed with one entire wall of HEPA filters. Fans blow air through these filters at high velocity (~100–150 lfpm *[51,52]*) and out through high-capacity return ducts located on the opposite wall. Although the term laminar flow is not an accurate description of the fluid dynamics of the airflow under such conditions, the effect is that smoke particles injected into the LAF air stream are swept straight across the room, parallel to the floor, and out through the return. It is as though a piston of clean air is being pushed across the room, driving any contaminants out through the return ducts. To enhance patient protection, all caregivers should work downstream from the patient so as not to impede the protective airflow across the bed. Such rooms provide more than 100 air changes per hour. The high velocity of the airflow can create uncomfortable drafts and excess noise. Housing patients in such an environment is an extreme measure and can be problematic during long periods of convalescence. Because of high cost and limited availability, these LAF systems are difficult to provide for all immunosuppressed patients. Therefore, less drastic ventilation control procedures are often recommended *(53,54)* (Table 84-3).

The problem most frequently associated with contaminated hospital air is construction activity (55). Control of aerosol generation, airflow, filtration, barrier penetration, and traffic requires careful monitoring and supervision to maintain specially ventilated areas (55). Air filtration and increased room air changes help to prevent infection in areas adjacent to construction activity *(56,57)*. Patients must be continuously confined in such rooms to be totally protected. Items brought into such areas can also be contaminated *(58)* with fungi from outdoors. The ventilation procedural practices in the patient's room and construction and maintenance practices must be carefully controlled throughout critical care facilities *(59)* (see also Chapter 83).

TABLE 84-3

Components of a Protected Environment

Sealed room (windows and utility connections)
Increased room air changes (=12)
Highly filtered air (=95% efficient @ 0.3-μm particles)
Positive pressure rooms (=10% or =125 cfm) supply over exhaust/return air volume
Directed airflow (airflow from the "clean" patient to the "dirty" patient)
Leakage total for room at <0.1 cfm/ft^2
Procedural practice modification
Self-closing doors

TABLE 84-4

Infectious Diseases Requiring Special Ventilation

Herpes zoster, disseminated
Tuberculosis, pulmonary or laryngeal
Varicella (chickenpox)

Airborne Infectious Disease Control

Negative-Pressure Isolation: Airborne Infection Isolation Room Hospitals should house patients, who have infectious diseases spread by the airborne route, in negative-pressure isolation rooms to prevent the escape of pathogens from the room to surrounding areas (Table 84-4). Patients harboring *M. tuberculosis* can pose an occupational risk to the caregiver (see also Chapter 38). With the development of antibiotic-resistant *M. tuberculosis,* infections may be difficult to treat and may be fatal in immunocompromised healthcare workers. During contagious stages of the disease, patients can create infectious aerosols by coughing, speaking, singing, or sneezing. The infectious droplets can dry in air to form droplet nuclei 1 to 5 μm in size and float for long periods, increasing the probability of inhalation. A single inhaled tubercle bacillus may be able to produce an infection. Although tuberculosis patients must be isolated to minimize the risk of transmission of infection, the other infectious diseases spread by the airborne route also require isolation using special ventilation *(11,60)*.

In designing ventilation for isolation rooms, the area of the infected patient should be considered dirty (Fig. 84-3). The current strategy is to provide negative pressure to ventilate the room with exhaust exceeding supply by more than 10% or by more than a 125-cfm difference. It must be noted that the relatively low differential for air volume requires significant sealing of the room to prevent leakage. A sufficient seal will allow achievement of the >0.01 inches of water column pressure requirement. This usually means sealing the electrical and plumbing as well as the ventilation connections in each room. The room air should be exhausted to the outside or, if returned for reuse, should be filtered through a HEPA filter. This prevents air contaminated by the patient from escaping into the rest of the hospital and reduces the concentration of airborne tubercle bacilli within the room.

The room air exchange rate has been studied with respect to particle removal *(11)*; a point of diminishing returns is reached at approximately 12 to 15 room air exchanges per hour. The retrofit of older space to the higher air exchanges is difficult and not practical unless new design and construction are planned. To maintain relative pressures, one must ensure that the ventilation in place is working. The control of the airflow depends on the anticipation of exhaust systems deterioration from the accumulation of dirt and lint on fan blades and turning

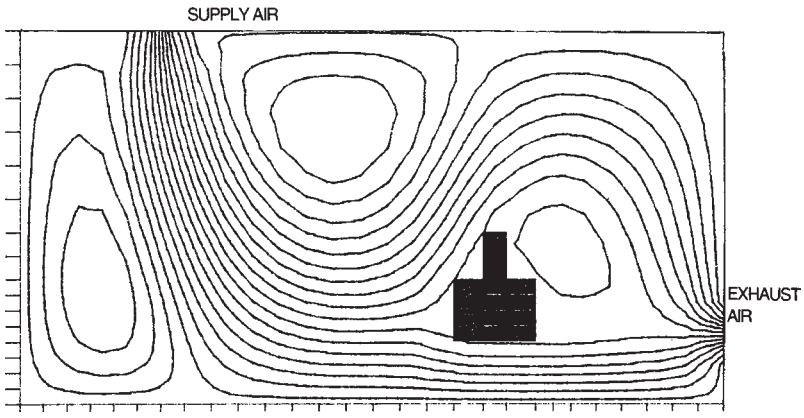

FIGURE 84-3 Computer simulation of airflow pattern in a patient room that can be used to visualize air patterns in special ventilation rooms. In this example, airflow from the supply air covers the healthcare worker area, passing the "dirty" patient before exhausting.

vanes. Cleaning the air pathway and exhaust fans helps to ensure consistent pressure relationships.

Installing effective negative-pressure ventilation is more challenging than installing positive-pressure ventilation. The negative-pressure system is easily compromised by air infiltration, and extra attention must be paid to sealing all ducts, doors, walls, and windows of the room. Even if the system is well sealed, it is more difficult to create directional airflow using suction. The clean (employee area) to dirty (patient area) airflow pattern should also be incorporated into isolation room design. The effectiveness of such design features, although intuitive and associated with clean room ventilation methods, must still be verified. There are difficulties in applying exhaust ventilation to clear a room of low concentrations of infectious particles. One study reported that when the concentration of microorganisms is low, a 14-fold increase in fresh air ventilation only reduces concentrations by 10% *(10)*.

Clearly, additional measures are required to make the room of the infectious patient safe. Source control measures, such as surgical masks for patients, local exhaust ventilation near the patient's head, and a respiratory protection plan for employees, are necessary for a comprehensive plan. UV light fixtures mounted high on the walls of the room have been shown to reduce the concentration of airborne bacteria. Mermarzadeh (61) redemonstrated that UV light is effective in reducing airborne contaminants. It must be remembered that when using UV light or portable filters to enhance ventilation for particle removal, the devices do increase equivalent room air changes for airborne infectious diseases control but do not satisfy fresh air requirements (13). Likewise, portable filters with extra features besides filtration are often extraneous and do not enhance air quality. Studies of filters-plus enhancers, like photo activation, have not been proven in a clinical setting to prevent disease.

Maintenance Considerations Design of sophisticated hospital ventilation systems must include ongoing routine maintenance as part of the budget for the project (14). Ventilation systems rapidly fail if not carefully installed, monitored, and repaired as needed. Deferred maintenance is a common problem in many hospital systems. In addition, sophisticated ventilation systems have failed to perform as specified because of inadequate installation. Failure to provide the designed supply of air in special ventilation areas by installing a fan with insufficient delivery capability will create ventilation deficiencies. Likewise, a void in the caulk around a window in a positive-pressure room can allow windblown spores to enter the patient's room, bypassing the filtration system and exposing the patient. Improperly installed humidification or cooling systems can allow moisture buildup, creating ideal growth conditions in the air-handling system for potentially lethal mold. Poorly designed gaskets and mounting apparatus can allow dirty air to bypass the HEPA filters and contaminate clean areas. The failure to maintain the system may cause the air balance to change because of increased accumulation of lint and dust on filters; this may decrease the exhaust ventilation. Such changes could alter the negative air balance and cause the room to become positively pressurized (Table 84-5).

When designing a high-performance air-handling system, it is vitally important that all components are easily accessible for routine inspection and maintenance. Filter change-out must be performed according to safe maintenance practice *(66)*. Filter efficiency actually increases during use as trapped particles increase the density of the filter media. At the end of a filter's useful life, it is so loaded with particles that it begins to impede system airflow. Monitoring devices such as manometers or gauges should be installed to measure the pressure drop across filters, and when the indicator exceeds manufacturer's specifications, the filter should be changed. Often, these measuring devices are not operable because of neglected maintenance (62). It is difficult to remove and replace the filter without dislodging trapped contaminants and sending them downstream. The point-of-use filter (placed at the end of the duct just above the diffuser) in the bone marrow transplantation unit minimizes this effect by preventing more than 95% of the released particles from reaching the patient-care area *(63)*.

Fans, cooling coils, and condensate pans must be readily accessible for cleaning and repairs. Studies and reports indicate that failure to design hospital HVAC systems with provisions for routine maintenance access can result in untoward clinical consequences (14). Training of personnel in the principles and importance of ventilation is essential. Often, maintenance personnel shut down critical fan systems without notifying persons in the affected areas. Such shutdowns are a real threat because of the lack of ventilation control during those times. Fan systems must be routinely maintained, and shutdowns must be carefully

TABLE 84-5

Ventilation Hazards

Problem	*Consequences*	*Possible Solutions*
Water-damaged building materials *(18)*	Water leaks can soak wood, wallboard, insulation, wall coverings, ceiling tiles, and carpeting. All can provide microbial habitat when wet. This is especially true for fungi growing on gypsum board	1. Incorporate fungi static compounds in building materials in areas at risk for moisture problems 2. Replace water-damaged materials 3. Test for moisture and dry in <72 h
Filter bypasses *(51)*	Rigorous air filtration requires airflow resistance. Air stream will elude filtration if openings are present because of filter damage or poor fit	1. Use pressure gauges to ensure that filter is performing at proper static pressure 2. Make ease of installation and maintenance criteria for filter selection 3. Properly train maintenance personnel in HVAC issues 4. Design system with filters downstream from fans 5. Avoid water on filters or insulation
Improper fan setting (62)	Air must be delivered at design volume to maintain pressure balances. Airflow in special vent rooms reverses	1. Routinely monitor airflow and pressure balances throughout critical parts of HVAC system
Ductwork disconnections *(63)*	Dislodged or leaky supply duct runs can spill into or leaky returns may draw from hidden areas. Pressure balance will be interrupted, and infectious material may be disturbed and entrained into hospital air supply	1. Design a ductwork system that is easy to access, maintain, and repair 2. Train maintenance personnel to regularly monitor airflow volumes and pressure balances throughout the system 3. Test critical areas for appropriate airflow
Airflow impedance (12)	Debris, structural failure, or improperly adjusted dampers can block ductwork and prevent designed airflow	1. Design and budget for a duct system that is easy to inspect, maintain, and repair 2. Alert contractors to use caution when working around the HVAC system during the construction phase 3. Regularly clean exhaust grills 4. Provide monitoring for special ventilation areas
Open windows *(11,22)*	Open windows can alter fan induced pressure balances and allow dirty-to-clean air flow	1. Use sealed windows 2. Design HVAC system to deliver sufficient outdoor dilution ventilation 3. Monitor CO_2 levels in all occupied areas to ensure adequate fresh air supply 4. Sign windows where fire code prohibits sealing
Dirty window air conditioners *(21,22)*	Dirt, moisture, and bird droppings can contaminate window air-conditioners, which can then introduce infectious material into the hospital room	1. Design such devices out of new construction 2. Where they must be used, make sure that they are routinely inspected and cleaned
Inadequate filtration *(60)*	Infectious particles pass through filter into vulnerable patient areas. Specify appropriate filters during new construction design phase	1. Specify appropriate filters during new construction design phase 2. Make sure that HVAC fans are sized to overcome pressure demands of filter system 3. Inspect and test filters for proper installation
Maintenance disruptions *(59)*	Fan shut-offs, dislodged filter cake contaminates downstream air supply and drain pans, compromises airflow in special ventilation areas	1. Be sure to budget for rigorous maintenance schedule when designing a facility 2. Design system for easy maintenance 3. Ensure good communication between engineering and maintenance personnel 4. Institute an ongoing training program for all involved staff members

(*Continued*)

TABLE 84-5

Ventilation Hazards (*Continued*)

Problem	*Consequences*	*Possible Solutions*
Duct contamination *(18,19)*	Debris is released during maintenance or cleaning	1. Provide point-of-use filtration in the critical areas 2. Design air handling system with insulation on the exterior of the ducts 3. No fibrous sound attenuators 4. Decontaminate or encapsulate contamination
Depressurized hospital building *(64,65)*	Infiltration of unfiltered air into the building during construction caused aspergillosis in oncology patients	1. Ensure building pressure by oversupply of air volume by rebalancing or upgrading building ventilation 2. Add doors and weather-stripping to prevent air movement during periods of air imbalance 3. Difficult issue with high-rise buildings

Useful equipment: Moisture Meter Model Tramex Moisture Encounter Professional Equipment Item #M253, approximately $300,00, 1-800 334-9291; Digital pressure gauge, Energy Conservatory, Minneapolis, MN, approximately $800.00, 612-827-1117; Copper-8-quinolinolate, Micropel SWR Surface Shield, Microban Systems Inc. Bradock, PA, 412-351-8686; Infra Red Camera, Fluke Thermal Imager, Fluke Corporation, PO Box 69165, Seattle, WA 98168-9987.
CO_2, carbon dioxide; HVAC, heating, ventilation, and air-conditioning.

planned. Likewise, plans for emergency outages must also include provisions for backup motors or redundant systems. For example, contingencies for failure of the ventilation system in a bone marrow transplantation unit should include changes of procedural practice during the absence of ventilation control. For example, on the patient-care unit, should the routine cleaning and patient visitation be temporarily suspended during fan outages? If malfunction is persistent, should supplemental ventilation be provided with portable systems? Such scenarios should also be considered for the ventilation for infectious disease isolation in anticipation of planned or unplanned outages. Finally, it is crucial that funds for ongoing maintenance and training are included in the hospital budget.

Provisions must be made for additional patient protection during construction and remodeling projects (62,*63*). When wall cavities are opened, large quantities of spores might be released from water-damaged areas hidden from view *(67)*. Protective air environments must be secured from penetration by dust and debris generated during remodeling projects. During a large construction project at a Midwestern hospital, the infection control team purchased an optical particle counter to monitor the operating theaters and ensure that the ventilation system was controlling the air quality during construction *(68)*. Microbiologic air monitoring can also be used, but baseline data must first be generated along with construction monitoring during the project. Results are often hard to interpret, and time spent would be lost to the more important aspect of monitoring the compliance with construction specifications related to infection control during construction. On the other hand, commissioning of ventilation systems by air sampling would ensure that specifications for filter installation and operation have been met.

Verification of Ventilation Parameters for Special Ventilation Rooms Infection control airflow design specifications should also be verified *(64)*. The parameters important for verification are associated with pressurization, room air exchanges, and filtration. Nicas et al. *(69)* and Rice et al. *(70)* showed considerable variation of airflow when special ventilation rooms were tested. Rice et al. reported a large pressure variation for positively pressurized rooms primarily because of the maintenance manipulation of dampers or fan belts. Negatively pressurized rooms had much lower pressure differentials and were considered more stable, but the airflow direction changed from negative to positive more frequently. Saravia et al. showed that most airborne infection isolation (AII) rooms, when tested, were deficient. In the name of preparedness for infectious diseases, verification of ventilation parameters is essential (71). The fluctuation from negative to positive was probably due in part to a low-pressure differential at or about 0.25 Pa (250 Pa per 1.0 inches water gauge). Recently, Streifel and Marshall (72) clarified parameters that could be measured before occupancy of special ventilation areas. Table 84-6 is a listing of the parameters, and notably, the pressure measurements are listed. The pressure performance must be considered as a range because of constant variation of outdoor conditions, elevator movement, and doors being used *(73)*.

Testing and proving that airflow is appropriate, air exchanges are sufficient, and filtration is appropriate permit mechanical ventilation to be ruled out as a source for acquisition of *Aspergillus*. Other considerations can, therefore, be explored.

Air-Sampling Methods The nonviable airborne particle can be detected with the use of a particle counter, optical or laser, that allows real-time air quality analysis. It is important to differentiate particle sizes. The most useful devices for measuring particle sizes are those that determine particle size diameters >0.5, 1.0, and 5.0 μm per cubic foot (74). The particles at >0.5 μm are used for assessing a clean room, and Military Standard 209 (e) The International Standards Organization Standards are used to classify clean rooms with particles per unit volume of air less

TABLE 84-6

Recommended Measurements for Special Ventilation Rooms

	Protective	*Airborne Infection*
Pressure differentials	>2.5 Pa (0.01 in. w.g.[a])	>2.5 Pa (0.01 in. w.g.)
Air exchanges per hour	>12	>12
Filtration	99.97% @ 0.3 μ DOP[b]	90% (dust spot)
Room airflow direction	Out	In
Clean to dirty airflow in room	Patient clean	Patient dirty
Ideal pressure differential	>8 Pa	>2.5 Pa
Room seal	<0.1 cfm/ft^2	<0.1 cfm/ft^2

[a]Water gauge.
[b]Dioctyl phalate.

TABLE 84-7

Media and Incubation Temperatures for Culturing Air Samples

Appropriate selection of growth media helps to expedite identification

Sabouraud, malt extract with inhibitor, inhibitory mold agar, etc.

Incubation temperature

At 25°C, greater numbers of airborne fungi will grow; lower temperatures help to distinguish infiltration or filtration deficiencies

At 35°C, the temperature selects for pathogen recovery; A. fumigatus and A. flavus are thermotolerant

than a certain number. The classification is based on increments of 10, and a HEPA filtered (99.97% efficient at 0.3-μm diameter particles) operating room or BMT environment with no people should be capable of class 1,000 clean room status or better. The definition of a class 1,000 clean room is that there are <1,000 particles per cubic foot >0.5 μm in diameter. Such information is especially useful for ensuring filtration integrity or infiltration in a critical environment before the areas are occupied. These devices are useful for determining the cleanest areas. Problem solving with particle counters and pressure gauges help determine potential sources of particles being generated. The class of the room designation can be a useful guideline but should not have such a specification for an absolute number that cannot be exceeded. Airborne particle counts vary a great deal in healthcare, the status quo should demonstrate low particle counts with no activity. The lowest counts should occur in areas with the best ventilation.

The viable airborne particle analysis is more complex, because laboratory expertise is necessary. The selection of media, incubation temperature, and skill for identification of environmental microbes are factors that must be considered if an environmental sampling program is initiated. The purpose for sampling should include determination of what the sampling is expected to evaluate. For example, an air-sampling search for human-shed microbes such as *M. tuberculosis* or staphylococcal species should not be considered because of the difficulty in culturing the slow-growing *M. tuberculosis* and because staphylococcal species are frequently shed from humans. Aerosols generated by a medical device such as a drill may be instructive for air sample evaluations but certainly are not routine in any setting. Air sampling from a practical point of view should be considered only for evaluation of the presence of airborne fungi *(75)*.

Evaluation of the air for airborne fungi yields information that may be helpful in preventing infection or determining the source of airborne opportunistic environmental fungi *(76)*. Air sampling for airborne fungi should be used for determining the levels in areas where patients are at risk for infections from these opportunistic fungi. The media used for sampling a hospital environment should be capable of isolating clinically relevant microorganisms. Because the fungi are capable of growth on a variety of media, clinical media such as Sabouraud or inhibitory mold agar provide direct morphologic identification from the recovered isolates. Some environmental media, although excellent for total recovery, may require extensive subculturing for identification (Table 84-7).

The presence of fungi capable of growth at body temperature is of particular concern. The difference between fungi that grow at room temperature (25°C) and body temperature (37°C) are generally greater than one order of magnitude except in highly filtered environments (Table 84-7). The most common in-hospital exposure occurs from improperly filtered incoming air or from internal sources that were disrupted because of construction or maintenance. Air sampling will not prevent infections during construction. Air sampling can provide information that should inform infection control professionals that the air quality is good enough for safe patient care, because control measures are in place. It is difficult to detect the short-term high-dose exposures that occur because of environmental disruption.

There are a variety of samplers capable of viable particle air sampling. These include volumetric samplers and slit or sieve impactors. It is important that a volume of air is sampled. Settle plates depend on gravity, but single spores <5.0 μm in diameter are buoyant aerodynamic particles that do not settle rapidly. Clumps of particles settle, but perhaps the most problematic particles are those that are capable of entering the lungs. These respirable particles are <5.0 μm in diameter. Collecting the particles in sufficient quantity is essential to detect low concentrations of spores causing healthcare-associated infection. Arnow et al. (18) reported infection rates of approximately 1.2% with *Aspergillus flavus* and *A. fumigatus* at 2.2 and 1.1 colony-forming units (CFU)/m^3, respectively. Rhame et al. *(76)* reported a 5.4% infection rate with *A. fumigatus* at 0.9 CFU/m^3. A major problem with most samplers used in hospitals is low sample volume capability. Most samplers are designed to sample dirty environments. Samplers that sample 1 cfm may

fail to detect spores at levels <1.0 CFU/m^3. Hospital air samples should be at least 17 ft^3 or 0.5 m^3 to detect low levels of spores. Disadvantages of many samplers include low-volume sampling, drying of media with long sampling times, difficult manipulation of culture plates, and difficult calibration. A slit to agar sampler with a timer up to 60 minutes may be the best choice of sampler dependent on the type of timer, noise levels, and portability.

Interpretation of Data Timing for detecting airborne fungal levels is important for interpretation of results. For example, activity evaluation with an air sampler may reveal high concentrations of airborne fungi during the renovation activity of a water-damaged bathroom. Rather than sample for the probability of specific pathogenic microorganisms, it is best to contain the bathroom before demolition to prevent migration of the problematic spores. The best use of air sampling is before occupancy to determine proper filter installation and room pressurization. The purpose of such sampling is to establish rank order for the cleanest areas. The best filtration should demonstrate the lowest particle or viable airborne fungal counts. Such numbers are best demonstrated as baseline before occupancy. Subsequent sampling should take into account people and conditions such as incorrect airflow in a protective environment. Exposure to high levels of an airborne infectious agent over a short time is probably the greatest risk to the host. The ability to capture such events is difficult. The sampling of the environment should be to determine if the ventilation systems work according to specification. Therefore, the areas with the best filtration, pressurization, and air exchanges should have the lowest airborne fungal counts. This should also be true for nonviable airborne particles detected with a particle counter.

If pathogens (*A. fumigatus*, *A. flavus*, or other opportunists capable of growth at body temperature) are recovered from protected environments, consideration should be taken for single-plate hits versus multiple-plate hits from pathogenic fungi. Random isolate recoveries may be represented by a single colony on a plate. Greater than two colonies, for example, *A. fumigatus*, may represent a point source within the patient-care environment. Repeat sampling under such circumstances should determine if it was a passing phenomenon (Table 84-8).

Interpretation of the results from air sampling requires a comparison of sample locations. If sampling is requested, the cleanest environment (i.e., operating rooms or BMT unit) should have the lowest numbers of microorganisms recovered. The basic comparison should be from clean to cleanest in CFU per cubic meter. For better results, such comparisons should be done with culture media incubated at room temperature. Room temperature incubation at approximately 25°C is more sensitive for fungal recovery. Falvey (77) in a 10-year study showed 82% more fungi grew at 25°C than at 35°C incubation temperature. The comparison samples for detecting filtration integrity or potential infiltration should also be incubated at room temperature. Qualitative analysis, however, of airborne pathogens such as *A. fumigatus* is better at close to body temperature (>35°C), because the other mesophilic fungi are inhibited, allowing the pathogens to be more easily detected. The pathogens are easily obscured when the samples are incubated at room temperature. Also, the rank order comparison is difficult at the higher temperature, because the differences in levels in highly filtered areas are not very great. For example, the difference in recovery from media incubated at room temperature for samples taken from the nurses' station in the BMT unit versus those taken from HEPA-filtered rooms might be 55 and 4 CFU/m^3, respectively, whereas the same samples incubated at 35°C might yield 10 and 4 CFU/m^3, respectively. The samples incubated at room temperature are intended to demonstrate ventilation deficiencies, whereas the samples incubated at body temperature should be able to detect pathogens. Pathogen content should be <1.0 CFU/m^3 with repeat sampling. Invariably *A. fumigatus* shows up as a single isolate with few, if any, other microorganisms on the sample plate. A combination of factors that demonstrate the cleanest environment with the lowest pathogen counts are important for data interpretation. The value of comparisons with outside recoveries is that levels of *A. fumigatus* are often higher outside the hospital than inside, for example, 9.0 vs. 1.0 CFU per sample. When adjusted for CFU per cubic meter, outside samples have much higher levels than inside ones, allowing an indoor-to-outdoor ratio of <1. However, if the inside levels are higher than outside levels (except during snow cover or after rain), then an internal source may be suspect. The recovery of two or more colonies of a pathogen from media incubated at 35°C may indicate an internal point source *(75)*.

TABLE 84-8

Interpretation of Air Sample Data

- Rank order determination
  - Clean to cleanest with the lowest counts in the areas with proper ventilation control (pressure, air exchanges, and filtration)
  - Lowest counts in the areas with best filtration
  - Comparison data necessary (outdoor vs. lobby vs. patient-care area)
- Indoor-to-outdoor ratio
  - I/O < 1 normal
  - I/O > 1 potential problems
- Consider outdoor conditions and comparison data colony types
- Qualitative information
  - Pathogen recovery with results >1 CFU pathogen per plate is a potential indoor source
  - Comparison to determine homogenous vs. heterogeneous population
- Temperature selectivity
  - Pathogens grow at temperatures >35°C
  - Total fungi more sensitive to I/O at 25°C

CFU, colony-forming unit.

CONCLUSIONS

It is important that infection control, environmental, engineering, and maintenance personnel actively monitor the proper operation of the HVAC system. Objective information, from

pressure gauges and particle counters, provides real-time analysis of the critical special ventilation environmental parameters. Careful management of all maintenance, surveillance, repair, and construction activities should be coordinated in such a manner as to ensure that precautions to protect the health and well-being of all patients and staff are implemented. Use of pressure (airflow direction), room air changes per hour, and filtration verification specifications are essential for effectively maintaining protective and AII environments. The coordination of safety issues surrounding the susceptible patients and economic pressures is a challenge for achieving energy management goals when reducing ventilation for cost savings is proposed. Vigilance using medical technology and environmental source management will do more for preventing the spread of airborne infectious diseases than environmental sampling will.

Protection from Bioaerosols

Concern for the protection of buildings is imminent, especially because terrorism is part of the current state of affairs in the world order. Likewise, keeping aging infrastructure up to code as the technology advances for patient treatment is a costly effort. Previous sections of this chapter consider the ventilation requirements for AII. For rooms, the described ventilation parameters will help maintain the individual room control of microbial agents spread by the airborne route. The concern for the emergency room waiting areas and sections of the hospital needing to house potentially infectious patients is a challenge. Current fire code requirements for smoke control will aid in the development of a strategic plan for isolating a ward. Hospitals are segmented into smoke control zones, which are smoke compartments. These zones have ventilation dampers and fire-stopped walls that will evacuate smoke if fires are detected in that zone. Engineering concepts are being explored to use the smoke-control dampers and exhaust systems to help isolate the areas with infectious agents. The criteria for isolation would not be as extreme as the smoke management requirements, but the mechanism should already be in place for establishing the depressurized zone for an AII patient-care unit. We can establish isolation methods for preparedness for a biological event by employing methods used by carpenters during construction in healthcare facilities (74,78).

http://www.cdc.gov/niosh/bldvent/2002-139.htm
http//www.health.state.mn.us/oep/training/bh pp/isolation.html
http://www.cdc.gov/niosh/docs/2003-136.pdf

In maintaining the ventilation infection control systems, it is vitally important to focus on what works, especially on what works consistently. To provide the best possible hospital air quality, state-of-the-art technology is needed. It is equally important, however, to emphasize effective communication and common-sense procedures that will account for the human element, permit the system to function as designed, and meet the goal of providing the best in healthcare. Too many facilities are focused on air sampling for preventive measurements of air quality. The results using culture to determine if an area is dirty allows time to pass before decisive action is taken. Common sense would tell us that if the floor is dirty with dust, cleaning it before culturing provides safety and efficacy. Efforts must be taken to ensure ventilation proficiency with the ventilation parameters that will help to control the airborne infectious agents that are potentially pathogenic to humans.

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SECTION XIII
Antimicrobial Agents in Healthcare Epidemiology and Infection Control

CHAPTER 85

Mechanisms of Bacterial Resistance to Antimicrobial Agents

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The vast majority of antimicrobial agents employed in clinical settings are either natural products or chemical derivatives of natural products. The producers of these agents in nature are generally the microbes themselves. The purpose of this antibiotic production by microbes has traditionally been attributed to gaining a selective advantage in a mixed microbial environment. More recently, recognition that the natural production of antibiotics occurs at generally low levels and that exposure to subtherapeutic concentrations of some antibiotics alters bacterial transcription profiles has led to the concept of antibiotics as "signaling molecules" in nature. Since the production of antibiotics has been occurring in the microbial environment for (presumably) eons, it stands to reason that mechanisms to avoid their lethal action have been developed as well, either by species that produce the antibiotics or those that must share limited space and resources with those that do. In many instances, therefore, our discovery and growing use of antibiotics has led not to the development of resistance genes in bacteria but merely to the natural selection of intrinsically resistant species or the efficient scavenging of preexisting resistance genes by normally susceptible human pathogens. The emergence of *Lactobacillus* species during therapy with vancomycin and of *Stenotrophomonas maltophilia* during therapy with imipenem are examples of selection of intrinsically resistant species. Other phenotypes of resistance reflect more of the ease with which susceptible bacteria can mutate either structural or regulatory genes intrinsic to their species in a manner that results in decreased antibiotic susceptibility. Examples of this type of resistance include extended-spectrum cephalosporin resistance in *Enterobacter* species, fluoroquinolone resistance in many different species of bacteria, or the emerging resistance to linezolid in enterococci and staphylococci. Resistance to some antibiotics, in some species, is not readily achievable by mutation, and thus, must be acquired from other sources. This so-called acquired resistance accurately characterizes many different resistance phenotypes, including ampicillin resistance in *Escherichia coli*, penicillin resistance in staphylococci, and vancomycin resistance in enterococci. Finally, when antimicrobial agents are developed specifically to avoid the lethal action of acquired resistance genes, mutations within the acquired genes can lead to resistance to the newer agents. The emergence of resistance to extended-spectrum cephalosporins in *Klebsiella pneumoniae* and *E. coli* can represent this sort of amplified resistance.

Antimicrobial agents are effective because they target metabolic pathways or enzymes that are specific to bacteria and not to the host. A variety of mechanisms have been shown to result in bacterial resistance. Among these mechanisms are alterations in the antibiotic target such that binding or inhibition of function is decreased to the point of clinical irrelevance, decreased permeability that results in the inability of the agent to reach its target at a critical concentration, efflux of the agent from the cell, and destruction or modification of the antibiotic.

The expression of resistance and virulence by bacteria is often linked but sometimes in unpredictable ways. Selection of rifampin or streptomycin-resistant mutants in the laboratory is often associated with a decrease in the virulence of the strains when tested in animal models (1).

It is presumed that the point mutations in the targets (RNA polymerase in the case of rifampin, the ribosome in the case of streptomycin) lead to subtle but not fatal decreases in function in these resistant strains, conferring a competitive survival disadvantage relative to wild-type strains. Interestingly, continued passage in animals in the absence of antibiotic selective pressure does not always result in reversion to the susceptible genotype. Instead, compensatory mutations frequently occur that mitigate the deleterious effects of the primary mutation, restoring virulence while maintaining resistance (1). Acquired resistance and virulence determinants may also coalesce in environments that favor them, such as the modern hospital. Reports suggest that the worldwide rise of ampicillin- and vancomycin-resistant *Enterococcus faecium* is because of the emergence and spread of genetically related strains enriched for high levels of ampicillin resistance as well as a variety of putative virulence determinants *(2)*.

ANTIMICROBIAL RESISTANCE TRANSFER

Although the primary concern of the healthcare epidemiologist is the prevention of the spread of bacterial strains among hospitalized patients, it is worthwhile to consider mechanisms by which resistance genes can spread among bacterial strains. A full discussion of the mechanisms of resistance transfer is beyond the scope of this chapter. Nevertheless, a few basic concepts should be understood.

Antimicrobial resistance determinants are commonly incorporated into extrachromosomal, independently replicating elements known as plasmids. Plasmids vary greatly in size (3 to >200 kb) and in the number of incorporated resistance determinants. In addition to genes responsible for replication and for antibiotic resistance, many plasmids also possess genes that stimulate their transfer between strains within a given genus, and occasionally, between strains of different (although usually closely related) genera. Large, transferable plasmids have been implicated in the spread of ceftazidime resistance among strains of Enterobacteriaceae, particularly in intensive and chronic care settings (*3,*4). Many of these plasmids also possess genes encoding resistance to a range of non–β-lactam antimicrobial agents, resulting in the elimination of several antibacterial options with a single transfer event (*3,*4). Transferable plasmids have also been identified in gram-positive genera, perhaps best characterized by the pheromone-responsive plasmids found in strains of *Enterococcus faecalis* (5). The widespread emergence of high-level gentamicin resistance in enterococci (see below), resulting from the production of a modifying enzyme most commonly encoded on plasmids, is a testament to the efficiency of plasmids in disseminating resistance determinants in this genus *(6,7)*. Enterococci are also known to possess "broad host-range" plasmids. These plasmids transfer at a lower efficiency than do the pheromone-responsive plasmids but have the advantage of being able to transfer to a wide variety of species. Evidence implicates broad host-range plasmids in the exchange of important resistance genes between enterococci and staphylococci, including β-lactamase production and high-level vancomycin resistance *(8,9)*.

Plasmids need not encode their own transfer genes in order to spread between strains. Nonconjugative plasmids may be mobilized for transfer by conjugative plasmids. In addition, the presence of insertion sequences (ISs) (small regions of DNA capable of independent movement between replicons) has been shown to facilitate the co-integration of conjugative and nonconjugative plasmids, resulting in a larger, conjugative element *(10)*. Appropriately sized plasmids may also be spread by transduction, resulting from the aberrant incorporation of plasmid rather than bacteriophage DNA into the phage head.

In addition to plasmids, antimicrobial resistance determinants are frequently incorporated into mobile elements known as transposons. Transposons may be rather simple elements whose mobility results from the presence of ISs flanking an antimicrobial resistance determinant (composite transposons), an arrangement in which mobility is due entirely to functions encoded by the ISs *(11)*. Alternatively, transposons may be complex structures incorporating several genes. Tn*21* is a Tn*3*-family transposon that has been found to contain a genetic locus (*tnpI*) that serves as a "hot spot" for the integration of a variety of antimicrobial resistance genes *(12)*. Consequently, several Tn*21*-like transposons conferring resistance to a number of different antimicrobial agents, in varying combinations, have been described *(13)*. These loci, referred to as integrons, appear to be important mechanisms for the dissemination of antimicrobial resistance genes in many gram-negative bacilli *(14,15)*. Integrons may be critical vehicles of microbial genetic evolution and have only recently been employed by bacteria for purposes of stockpiling resistance determinants (16). Another Tn*3*-family transposon, Tn*1546* *(17)*, confers resistance to vancomycin and teicoplanin in enterococci and, more recently, in *Staphylococcus aureus*. It encodes nine genes involved in the regulation of transposition and the expression of glycopeptide resistance. More recently, a Tn*21*-based complex transposon carrying β-lactamase-mediated carbapenem resistance has been described in *K. pneumoniae (18)*.

In general, transposons participate in the transfer of antimicrobial resistance determinants by virtue of their ability to move between bacterial chromosome and transferable plasmid. Exceptions to this rule are the conjugative transposons of gram-positive bacteria, which can transfer between strains without the necessity of a plasmid intermediate *(19)*. These transposons possess their own genes responsible for transfer between microorganisms. In general, conjugative transposons encode resistance to tetracycline via the *tetM* gene, although some have been found to encode resistance to multiple antimicrobial agents *(19)*. In addition to the transfer of the elements themselves, some investigators have found that the presence of conjugative transposons stimulates the transfer or deletion of unrelated chromosomal genes, raising the possibility that these elements could be involved in the transfer or deletion of a range of unrelated resistance determinants *(8,20,21)*. A transposon in the Tn*916* family has been described that encodes VanB-type vancomycin resistance in *E. faecium (22)*. Conjugative transposons may also transfer determinants for antibacterial activity as well as antibiotic resistance. Several lactococcal and one enterococcal Tn*916*-like elements encoding determinants for production

of the antibacterial peptide nisin have been described *(20)*. Many larger conjugative elements, especially those from gram-negative bacteria, have been generally categorized as integrating conjugative elements *(23)*.

Other mobile elements involved in the spread of antimicrobial resistance are the IS elements. These elements do not encode antimicrobial resistance themselves but may aid in the spread of resistance determinants via the formation of composite transposons or by serving as areas of homologous recombination between plasmid and chromosome. Insertion of IS elements may also result in the activation of poorly expressed genes via the presence of promoter sequences within the end of the mobile element *(11)*. Evidence indicates that the expression of imipenem resistance in some strains of *Bacteroides fragilis* is due to the insertion of IS elements upstream of an unexpressed chromosomal gene encoding a carbapenemase *(24)*. IS elements have also been implicated in plasmid:chromosome integration with subsequent transfer of chromosomal segments using the plasmid origin of transfer in *E. faecalis (25)*.

Our ability to thwart the spread of resistance determinants between bacterial strains in the natural environment is poor. Factors affecting transfer between strains are poorly understood, but, in some cases, may involve exposure to antimicrobial agents. Transfer of conjugative transposons, for example, has been shown to be increased *in vitro* and *in vivo* after exposure of the donor strain to tetracycline *(26,27)*. It is, therefore, reasonable to presume that environmental pressure from the overuse of antimicrobial agents plays some role in the spread of these determinants. In addition, the comingling of resistant strains of bacteria in the human gastrointestinal tract resulting from hospital and antibiotic exposure as well as from inattention to appropriate infection control techniques probably plays a role in the spread of resistant strains. In some cases, institution of infection control measures (such as barrier precautions for infected and colonized patients) has been shown to abort serious outbreaks of resistant microorganisms *(28,29)*. In others, decreasing use of an antibiotic has been associated with a reduction in the prevalence of resistant strains in an institution *(30)*. As such, judicious use of antimicrobial agents and proper attention to infection control recommendations are likely to be our best weapons to combat the spread of resistant bacteria for the foreseeable future.

β-LACTAMS

Mechanism of Action

Targets of β-lactam antibiotics are a series of enzymes involved in the last step of peptidoglycan (cell wall) synthesis. This step involves a cross-linking reaction carried out by transpeptidases in which the terminal D-alanine of the pentapeptide stem of the peptidoglycan is cleaved. The energy resulting from this cleavage is used to form a peptide bond between the fourth residue of the pentapeptide (also D-alanine) and the cross-bridge, which is itself linked to the e-amino of diaminopimelic acid (in gram-negative microorganisms) or lysine (in gram-positive microorganisms) (Fig. 85-1). This cross-link is absolutely required for structural integrity of the bacterial cell wall. β-Lactam antibiotics, such as penicillin, are structural analogs of the pentapeptide terminal D-alanyl:D-alanine target covalently bound by the transpeptidases. The fact that these transpeptidases also bind penicillin (and other β-lactams) covalently has resulted in referral to them as penicillin-binding proteins (PBPs).

Mechanisms of β-Lactam Resistance

Target Resistance The binding affinity of β-lactams for their targets, the PBPs, varies with the β-lactam and the PBP. Enterococci, for example, are intrinsically resistant to the cephalosporins because these β-lactams do not bind one enterococcal PBP with high affinity *(31)*. Within the genus *Enterococcus*, *E. faecium* tend to be more resistant to penicillins because many strains express a low-affinity PBP (PBP5) that carries out cell-wall synthesis at penicillin concentrations that inhibit the other PBPs *(32)*.

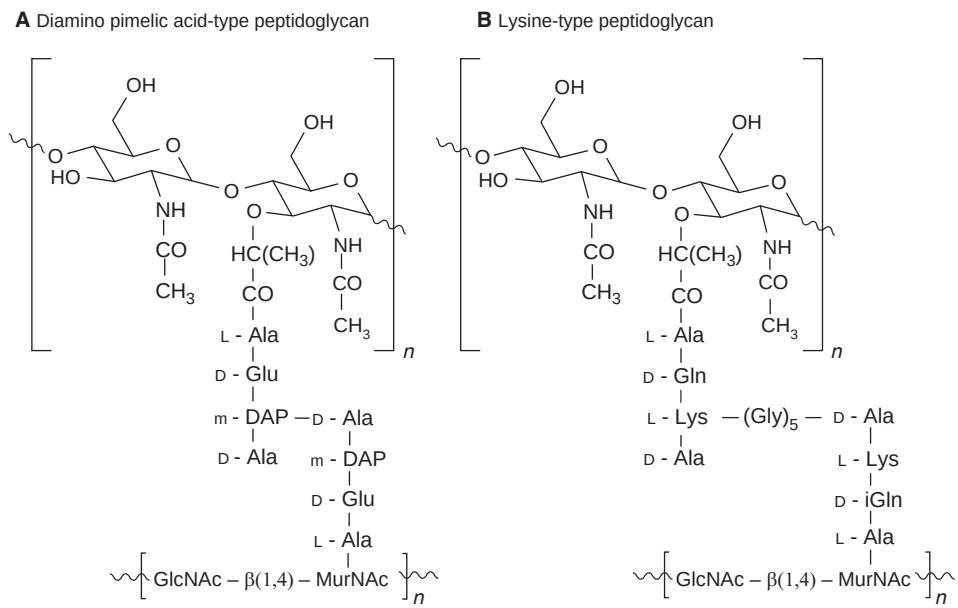

FIGURE 85-1 The two major peptide cross-links found in bacterial peptidoglycan. **A:** Cross-link between diamino pimelic acid and D-alanine, commonly found in peptidoglycan of gram-negative bacteria. **B:** Cross-link between Lysine and D-alanine, more commonly found in gram-positive species. The pentaglycine linkage in this figure represents the cross-links found in *S. aureus*. (Adapted from Royet J, Dziarski R. Peptidoglycan recognition proteins: pleiotropic sensors and effectors of antimicrobial defences. *Nat Rev Microbiol* 2007;5(4):264–277).

Many cases of PBP-mediated β-lactam resistance result from the intrinsic characteristics of the PBPs of a given strain. PBP-mediated resistance may also be acquired. Resistance resulting from mutation can be readily demonstrated in the laboratory *(33)*. Resistance to oxacillin in clinical *S. aureus* strains has been attributed to point mutations in PBP genes *(33)*. In species that are naturally transformable (that can absorb naked DNA from the environment), the formation of mosaic PBP genes is common. Cloning and sequencing of *Streptococcus pneumoniae* or *Neisseria gonorrhoeae* genes encoding abnormal, low-affinity PBPs responsible for penicillin resistance has shown significant sections of these genes to be of foreign origin. In *S. pneumoniae*, the origin appears to have been from oral streptococci *(34)*; in *N. gonorrhoeae*, from oral commensal neisserial species *(35,36)*. The evolution of mosaic genes most likely occurred via DNA transformation followed by homologous recombination across areas of PBP sequence homology between the native and foreign DNA. Entire low-affinity PBPs can also be acquired by normally susceptible bacteria. Methicillin-resistant *S. aureus* (MRSA) has most commonly acquired low-affinity PBP2a, encoded by the *mecA* gene. The *mec* region is located within a larger mobile element (designated SCC*mec*) that varies in size depending on how much extra DNA it contains *(37)*. Healthcare-associated strains (which are resistant to several unrelated classes of antimicrobial agents) contain a larger SCC*mec*, reflecting the insertion of additional DNA, some of which encodes additional antimicrobial resistance. In contrast, the recently described MRSA arising in the community (which is generally susceptible to a range of other antimicrobial agents) contains a relatively small SCC*mec* that encodes only resistance to methicillin *(38)*. The *mec* region may have been acquired from coagulase-negative staphylococcal species *(39)*.

The expression of resistance encoded by mosaic or acquired PBPs is often dependent on very specific conditions. Several staphylococcal genes, called *fem* (factors essential for methicillin resistance) or *aux* (auxiliary) factors, have been identified—the inactivation of which results in reversion to susceptible phenotype despite the expression of PBP2a *(40)*. In most cases, these *fem* genes encode enzymes responsible for the synthesis of peptidoglycan precursors. Similarly, the expression PBP-mediated resistance in *S. aureus*, *E. faecalis*, and *E. faecium* is dependent upon the presence of specific glycosyltransferases with which the low-affinity transpeptidases can work *(41–43)*.

Enterococci are intrinsically resistant to some β-lactams, especially the cephalosporins, at high levels. Resistance is related to the low affinity of these compounds for the enterococcal PBP5 *(32,44)*. Strains resistant to even higher levels of the penicillins, in the absence of production of β-lactamase, have been described with increasing frequency *(45,46)*. These strains include several species, but *E. faecium* is most commonly reported from clinical laboratories. Most of these high-level resistant strains have one or more point mutations in *pbp5* that are thought to lower the affinity for penicillin and other β-lactams *(47)*. Accumulation of point mutations has been associated with lowered affinity and elevated minimum inhibitory concentrations (MICs) in the laboratory, supporting the notion that these point mutations contribute to higher levels of resistance *(48)*. Enterococcal strains expressing high levels of resistance to β-lactams through low-affinity PBPs are also more resistant to β-lactam–aminoglycoside synergism, even in the absence of high levels of aminoglycoside resistance *(49)*. Single-agent β-lactam therapy is precluded for such strains, leaving the glycopeptides as the antibiotic class of choice. The continued spread of glycopeptide resistance in penicillin-resistant enterococci (see below) is a problem at many large centers *(46)*.

β-Lactamase–Mediated Resistance A more important (than target resistance) and frequent mechanism of bacterial resistance to β-lactam antibiotics, especially in gram-negative bacteria, is the production of β-lactamases—enzymes that hydrolyze the β-lactam ring (Fig. 85-2). The reactive β-lactam ring is required for the formation of a covalent bond between the antibiotic and its PBP target. Destruction of this ring results in the loss of antimicrobial activity. The β-lactamases form a broad family of enzymes and, along with the PBPs, are classified as serine D, D-peptidases *(50)*. The homologies between many β-lactamases and PBP have led to the suggestion that β-lactamases have evolved from PBPs.

Two classification schemes for the β-lactamases are widely used. The first is based on primary structure and has been proposed by Ambler et al. *(51,52)* (Table 85-1). The other scheme (Bush–Jacoby–Medeiros classification) relies on the substrate specificity of the enzymes (53) (Table 85-2). There are many more classes and subclasses in this scheme, since single-point mutations in the gene encoding an enzyme may result in substantial changes in substrate specificity. The Ambler scheme is more frequently employed, likely because of its comparative simplicity.

Staphylococcal β-lactamase production became widespread within a few years of the clinical introduction of penicillin *(54,55)*. By the mid-1940s, β-lactamase–producing *S. aureus* strains were prevalent within hospitals, necessitating the introduction of vancomycin and semisynthetic penicillins such as methicillin, nafcillin, and oxacillin. In contrast to observations of class A enzymes in gram-negative bacilli, staphylococcal β-lactamase has not evolved to a broader spectrum over the decades. The importance of β-lactamase production in gram-positive bacteria remains essentially restricted to staphylococci.

The epidemiology of β-lactamase–mediated resistance in gram-negative bacilli is far more complex than in gram-positive bacteria. Hundreds of different β-lactamases have been described in gram-negative bacteria over the past 3 decades. The most problematic and prevalent of these enzymes are those that confer resistance to expanded spectrum cephalosporins. Earlier versions of these extended-spectrum β-lactamases (ESBLs) were progeny of narrower spectrum enzymes that fall, like the staphylococcal β-lactamase, into Ambler class A. The most common enzymes of this class among clinical isolates are related to the widely prevalent TEM-1 and SHV-1 enzymes (53). TEM-1 is widely prevalent as the cause of ampicillin resistance in *E. coli*, *Haemophilus influenzae*, and in some cases *N. gonorrhoeae*, whereas SHV-1 is the chromosomal β-lactamase found in most *K. pneumoniae* strains. TEM-1 and SHV-1 are broad-spectrum β-lactamases that hydrolyze

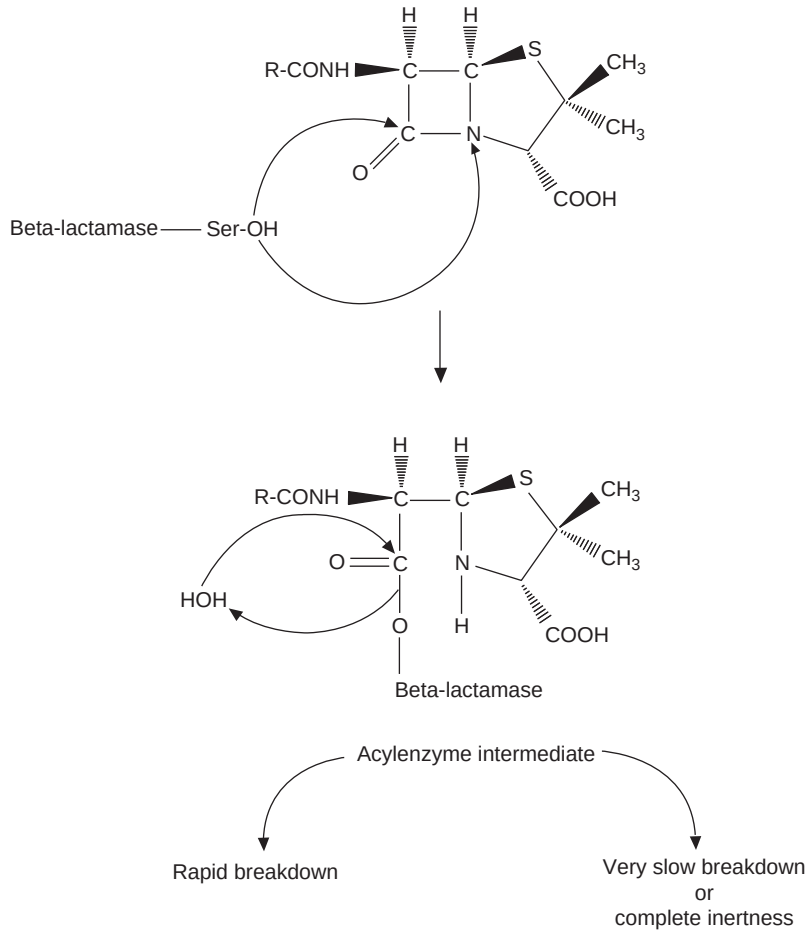

FIGURE 85-2 Reactions of serine-type peptidases (which include many β-lactamases) with the four-membered β-lactam ring of β-lactam antibiotics. Rapid breakdown is characteristic of lactamases, whereas slow breakdown or complete inertness is characteristic of PBPs. (Modified from Ghuysen JM. Serine β-lactamases and PBPs. *Annu Rev Microbiol* 1991;45:37–67).

the penicillins (ampicillin, mezlocillin, and piperacillin) with greater efficiency than the cephalosporins *(56)*. ESBLs result from the accumulation of point mutations within the TEM-1 or SHV-1 enzymes that serve to "open up" the active site of the enzyme, allowing binding of the bulky extended-spectrum cephalosporins. These point mutations are often found in association with cellular characteristics that serve to enhance the phenotypic expression of resistance, such as the location downstream of strong promoters (leading to increased β-lactamase quantity) and reductions in the expression of outer membrane proteins (OMPs; porins that serve as conduits for the entry of antibiotics into the periplasmic space). Genes encoding TEM- and SHV-related ESBLs are most commonly found on transferable plasmids with resistance determinants to numerous other antimicrobial classes. Strains elaborating ESBLs, most commonly *Klebsiella*, have been responsible for several outbreaks of infection and colonization in Europe and the United States. Outbreaks have been ascribed to clonal dissemination, plasmid dissemination, or both *(30,57,58)*.

TABLE 85-1

Molecular Classification of β-Lactamases

Class	*Examples*
A	TEM, SHV (gram-negative microorganisms), PC1 (*S. aureus*)
B	Metallo-β-lactamases of *S. maltophilia*, recently described NDM-1 in *Klebsiella* and others.
C	AmpC (clinically relevant particularly for *Enterobacter* spp., *C. freundii*, *S. marcescens* and *P. aeruginosa*)
D	OXA-type enzymes (found commonly in *A. baumannii*)

(From Ambler RP. The structure of β-lactamases. *Philos Trans R Soc Lond B Biol Sci* 1980;289:321–331.)

Mutations to extend the spectrum of TEM-1 or SHV-1 and allow hydrolysis of extended-spectrum cephalosporins commonly yield increased susceptibility to inhibition by β-lactamase inhibitors. In the clinical setting, however, the production of multiple enzymes and/or overproduction of individual enzymes often confer *in vitro* resistance to β-lactam/β-lactamase inhibitor combinations in ESBL producers. The relative scarcity of ESBL producers has made controlled studies of the efficacy of different therapies impractical, but carbapenems have been most effective in animal studies of infections with ESBL producers as well as in case reports and small series. Most of the clinical experience has been with imipenem *(57,59)*.

In the past decade, resistance to extended-spectrum cephalosporins in Enterobacteriaceae has been increasingly attributed to the expression of β-lactamases of the CTX-M family. They are naturally resistant to cephalosporins. They fall into Ambler class A, are generally more active against ceftriaxone and cefepime than

TABLE 85-2

Bush–Jacoby–Medeiros Functional Classification Scheme for β-Lactamases

Group	*Description*	*Examples*	*Molecular Class*
1	Cephalosporin hydrolyzing enzymes not inhibited by clavulanic acid	AmpC	C
2a	Penicillin hydrolyzing enzymes inhibited by clavulanic acid	*Bacillus licheniformis* 749, TEM	A
2b	Broad-spectrum enzymes inhibited by clavulanic acid	TEM-1	A
2be	Extended-spectrum enzymes inhibited by clavulanic acid	TEM 3–26	A
2c	Carbenicillin hydrolyzing enzymes inhibited by clavulanic acid	PSE-1.3.4	A
2d	Cloxacillin hydrolyzing enzymes inhibited by clavulanic acid	OXA-1–11	D
2e	Cephalosporin hydrolyzing enzymes inhibited by clavulanic acid	Inducible cephalosporinase from *Proteus vulgaris*	A
3	Metallo-β-lactamases	*S. maltophilia* GN12873	B
4	Penicillin hydrolyzing enzymes not inhibited by clavulanic acid	*B. fragilis* G237	?

(From Bush K, Jacoby GA, Medeiros AA. A functional classification scheme for beta-lactamases and its correlation with molecular structure. *Antimicrob Agents Chemother* 1995;39(6):1211–1233.)

ceftazidime, are susceptible to inhibition by β-lactamase inhibitors, are plasmid-mediated, and unlike the ESBL TEM and SHV variants, are very commonly found in *E. coli* as well as *K. pneumoniae*. In fact, the growing worldwide problem of increasing cephalosporin resistance in *E. coli* is almost exclusively attributed to the spread of CTX-M-type enzymes (60). The expression of these enzymes is frequently associated with resistance to fluoroquinolones, creating significant problems for empirical therapeutic regimens for community-acquired *E. coli* infection (60).

Resistance to extended-spectrum cephalosporins may also be conferred by the expression of regulatory mutants of Ambler's class C β-lactamases. These enzymes are broadly active cephalosporinases (which also hydrolyze penicillins) and are resistant to clinically achievable concentrations of β-lactam/β-lactamase inhibitor combinations (53). They are encoded by the *ampC* gene—a chromosomal gene widely disseminated among Enterobacteriaceae and *Pseudomonas aeruginosa*. In some species, such as *E. coli*, *ampC* is poorly expressed and not under regulatory control due to the absence of the *ampR* gene. The product of the *ampR* gene interacts with different cell wall breakdown products in a manner that results in AmpR becoming either a suppressor or an activator of *ampC* transcription *(61–63)*. Under normal circumstances, cells with inducible AmpC β-lactamases employ AmpD (a cellular amidase encoded by *ampD*) to reduce intracellular quantities of cellular breakdown product anhydro-muramyl-tripeptide, which results in an excess of uridine diphosphate (UDP)-muramyl-pentapeptide. UDP-muramyl-pentapeptide interaction with AmpR maintains AmpR as a repressor of *ampC* transcription. When exposed to certain antibiotics that favor the production of anhydro-muramyl-tripeptide (such as cefoxitin, clavulanic acid, and imipenem), the ability of AmpD to convert this substrate is overwhelmed, and interaction between anhydro-muramyl-tripeptide and AmpR converts AmpR into an activator of *ampC* transcription (induction). *ampR* is present and *ampC* is under regulatory control in *Enterobacter* species, *Serratia marcescens*, *Citrobacter freundii*, and *P. aeruginosa*, among others *(63–65)*. Imipenem is an efficient inducer of *ampC* expression, but it is a poor substrate for the *ampC* β-lactamase. It therefore remains active even in the presence of induced β-lactamase (as long as a concomitant mutation that decreases the entry of imipenem into the periplasmic space is not present—see below). Newer cephalosporins such as ceftazidime, ceftriaxone, and others are efficiently hydrolyzed by the AmpC but are poor inducers, and therefore, appear active *in vitro* against bacteria expressing inducible AmpC.

Unfortunately, the oxyiminocephalosporins (e.g., ceftazidime, cefotaxime, and ceftriaxone) are very good selectors of mutants that express high levels of the ampC β-lactamase constitutively. Their ability to select constitutive mutants results from their status as weak inducers. Constitutive AmpC production commonly results from null mutations in *ampD*, with subsequent intracellular accumulation of anhydro-muramyl-tripeptide and constitutive activation of *ampC* expression *(61)*. Thus, from among a population of microorganisms, the small number (1 in 10^{6-7}) of preexisting cells with mutations *ampD* are selected for growth by the presence of antibiotic with potent activity against strains in which *ampC* expression is repressed. Once constitutive expression occurs, the strains are essentially resistant to all β-lactams except for carbapenems and cefepime *(64)*. Cefepime's major advantage in this regard appears to be its status as a zwitterion, allowing it to achieve high periplasmic concentrations by rapid passage through the outer membrane. Caution should be exercised in using cefepime to treat deregulated *ampC* mutants of *Enterobacter* species, however, since reports of the emergence of cefepime resistance (associated with a reduction in an OMP) in these strains during therapy have been published *(66)*.

In a study of *Enterobacter* bacteremia by Chow et al. *(67)*, the major class of antibiotics associated with selection of resistance was the newer cephalosporins as opposed (especially) to the newer penicillins. Concomitant use of aminoglycosides did not prevent the emergence of this resistance.

In this study, resistance developed in 19% of all patients treated with newer cephalosporins. Therapeutic failure occurred in about half of those patients. For all patients infected with a multiply resistant strain, the mortality rate was significantly increased. Infection with a multiply resistant strain was closely associated with prior use of a new cephalosporin. Although cephalosporins have been most frequently associated with the emergence of AmpC mutants in the clinical setting, virtually any antibiotic active against repressed strains but inactive against overexpressing strains should be avoided when treating *Enterobacter* infections.

Plasmid-encoded versions of AmpC enzymes have been observed in several species of Enterobacteriaceae, including *E. coli* and *K. pneumoniae*, among others *(68)*. These strains express high levels of the AmpC enzyme constitutively and have resistance profiles identical to multiply β-lactam–resistant *Enterobacter* species and *P. aeruginosa*. The most prevalent of these enzymes is CMY-2, derived from the *Citrobacter* AmpC enzyme *(69)*. The carbapenems are the only therapeutically reliable β-lactams against these strains. It is noteworthy, however, that one such enzyme, designated ACT-1, was identified in a porin-deficient strain of *K. pneumoniae*, where it conferred resistance to imipenem and was associated with failures of this antibiotic in clinical settings *(70)*.

Resistance to β-lactam/β-lactamase inhibitor combinations can result from several different mechanisms, all of which involve the production of β-lactamase. As noted above, expression of an AmpC enzyme confers resistance to both cephalosporins and β-lactam/β-lactamase inhibitor combinations. Resistance to inhibitor combinations alone can be conferred by increased production of a normally susceptible enzyme (i.e., TEM-1), permeability defects, or a combination of both mechanisms *(71)*. Specific inhibitor-resistant enzymes can also result from mutation of TEM-1 or SHV-1, similar to extending the cephalosporin spectrum of these β-lactamases *(72)*. Resistance to both extended-spectrum cephalosporins and β-lactam/β-lactamase inhibitor combinations is quite common in the clinical setting. This phenotype can be conferred by production of AmpC enzymes, by the increased production of an ESBL, or by the expression of more than one enzyme (one an ESBL, the other a more common enzyme such as SHV-1) *(73,74)*.

Carbapenem hydrolyzing enzymes are increasingly identified. *S. maltophilia* is an intrinsically carbapenem-resistant species that can emerge as an important pathogen in clinical settings *(75)*. It owes its resistance to the synthesis of an inducible, zinc-dependent carbapenemase encoded on the chromosome. Cation (usually zinc)-dependent β-lactamases (generally classified as IMP or VIM enzymes) capable of hydrolyzing carbapenems have been described in several species *(76)*. Among anaerobic bacteria, a French study showed that approximately 1% to 2% of examined *B. fragilis* isolates carried a carbapenemase gene, although the gene was expressed in only about half of these *(77)*. In *Acinetobacter baumannii*, carbapenem resistance has been associated with the expression of class D enzymes (OXA type) *(78)*. Finally, class A carbapenemases—previously described as chromosomally encoded enzymes occurring in scattered isolates of *Enterobacter* and *Serratia (79)*—have now spread among gram-negative bacteria via plasmids. The most common variants are the *K. pneumoniae* carbapenemases (KPCs). In 2001, a novel class A carbapenemase, encoded on a 50-kb nonconjugative plasmid, was described in a clinical *K. pneumoniae* isolate displaying high-level imipenem resistance (16 μg/mL) and termed at that time KPC-1 *(80)*. Kinetic studies revealed that the purified enzyme hydrolyzed not only carbapenems, but penicillins, cephalosporins, and—in stark contrast to the class B metallo-carbapenemases—aztreonam as well. Concomitant losses of porin genes (*ompK35* and *ompK37*) were also felt to play a small role in carbapenem resistance, as MICs for carbapenems were reduced in *E. coli* transformants with $bla_{\text{KPC-1}}$ as compared to the parent strain (although still above the susceptible range). Shortly after this report, an outbreak of KPC-producing *K. pneumoniae* was described among ICU patients in a New York medical center (81); over the succeeding years, KPC β-lactamases have disseminated not only among most continents on the earth but also among numerous other Enterobacteriaceae and to other families of microorganisms, such as *P. aeruginosa (82)*. The combination of carbapenem resistance, an inhibitor-resistant phenotype (83), resistance to monobactams, and the (largely unexplained) success of *Klebsiella* species expressing these enzymes at, disseminating geographically render these microorganisms particularly difficult to treat.

β-Lactamase Expression Combined with Reduced Access

The ultimate outcome of an interaction between a β-lactamase molecule and a β-lactam antibiotic will depend not only on the intrinsic activity of the β-lactamase but also on the quantity of the two molecules present at the time of interaction. Weak β-lactamases in sufficient concentration will be able to successfully defend against β-lactam attack, whereas even highly active β-lactamases can be overwhelmed by a sufficient quantity of β-lactam antibiotic. The ability of gram-negative bacilli to restrict β-lactam access to the periplasmic space and to concentrate β-lactamases within that space offers a powerful advantage for tilting the balance of power in favor of the β-lactamase. In *P. aeruginosa*, a single OMP—OMP D2—is required for transport of imipenem into the periplasmic space (84,*85*) (Table 85-3). Strains that decrease the expression of OMP D2 are resistant to imipenem only in the presence of the expression of the AmpC β-lactamase, even though it is an inefficient hydrolyzer of imipenem (84). This same combination of mechanisms has been shown to lead to carbapenem resistance in *Enterobacter* species and *Proteus rettgeri (67,86,87)*. Clinical isolates of carbapenem-resistant *K. pneumoniae* expressing a plasmid-mediated AmpC β-lactamase combined with the loss of expression of two nonspecific porins have also been reported *(70)*.

The balance can also be tipped in favor of the β-lactamases by pumping the β-lactam molecules out of the periplasmic space. A full description of the different pump classes is beyond the scope of this chapter. The reader is referred for more detailed information to an excellent review *(88)*. Analysis of the *P. aeruginosa* genome suggests the presence of as many as 12 RND (resistant-nodulation–cell division) tripartite efflux pumps—pumps characterized by their broad substrate specificity (Table 85-4). Most of these pumps are minimally expressed at baseline, but their expression can be augmented by mutations that

TABLE 85-3

Susceptibility of Mutants of *Pseudomonas aeruginosa* M2297 to Carbapenems in Relation to their Expression of Chromosomal β-Lactamase and D2 Porin

Class I β-Lactamase[a]	*D2 porin*	*Imipenem*	*Ceftazidime*
Inducible[b]	+	1	1
Derepressed	+	1	32
Basal	+	0.12	1
Inducible	–	16	1
Derepressed	–	16	32
Basal	–	0.5	1

[a]The amount of β-lactamase produced by the inducible microorganisms depended on the presence and concentration of inducers. Derepressed mutants made the enzyme copiously regardless of induction, and basal mutants had only a trace level.
[b]Note that β-lactamase–inducible or derepressed microorganisms were less susceptible to imipenem than were the basal mutants. This protection gave clinical resistance (MIC ≥ 8 μg/mL) only when D2 porin was absent. Moreover, loss of the β-lactamase from the D2 porin-deficient microorganisms caused almost full restoration of imipenem susceptibility, confirming that resistance required both the enzyme and the impermeability. Ceftazidime, which is a labile weak inducer of the class I enzyme and which cannot traverse the pores formed by D2 porin, retained equal activity against β-lactamase-inducible and basal microorganisms irrespective of their D2 porin expression. However, its activity was lost against the derepressed mutants.
MIC, minimal inhibitory concentration.
(From Livermore DM. Carbapenemases: the next generation of β-lactamases. *ASM News* 1993;59:129–135.)

can be selected by exposure to antimicrobial agents. The degree of resistance conferred by pump activity alone is generally relatively modest, but their expression can augment the levels of resistance associated with more potent mechanisms of resistance, such as the expression of β-lactamase. One emblematic outbreak of infection caused by *P. aeruginosa* strains expressing the combination of the MexAB–OprM and MexEF–OprN RND pumps in association with β-lactamase expression and OMP reduction involved 67 patients and required cefepime–amikacin combinations (to which the strains were modestly susceptible) for successful treatment *(89)*.

TABLE 85-4

Resistance-Nodulation–Cell Division (RND) Pumps Characterized in *Pseudomonas aeruginosa* and their Substrate Specificities

RND Pump	*Substrates*
MexAB–OprM	Q, M, T, L, C, novobiocin, β-lactams except imipenem, aminoglycosides under low ionic strength conditions
MexCD–OprJ	Q, M, T, L, C, novobiocin, penicillins except carbenicillin and sulbenicillin, cephems except ceftazidime, flomoxef, meropenem
MexEF–OprN	Chloramphenicol, quinolones, trimethoprim, carbapenems
MexXY–OprM	Q, M, T, L, C, aminoglycosides, penicillins except carbenicillin and sulbenicillin, cephems except cefsulodin and ceftazidime, meropenem

Q,M,T,L,C, quinolones, macrolides, tetracyclines, lincomycin, chloramphenicol.

CYCLIC GLYCOPEPTIDES

The cyclic glycopeptides include vancomycin, teicoplanin (not available for clinical use in the United States), as well as a number of compounds such as avoparcin, ristocetin, actaplanin, and others that have not been used in human infections *(90)*. These antibiotics are highly active against gram-positive bacteria. Teicoplanin is more active against enterococci, whereas vancomycin tends to be more active against the staphylococci. Molecular weights of cyclic glycopeptides range from 1,200 to 2,000 Da. They all have a central-core heptapeptide, of which three amino acids are highly conserved. Some of these amino acids are crucial to the mode of action of this class. Other important glycopeptide components include the chlorine substituents and the sugars *(90)*.

Gram-positive bacteria, most commonly enterococci, expressing resistance to the cyclic glycopeptides have now been described throughout the world and are causes of significant morbidity and mortality in hospitalized patients *(91,92)*. The large majority of vancomycin-resistant enterococci (VRE) are *E. faecium* that also express resistance to ampicillin—the other major antimicrobial agent used to treat enterococcal infections *(46)*. They are also frequently resistant to fluoroquinolones, macrolides, penicillins, and to high levels of aminoglycosides *(93)*, rendering most therapies inactive. In the past few years, four new agents (quinupristin–dalfopristin, linezolid, daptomycin, tigecycline) have been introduced with *in vitro* activity against VRE, although only two (quinupristin–dalfopristin, linezolid) are approved by FDA for the treatment of VRE infections.

The cyclic glycopeptides bind to acyl-D-alanyl:D-alanine at the terminus of the pentapeptide of the peptidoglycan precursor *(90)*. Glycopeptides prevent cleavage of the terminal D-Ala that is required for establishing the peptide cross-link between adjacent peptide chains. Glycopeptide binding of D-Ala:D-Ala is also thought to cause a "steric" inhibition of transglycosylation, because the bulky antibiotic prevents the transglycosylase from interacting with the peptidoglycan. The vast majority of bacterial species synthesize peptidoglycan precursors terminating in D-Ala:D-Ala. The size exclusion limits of the porin proteins of gram-negative outer membranes preclude activity against gram-negative bacilli.

Enterococcal vancomycin resistance has been attributed to several different genetic clusters (*VanA–E*, *G*, and *L*) *(94–98)*. A seventh gene cluster conferring vancomycin resistance (*VanF*) has been described in the biopesticide *Paenibacillus popillae* but has not been found elsewhere *(99)*. The vancomycin resistance operons can be broadly separated into two groups: those that synthesize peptidoglycan precursors terminating in D-lactate (*vanA*, *B*, and *D*, hereafter referred to as the lactate operons) and those that synthesize precursors terminating in D-serine (*vanC*, *E*, *G*, and *L*, hereafter referred to as the serine operons). The lactate operons (specifically *vanA* and *vanB*) have spread widely throughout the world and are the predominant operons conferring acquired glycopeptide resistance. They are focused primarily in *E. faecium*. The serine operons are either intrinsic to some minor species of enterococci (*VanC* in *Enterococcus casseliflavus*, *Enterococcus flavescens*, and *Enterococcus gallinarum*) or have been described in only very rare isolates of *E. faecalis* (*vanE*, *G*, and *F*). *vanA* and *vanB* have been described in transposable elements *(21,24)* and are generally transferable to enterococcal recipients *in vitro*, whereas neither *vanD* nor the serine operons have been shown to be transferable. Structural comparisons of representative lactate and serine operons are shown in Figure 85-3.

Three functions of the different operons are essential to confer resistance to glycopeptides. First, the resistant substrate must be synthesized (Fig. 85-4). The *vanH* genes of the lactate operons encode a dehydrogenase that converts cellular pyruvate to D-lactate, whereas the *vanT* genes of the serine operons convert cellular L-serine to D-serine (hatched genes in Fig. 85-3). The second critical function is ligating the resistant substrate to D-alanine, forming the depsipeptide that is linked to the precursor UDP-muramyltripeptide to form the pentapeptide precursor. The ligase genes carry the designation specific to the different operons, *vanA*, *B*, *C*, *D*, *E*, or *G* (in black in Fig. 85-3). The third essential function is the depletion of the cellular pool of normal D-Ala–D-Ala dipeptide, ensuring that the precursors produced are almost exclusively of the resistant variety. In the lactate operons, the *vanX* gene encodes a dipeptidase that efficiently cleaves D-Ala–D-Ala, thereby ensuring incorporation of D-Ala–D-Lac into the pentapeptide precursors. The *vanY* gene of the lactate operons encodes a carboxypeptidase that cleaves the terminal D-Ala from normal pentapeptide precursor, depriving it of the bond breaking that provides the energy to make the peptide cross-link. The *vanY* gene is not essential for resistance but serves to amplify the level of resistance when it is expressed. The *vanC* operon encodes an enzyme with both dipeptidase and carboxypeptidase activity ($vanXY_C$). A homologous gene is also found in the *VanE* serine operon. The *vanG* operon, however, contains two open reading frames with *vanY* homology ($vanY_{G1}$, $vanY_{G2}$). It has been hypothesized that one or both of these enzymes may also possess dipeptidase activity *(97)*. The *vanA* operon contains a seventh gene, *vanZ*, that results in increased levels of teicoplanin resistance by an unknown mechanism *(100)*. The *vanB* operon contains a seventh gene, designated *vanW*, whose function is unknown at present *(101)*, but it is not required for resistance.

In all of the operons, expression of resistance is regulated by two-component regulatory systems encoded by the *vanS* and *vanR* genes (gray in Fig. 4) that are stimulated by the presence of one or more glycopeptides in the milieu *(101,102)*. VanR regulates the transcription of the

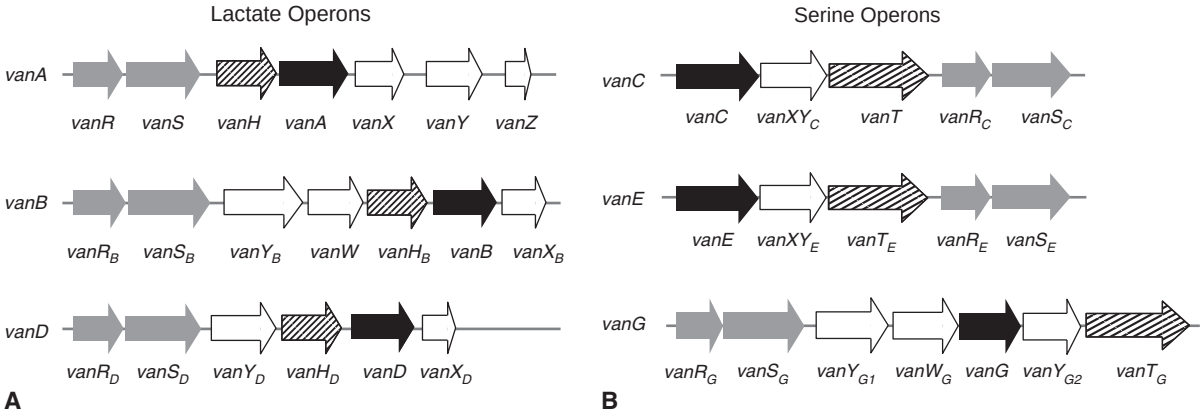

FIGURE 85-3 **A**: Depiction of lactate vancomycin resistance operons. Individual gene designations are found under the *a*rrows representing the extent and direction of transcription of the open reading frames. Gray represents regulatory genes. The hatched markings represent the dehydrogenase genes; the black, the ligase genes. (See text for specific functions of the different proteins.) B: Depiction of lactate vancomycin resistance operons. Individual gene designations are found under the arrows representing the extent and direction of transcription of the open reading frames. *Gray* represents regulatory genes. The *hatched markings* represent the serine racemase genes; the *black* the ligase genes. (See text for specific functions of the different proteins.)

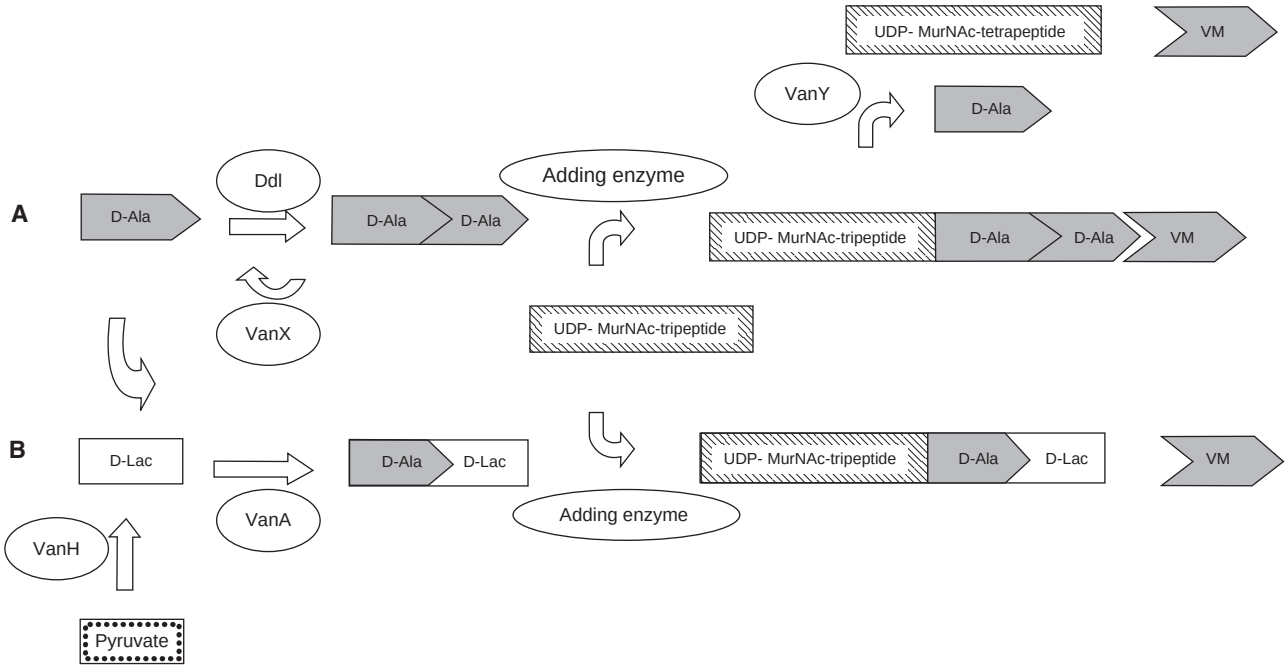

FIGURE 85-4 Schematic representation of peptidoglycan biosynthesis in glycopeptide-susceptible **(A)** and glycopeptide-resistant (VanA-type) **(B)** cells. The end result in vancomycin-resistant cells is peptidoglycan precursors terminating in D-lactate or D-serine, which bind vancomycin poorly. (From Gold HS. Vancomycin-resistant enterococci: mechanisms and clinical observations. *Clin Infect Dis* 2001;33(2):210–219).

polycistronic message that encodes the three proteins essential for vancomycin resistance. Depending on its phosphorylation state, VanR can serve as either a repressor or activator of transcription. The phosphorylation state of VanR is determined by VanS, the transmembrane sensor component of the two-component system. *vanA* strains are resistant to both vancomycin and teicoplanin, because the presence of both antibiotics induces expression of the *vanA* operon. *vanB* strains remain susceptible to teicoplanin because the operon is not induced by the presence of teicoplanin. Teicoplanin is not a viable therapeutic alternative, however, since mutations resulting in either constitutive expression of the operon or sensitivity of $vanS_B$ to induction by teicoplanin are frequent enough to lead to the emergence of resistance on therapy *(99)*.

Both *vanA* and *vanB* operons have been shown to be mobile. The *vanA* operon is characteristically encoded by a ca. 10-kb Tn*3*-family transposon designated Tn*1546 (17)*. This transposon has been found on plasmids, and it is presumed that the transfer of conjugative plasmids explains most of the genetic variability observed in *vanA* clinical isolates. *vanB* is characteristically encoded in the bacterial chromosome, although reports of plasmid-mediated *vanB*-type resistance have been published *(103,104)*. Transfer of *vanB*-type resistance to enterococcal recipients *in vitro* has been observed and is usually accompanied by the acquisition of large segments of chromosomal DNA *(105)*. Two transposons or transposon-like *vanB* elements have been described. Tn*1547* is a composite transposon whose mobility is conferred by flanking copies of IS*256*-related IS elements *(106)*. Tn*5382* (and its identical relative Tn*1549*) is a 33-kb transposon with similarities to the conjugative transposons seen frequently in many species of gram-positive cocci *(22)*. The contribution of these various transposons to the genetic variability observed in *vanB*-type enterococci is probably substantial.

Soon after the discovery of the vancomycin resistance operons in enterococci, *in vitro* studies suggested that the *vanA* operon could be transferred and expressed in *S. aureus*. As of early 2010, nine total cases of so-termed vancomycin-resistant *S. aureus* have been identified in the United States, with an additional two cases reported from India and Iran (107). Not all of these cases have undergone extensive genetic investigation. Fortunately, neither intra- nor interhospital spread of any of these microorganisms has been documented.

Mutational resistance to vancomycin in *S. aureus* has been sporadically reported over the past few years. In many cases, these strains have been isolated from patients (generally dialysis patients) who have been treated with long-term vancomycin therapy. Resistance is associated with enlargement of the staphylococcal cell wall, and the cell wall itself contains large numbers of unlinked precursors, which can potentially serve as targets for vancomycin binding (*108,*109). It has been postulated that resistance results from vancomycin being sequestered within the enlarged cell wall (soaked up like a sponge), preventing achievement of adequate concentrations of vancomycin at the cell membrane, where precursors are added to the growing peptidoglycan. It is likely that this mechanism of resistance is favored only in the setting of persistent and significant vancomycin exposure, since spread to other patients has not been documented and reversion to normal (susceptible) phenotype commonly occurs when *in vitro* selective pressure by vancomycin is removed. Animal data does suggest, however, that despite marginal MICs (*ca*. 8–16 μg/mL), this type of resistance will result in vancomycin treatment failure *(110)*.

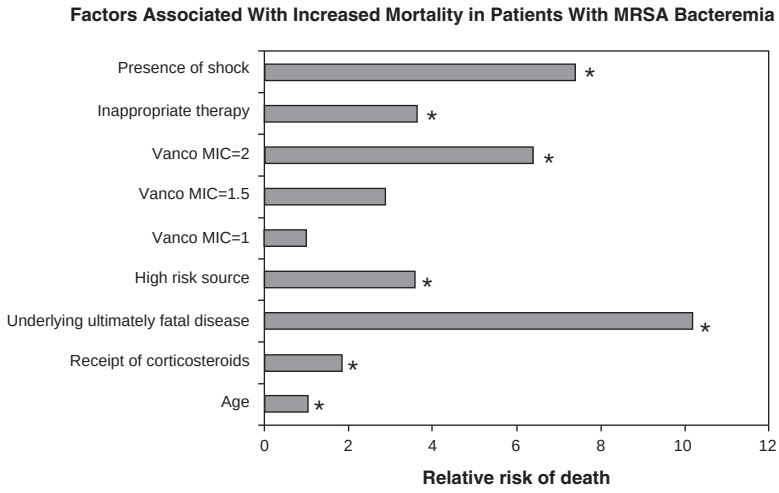

FIGURE 85-5 Factors associated with increased mortality in patients with MRSA bacteremia. * = $p \leq .05$. Note that vancomycin MIC of ≥2 is associated with nearly a sevenfold increase in the relative risk of mortality when empirical vancomycin therapy is used. (Adapted from Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin MIC on the treatment of methicillin-resistant *S. aureus* bacteremia. *Clin Infect Dis* 2008;46(2):193–200.)

A more subtle type of resistance to glycopeptides in *S. aureus* is perhaps best termed as "MIC creep." In recent years, some investigators have noted that, on average, MICs for vancomycin in staphylococci have been increasing. Some strains exhibit MICs that are 2 or 4 μg/mL, which were still within the susceptible range until both CLSI and EUCAST recently lowered their susceptibility breakpoints to ≤2. The rationale for this lowering of the breakpoints is the accumulating evidence from both laboratory and clinical studies that strains with vancomycin MICs >2 μg/mL respond poorly to vancomycin therapy (Fig. 85-5) *(111,182)*. These clinical and laboratory data are supported by pharmacodynamic estimates suggesting that appropriate targets cannot be reached with safe vancomycin doses for strains that exhibit that level of susceptibility.

AMINOGLYCOSIDES

Structure and Mechanism of Action

The aminoglycosides are made of three amino sugars in glycosidic linkage. As such, they are polycationic compounds. They are divided into two classes: the streptidine class, of which streptomycin is the only member in clinical use, and the 2-deoxystreptamine class, which includes all other clinically used aminoglycosides. Uptake of aminoglycosides into bacterial cells is via active transport through the cytoplasmic membrane. The intracellular target of all aminoglycosides is the 30S subunit of the ribosome. For streptomycin, only a single ribosomal-binding site exists, whereas for the others, multiple binding sites are available. In gram-negative microorganisms, aminoglycoside uptake probably occurs via a two-stage process in which the cationic antibiotic displaces magnesium ions linking lipid A subunits. This displacement results in disruption of the outer membrane and diffusion of the antibiotic into the periplasmic space. It seems likely that, in addition to its activity at the ribosome, disruption of the cytoplasmic membrane also plays a role in the activity of these agents. Binding to the 30S ribosomal subunit results in extensive translational misreading and synthesis of abnormal proteins, many of which integrate into the membrane, resulting in further disintegration. It is the sum of these effects that is thought to lead to the bactericidal activity of the aminoglycosides.

Mechanisms of Resistance

Simple mutation of genes encoding ribosomal proteins can result in streptomycin resistance, since only a single binding site exists for this antibiotic. Ribosomally resistant mutants have been described clinically, primarily in enterococci and mycobacteria. These mutants remain susceptible to the other aminoglycosides. Mutants with altered membrane transport (the so-called small colony–formers) can also be resistant to aminoglycosides. These cells have altered membrane proton motive force and are unable to transport aminoglycosides across the cytoplasmic membrane. Such mutants are less virulent than their wild-type parents *(112)*.

The primary mechanism of bacterial resistance to aminoglycosides is enzymatic modification of the antibiotic *(113)* (Fig. 85-6). Such chemical modifications prevent binding of the aminoglycoside to the ribosome and may also decrease transport. Three major classes of modifying enzymes have been described that depend on the particular modification involved: phosphorylases, adenyl transferases, and acetyl transferases (Table 85-5). Resistance to all aminoglycosides is achievable by a combination of different enzymes.

The emergence of enzyme-mediated resistance to aminoglycosides in enterococci is a significant clinical problem. Because of their intrinsic tolerance to the bactericidal activity of all cell wall–active agents, effective treatment of serious enterococcal infections requires the synergistically bactericidal combination of a cell wall–active agent and an aminoglycoside. Since the most common genes encoding aminoglycoside resistance in enterococci were derived from the staphylococci, these two genera will be discussed together. Gentamicin resistance in strains of *S. aureus* and *Staphylococcus epidermidis* first appeared in the United States and elsewhere in the mid-1970s *(114)*. In 1979, the first case of high-level resistance to gentamicin, which results in resistance to synergistic bactericidal activity in enterococci, was reported (115). Resistance to aminoglycosides has spread widely in both genera since the first reports.

High-level resistance to gentamicin in both staphylococci and enterococci results most commonly from modification of the antibiotic by the 6′-acetyltransferase-2″phosph otransferase (6′-AAC-2″-APH) bifunctional enzyme, encoded

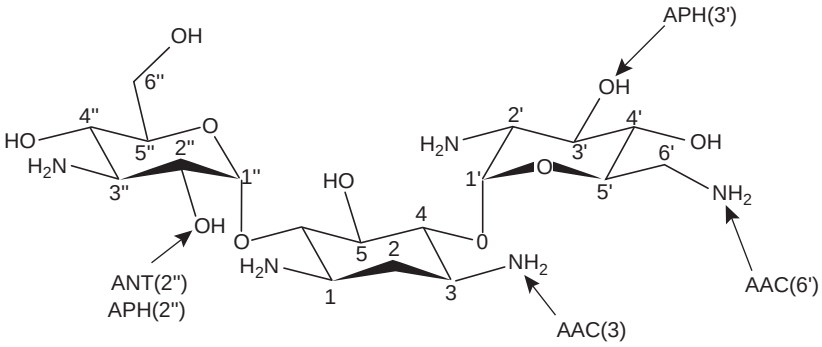

FIGURE 85-6 Prototypic aminoglycoside showing sites available for modification and modifications that have been shown to occur. (From Kotra LP, Haddad J, Mobashery S. Aminoglycosides: perspectives on mechanisms of action and resistance and strategies to counter resistance. *Antimicrob Agents Chemother* 2000;44(12):3249–3256).

by the *aacA–aphD* resistance gene *(116)*. The 6′-AAC component of the bifunctional enzyme confers resistance to amikacin, kanamycin, and tobramycin, whereas the 2″-APH component is primarily responsible for resistance to gentamicin and netilmicin. All strains that possess this gene are resistant to all of the above-mentioned aminoglycosides. Streptomycin, which is inactivated by a separate enzyme, is the single clinically available aminoglycoside not inactivated by the bifunctional enzyme. The nucleotide sequences of the genes responsible for the production of the bifunctional enzyme are identical in *S. aureus* and *E. faecalis*, and probably in *E. faecium*, *S. epidermidis*, and *Streptococcus agalactiae* as well *(116–121)*. These genes are often integrated into conjugative plasmids in both staphylococci and enterococci. In addition, the bifunctional enzyme gene has been found integrated into similar transposons in *S. aureus* (Tn*4001*), *S. epidermidis* (Tn*4031*), and *E. faecalis* (Tn*5281*) *(122–124)*. Two additional genes that confer resistance to aminoglycosides in enterococci have been described *(125)*. Unlike the bifunctional enzyme, these phosphotransferases do not confer resistance to a wide range of aminoglycosides. In addition, they may confer only relatively low levels of resistance (256 μg/mL) when tested by standard techniques, and therefore, may be missed in screening assays designed to detect the more common enzymes. Despite these lower levels of resistance, they do confer a resistance to cell wall–active agent–aminoglycoside synergism, so that they may prove to be important for the treatment of endocarditis.

TABLE 85-5

Aminoglycoside-Modifying Enzymes

Acetyltransferases	*Phosphotransferases*	*Adenyltransferases*
AAC(1)	APH(2″)-I	ANT(2″)-I
AAC(2′)-I	APH(3′)-I	ANT(3″)-I
AAC(3)-I	APH(3′)-III	ANT(4′)-I
AAC(3)-II	APH(3′)-IV	ANT(4′)-II
AAC(3)-III	APH(3′)-V	ANT(6)-I
AAC(3)-IV	APH(3′)-VI	ANT(9)-I
AAC(3)-VI	APH(3′)-VII	—
AAC(3)-VII	APH(3″)-I	—
AAC(3′)-VIII	APH(6)-I	—
AAC(3)-IX	APH(4)-I	—
AAC(3)-X	APH(7″)	—
AAC(6′)-I	APH(9)	—
AAC(6′)-II	—	—
AAC(6′)-APH(2″)	—	—
AAC(6)-III	—	—
AAC(6)-IV	—	—

(From Rather PN. Origins of aminoglycoside modifying enzymes. *Drug Resist Update* 1998;1:285–291.)

High-level gentamicin resistance in enterococcal isolates has spread rapidly in some hospitals, with one center reporting 55% of healthcare-associated enterococcal isolates resistant to gentamicin *(7)*. Gentamicin-resistant enterococci appear to be transmitted in the hospital setting on the hands of caregivers. Measures undertaken to limit such transmission have proven effective in containing outbreaks of infection and colonization with these microorganisms *(126)*. A growing body of evidence suggests that serious infection with these strains is associated with a worse prognosis than is associated with infections caused by susceptible isolates *(127–129)*. Episodes of failure (resulting in death or requiring surgical intervention for cure) in the treatment of enterococcal endocarditis caused by gentamicin-resistant strains have been reported *(119,128)*. Fortunately, most enterococcal infections can be successfully treated with a single agent. For more serious infections, it is essential to test all enterococcal isolates for high-level resistance to both gentamicin and streptomycin. Depending on the center, anywhere from 0% to 45% of enterococcal strains exhibiting high-level gentamicin resistance are reported to remain susceptible to streptomycin *(120,127)*. Combinations of cell wall–active agents and streptomycin should be effective in the treatment of strains exhibiting high-level gentamicin resistance but lacking high-level resistance to streptomycin, and vice versa *(119,121)*. At present, there is no reliable bactericidal combination of antibiotics against strains exhibiting high-level resistance to both gentamicin and streptomycin.

In gram-negative microorganisms, aminoglycoside-modifying enzymes are the most important mechanisms of resistance. In general, genes encoding such enzymes are carried on plasmids or transposons and are expressed constitutively. However, in the case of *S. marcescens* and *Providencia stuartii*, aminoglycoside acetyltransferases are normally encoded by chromosomal genes but are not well expressed *(130,131)*. It appears that, in these species, the chromosomally encoded acetyltransferases represent intrinsic housekeeping genes that are responsible for acetylating peptidoglycan *(132)*. Aminoglycosides bear structural resemblance to peptidoglycan and are acetylated as well. Normally these enzymes are produced in amounts sufficient to acetylate peptidoglycan but not to result in

resistance. Mutants that express these enzymes at high levels can be easily selected and probably account for many of the aminoglycoside-resistant strains of these species.

In recent years, a significant number of plasmid-encoded ribosomal methylase genes have been described as causes of aminoglycoside resistance in gram-negative bacteria. These enzymes methylate the ribosome, preventing aminoglycoside binding to the target sites. They have been described from both human and animal-derived isolates *(133)*.

Gram-negative bacteria also employ efflux pumps to assist with aminoglycoside resistance. In *P. aeruginosa*, the MexXY–OprM system is most commonly implicated in aminoglycoside efflux *(134)*, but MexAB–OprM and an analog of the *E. coli* small multidrug resistance type pump *emrE* (*emrE*$_{Pae}$) may also be involved *(135)*. The MexAB–OprM pump effluxes aminoglycosides *in vitro* but only when tested in low ionic strength media. An RND pump (AdeABC) has also been implicated in aminoglycoside resistance in *A. baumannii (136)*.

RESISTANCE TO THE FLUOROQUINOLONES

Structure and Mechanism of Action

The quinolone class of antibiotics can be historically traced to nalidixic acid. These antibiotics are potent inhibitors of cellular topoisomerases—enzymes required for winding and unwinding supercoiled, double-stranded DNA *(137)*. Quinolone antibiotics act by inhibiting DNA synthesis. Their targets are two Type 2 topoisomerases: DNA gyrase and topoisomerase IV. These two enzymes both exist as tetramers composed of different subunits (GyrA and GyrB of DNA gyrase; ParC and ParE of topoisomerase IV). DNA gyrase maintains negative supercoiling of DNA, whereas topoisomerase IV separates interlocked DNA strands formed during replication, facilitating segregation into daughter cells. Fluoroquinolones bind to the topoisomerase–DNA complexes and disrupt cellular processes involving DNA (replication fork, transcription of RNA, DNA helicase) *(138–140)*. The end result is cellular death by unclear mechanisms.

Fluoroquinolone affinity for the two targets varies with the compound, explaining to some extent differing potencies. The enzyme for which a particular fluoroquinolone has the greatest affinity is referred to as the primary target *(141–143)*. It is generally but not universally true that DNA gyrase is the primary target of fluoroquinolones in gram-negative bacteria, whereas topoisomerase IV is the primary target in gram-positive bacteria.

Alterations in Target Enzymes The most common mechanism of fluoroquinolone resistance is point mutations of the topoisomerase genes resulting in structural alterations in the topoisomerase enzymes. In *gyrA* and *parC*, resistance-associated mutations are often localized to a region in the enzyme that contains the active site tyrosine covalently linked to the broken DNA strand. This 130 base pair (bp) region of *gyrA* has been referred to as the quinolone-resistance-determining region (QRDR) *(144)*. X-ray crystallographic studies of a fragment of the *gyrA* enzyme suggest that QRDR mutations are clustered in three dimensions, supporting the hypothesis that this region constitutes a part of the quinolone binding site *(145)*. Frequent sites for resistance-associated mutations are serine 83 and aspartate 87 of DNA gyrase and serine 79 and aspartate 83 of *parC (146)*.

The level of resistance conferred by a point mutation in the primary target enzyme depends on the change of enzyme affinity created by the mutation and the affinity of the specific fluoroquinolone for the secondary target. As such, fluoroquinolones exhibiting strong affinity for both target enzymes may be less likely to promote the emergence of resistant strains in the clinical setting, since the activity against the secondary target may be enough to inhibit the bacterium even in the presence of primary target mutation. Consistent with this hypothesis, fluoroquinolone-species combinations for which single mutations result in significantly higher MICs (such as ciprofloxacin and *S. aureus* or *P. aeruginosa*) have readily selected resistant mutants in the clinical setting *(147)*.

Most highly resistant strains exhibit more than one mutation in both the *gyrA* and *parC* enzymes. It is noteworthy, in this context, that fluoroquinolone resistance conferred by enzyme mutations is, to some degree, a class resistance in which the activity of all fluoroquinolones is impacted. Thus, although single-point mutations conferring resistance to one fluoroquinolone may not yield MICs with clinically significant levels of resistance for another, the MICs for all fluoroquinolone will inevitably be increased. These preexisting mutations may then serve as the template to select additional mutations that result in more broad-spectrum fluoroquinolone resistance. Some experts suggest that this phenomenon should prompt clinicians to always use the most potent fluoroquinolone when treating infections, to prevent the emergence of resistance *(148)*. Some degree of skepticism about such recommendations is warranted, since potency varies with the microorganism (moxifloxacin may be more potent against *S. pneumoniae* than ciprofloxacin, but the reverse is true for *P. aeruginosa*), and fluoroquinolone concentrations achievable in many areas of the body (such as the gastrointestinal tract) may not approximate those needed to prevent the emergence of resistance. Such recommendations, therefore, should be tested in controlled clinical trials before they are widely adopted.

Mutations in *gyrB* and *parE* are less common than in *gyrA* and *parC* and cluster in the midportion of the subunit *(137)*. The true impact of these mutations on the expression of resistance remains to be determined.

Resistance Due to Decreased Intracellular Activity, Accumulation, or Extrusion Fluoroquinolones penetrate the outer membrane of gram-negative bacteria through porins, and so the absence of specific porins may theoretically impact the susceptibility. However, diffusion through outer and cytoplasmic membranes is generally sufficient to retain activity against strains solely lacking porins *(149)*. More important in reducing intracellular accumulation of fluoroquinolones is the expression of multidrug resistance pumps *(146)*. All of the pumps described above for *P. aeruginosa* have been shown to efflux fluoroquinolone antimicrobial agents *(150,151)*. A plasmid-mediated fluoroquinolone

efflux pump gene (*qepA*) has also been described, coexisting on a plasmid harboring resistance determinants to aminoglycosides, β-lactams, and other antibiotics *(152)*. By themselves, pumps generally confer only a low level of resistance to fluoroquinolones. However, their expression may amplify the level of resistance conferred by point mutations within the topoisomerase genes. By so doing, they may increase the risk that a given fluoroquinolone will select out resistant mutants through single-point mutations.

Transferable, plasmid-mediated resistance to fluoroquinolones through a gyrase protection mechanism has also been described (153,*154*). The genes conferring this resistance have been designated *qnr*. At least five similar proteins have now been described (QnrS, QnrB, QnrC, and QnrD), and this plasmid-borne mechanism of resistance to fluoroquinolones has now achieved worldwide spread *(155)*. By 2006, 20% of ceftazidime-resistant *K. pneumoniae* and 31% of ceftazidime-resistant *Enterobacter* species in a collection were found to possess at least one of the three then-known *qnr* genes *(156)*.

Enzymatic Modification of the Antibiotic The prevalence of a plasmid-associated gene encoding a variant of a common aminoglycoside acetyltransferase (*aac(6′)-Ib*-cr) was found to be over 50% in a collection of 78 fluoroquinolone-resistant isolates of *E. coli* from Shanghai (157). While acetylation (and inhibition) of ciprofloxacin was found to occur at the amino nitrogen on its piperazinyl substituent in isolates possessing this gene, this phenomenon was not observed for fluoroquinolones that do not possess an unsubstituted piperazinyl group. This mechanism of resistance, which may indeed be far more common than *qnr*-mediated resistance, can coexist with the latter as well as with topoisomerase mutations. It is likely that high-level resistance among fluoroquinolone-nonsusceptible microorganisms often results from a combination of the mechanisms described above.

Resistance to Newer Antimicrobial Agents

The emergence and spread of multiresistant enterococci in the past decade, accompanied by the inexorable increase in the prevalence of MRSA, has amplified the importance of finding new agents with clinically important activity against resistant gram-positive cocci. In contrast to the rather dismal situation with regard to novel antimicrobial agents directed at gram-negative pathogens, fully five such agents active against gram-positive bacteria have been licensed in the past decade or so and are discussed below. Indeed, the first four agents discussed exhibit activity *solely* against gram-positive pathogens.

Quinupristin–dalfopristin is a combination of two pristinamycins (one of the streptogramin A class, the other a streptogramin B) that have synergistic activity against *E. faecium* (although they are ineffective against *E. faecalis*) and *S. aureus*. The overall use of this combination has been limited by considerations of cost and toxicities and by the need to administer through a central venous catheter. Despite its limited use, two forms of resistance have already been noted in *E. faecium*. The first is a low-level resistance whose mechanism remains to be fully defined but which may involve activation of an efflux pump. Data from a recent clinical study reported that 21% of *E. faecium* isolated exhibited such low-level resistance *(92)*. This type of resistance has not been shown to be transferable, and its impact on therapy remains to be determined. High-level resistance to these mixtures can result from resistance to streptogramin A alone and was first described in staphylococci conferred by genes encoding streptogramin A acetyltransferases [*vat*(A), *vat*(B), and *vat*(C)] or adenosine triphosphate–binding efflux genes [*vga*(A), *vga*(B)]. Two acetyltransferase genes have now been described that confer resistance to quinupristin–dalfopristin in *E. faecium*—*vat*(D) [previously *sat*(A)] and *vat*(E) [previously *sat*(G)]. In most cases, these resistance genes are found along with an *erm* resistance gene *(158)*, suggesting that resistance to both streptogramin A and B may be necessary to confer clinically significant levels of resistance to quinupristin–dalfopristin in *E. faecium*. These genes have been found on transferable plasmids, suggesting that the potential for spread is significant.

Linezolid is the first licensed member of the oxazolidone class of antibiotics. It is active against most multiresistant gram-positive cocci including multiresistant enterococci and *S. aureus*. Linezolid acts by binding to the conglomeration of ribosomes, messenger RNA, and transfer RNA, known as the protein synthesis initiation complex. Resistance to linezolid has been associated with point mutations in the 23S ribosomal RNA (rRNA) subunit *(159)*. The most common mutation found in resistant isolates of staphylococci and enterococci has been a G → U change at position 2576 (*E. coli* numbering scheme). The degree of resistance seen in enterococci is related to the percentage of rRNA genes that have this mutation (160). This type of resistance has not been transferable in any of the cases examined to date. However, the known transferability of enterococci themselves within the healthcare setting creates concern that these strains could become prevalent. An outbreak of such strains in a liver transplant unit has been reported *(161)*. A more recent mechanism of resistance is encoded by the *cfr* gene, originally described as a chloramphenicol resistance mechanism in *Staphylococcus sciuri (162)*. The enzyme encoded by this gene provides posttranscriptional methylation of the 23S rRNA at position A2503 and affects the binding of at least four antimicrobial classes, leading to a multidrug-resistant phenotype. In 2008, the first report of *cfr*-mediated resistance to linezolid in staphylococcal clinical isolates (one *S. aureus*, one *S. epidermidis*) in humans in the United States was published *(163)*. The gene was found to be plasmid-borne in both isolates. This report was followed by other case reports, including one describing a clinical outbreak among 12 patients in a tertiary-care hospital in Spain (164), where clonally related strains of LRSA (linezolid-resistant *S. aureus*) were isolated from 11/12 patients, and all LRSA isolates possessed the *cfr* gene, whereas the G2675T substitution was identified in none. This outbreak was the first reported worldwide outbreak of LRSA and certainly the first outbreak depicting *cfr* gene–mediated linezolid resistance. The clinical consequences of this mechanism of resistance are only beginning to be described but could be severe. Although dissemination of *S. aureus* possessing this mechanism of resistance has thus far appeared to be secondary to clonal spread of a dominant isolate, the

occurrence of genetic transfer of resistance—multidrug resistance, at that—remains a possibility, given that the *cfr* gene is plasmid-borne.

Daptomycin is the first drug in the lipopeptide class of antibiotics to be licensed for therapeutic use in the United States. In 2003, daptomycin was approved for the treatment of complicated skin and skin structure infections; subsequent approvals were obtained for the treatment of *S. aureus* bacteremia *(165)*. The bactericidal action of this antimicrobial agent is confined to gram-positive microorganisms, including clinically important pathogens such as MRSA, VRE, coagulase-negative staphylococci, and penicillin-resistant pneumococci, and systemic delivery is achieved solely via the parenteral route. Daptomycin is a "natural" product, derived from the fermentation of *Streptomyces roseosporus*, and appears to act by forming pores in the bacterial membrane in the presence of physiological concentrations of calcium, resulting in ion leakage and cell death. Friedman et al. *(166)* have reported an accumulation of a variety of mutations in disparate genes (a lysylphosphatidylglycerol synthetase, a histidine kinase, and subunits of RNA polymerase) as being associated with resistance to this antibiotic. Muthaiyan et al. *(167)* have reported the results of transcriptional profiling studies of the action of daptomycin on *S. aureus*, arguably the most clinically significant microorganism treated with this drug. Induction of a complex cell wall stress stimulon (including genes encoding proteins involved in peptidoglycan biosynthesis and currently defined as genes altered in their expression by cell wall–active agents such as oxacillin, D-cycloserine, and bacitracin, as well as those shown to be controlled by the two-component regulator VraSR upon vancomycin challenge of *S. aureus*) was demonstrated with exposure to daptomycin, suggesting that the mode of action of this antibiotic does include the inhibition of cell wall synthesis. However, comparison of the daptomycin transcriptosome with the membrane-active agents carbonyl cyanide *m*-chlorophenylhydrazone and nisin also suggested a membrane-depolarizing action of daptomycin. The latter is consistent with previous studies of this agent, where the bactericidal activity of daptomycin was correlated with bacterial membrane depolarization *(168)*. The relative contributions of each of these potential mechanisms of action to the activity of this drug against any particular isolate have not yet been fully elucidated. When examining well-characterized isolates of MRSA rendered resistant to daptomycin via serial passage in sublethal concentrations of the antibiotic, resistant strains have demonstrated decreased cell membrane fluidity, increased synthesis, and positional shifting of total lysylphosphatidylglycerol and increased expression of a gene associated with the latter phenotype *(169)*. Additionally, the expression of the *dlt* operon, which increases positive surface charge, was increased in resistant isolates. Since daptomycin is itself a cationic antimicrobial peptide, this might be postulated to decrease binding; however, relative net positive surface charge was not increased in the mutants despite increases in the *dlt* operon, suggesting that a simple charge repulsion mechanism could not entirely explain the daptomycin-resistant phenotype. Most interestingly, daptomycin-resistant mutants demonstrated a thickened cell wall, resulting in a parallel increase in MICs to the glycopeptide antibiotic vancomycin. Although not universal *(170)*, these latter findings of cell-wall thickening have been substantiated elsewhere *(171)*, suggesting an explanation for the often observed—and clinically challenging—co-resistance to daptomycin and vancomycin manifested in clinical isolates of MRSA. Finally, although not a classic mechanism of resistance, it must be noted that the use of daptomycin in patients with pulmonary infections caused by gram-positive agents has been seriously compromised by the propensity of this drug to bind to pulmonary surfactant. In *in vitro* test-tube studies with bovine-derived surfactant, daptomycin showed a 16-fold to 32-fold loss of potency against *S. aureus* in 1% surfactant and a >100-fold loss in a 10% surfactant media (172). Insertion of daptomycin into surfactant aggregates likely represents the mechanism of inhibition of the antibiotic in this scenario. Daptomycin is, thus, not recommended for the treatment of pneumonia.

Telavancin, the newest antimicrobial agent in the gram-positive arsenal, is a lipoglycopeptide antibiotic approved for clinical use earlier this year. Telavancin is a semisynthetic derivative of vancomycin, possessing a hydrophobic side chain appended to the vancosamine sugar *(173)*, as well as another hydrophilic group. The mechanism of action of this drug involves the inhibition of peptidoglycan synthesis via binding to D-Ala–D-Ala-containing residues of peptidoglycan intermediates, similar to the mechanism of action of vancomycin; however, unlike vancomycin, a second mechanism of action may involve perturbations of bacterial membrane function *(173,174)*. Lunde et al. have demonstrated in flow cytometry assays that telavancin caused membrane depolarization (without cell lysis) in phenotypically diverse, actively growing *S. aureus* cultures that was both time- and concentration-dependent. This depolarization was found to be linked to interaction with the cell wall precursor lipid II. As yet, there is a paucity of literature regarding resistance to telavancin among gram-positive bacteria, although resistant microorganisms have been created in the laboratory via serial passage through antibiotics. As is the case with vancomycin and teicoplanin, telavancin induces the *vanA* operon in *vanA*-containing strains of enterococci, thus rendering these microorganisms intrinsically resistant; similar to the antibiotic teicoplanin, induction in *vanB* strains does not take place to the same degree *(175)*. Resistance in *S. aureus* appears as yet to be rare.

Tigecycline is a broad-spectrum antimicrobial alternative for treating infections due to several resistant pathogens, including MRSA and ESBL-producing *K. pneumoniae*. Tigecycline's broad spectrum is due to its resistance to the commonly encountered tetracycline-resistance efflux or ribosomal protection mechanisms. *P. aeruginosa* and *Proteus* spp. are resistant to tigecycline because they express efflux pumps that effectively extrude the antibiotic *(176)*. Resistance to tigecycline in other gram-negative species has also been reported in association with the activation of normally repressed AcrAB-type RND efflux pumps *(177)*.

CONCLUSION

Despite our best efforts, the elusive promise of the "perfect" antibiotic has not been realized. Experience with the use of antibiotics in the clinical setting has taught us that

resistance often emerges soon after the clinical introduction of any antibiotic, and in some cases, these resistance determinants spread rapidly once they are present in human pathogens. Resistance may be promoted by the excessive and injudicious use of antimicrobial agents, as well as by poor infection control practices employed in the hospital, day-care centers, and the home. Guidelines for the prevention of resistance in hospitals have been issued jointly by the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (178). The guidelines suggest a number of strategies including some aimed at testing the hypotheses and proposals contained within the document. We hope that these suggestions will be implemented, so that optimal programs based on data can be introduced.

Since it is our behavior and practices that have amplified the problem of resistance, it stands to reason that altering these behavior patterns may contribute to its control or eradication. A detailed understanding of the mechanisms by which resistance emerges within and spreads among bacterial species is an essential component of any strategy to control antimicrobial resistance in the hospital setting. Intelligent, mechanism-based strategies employing an appropriate mix of infection and antibiotic control offer the best hope for controlling the spread of resistance as well as for the conservation of important and increasingly scarce economic resources.

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CHAPTER 86

Antimicrobial Resistance and Healthcare-Associated Infections

Gary L. French

HOSPITAL PATHOGENS TEND TO BE ANTIMICROBIAL RESISTANT AND MULTIPLY RESISTANT

To be successful as hospital pathogens, healthcare-associated bacteria must be able to establish themselves and survive in the hospital environment, colonize the mucosa and skin of patients and staff members, survive on various surfaces during patient-to-patient transmission, and resist antibiotic and sometimes antiseptic therapy (1). Inherent multiple antibiotic resistance, and the ability to acquire additional genetic resistance factors in the face of increasing use of antibiotics, are important for survival. Numerous reports show that microorganisms causing healthcare-associated infection and colonizing patients and healthcare workers are more antibiotic-resistant than those in the community and that, within the hospital, resistance rates are high in units (such as intensive care, hematology and oncology, and renal and liver units) where antimicrobial use is highest. Indeed, risk factors for colonization and infection with multidrug-resistant (MDR) pathogens include prolonged hospital stay, prior antimicrobial therapy, and admission to intensive care units (ICUs).

EMERGENCE OF ANTIBIOTIC RESISTANCE IN HEALTHCARE-ASSOCIATED PATHOGENS

Innate and Acquired Antimicrobial Resistance

In his initial studies in 1929, Fleming noted that penicillin was highly active against some microorganisms, especially the gram-positive staphylococci and streptococci, but inactive against others, especially the gram-negative coliforms *(2)*. This phenomenon of innate susceptibility or resistance to different agents among different bacterial species continued to be seen with broad-spectrum antimicrobials. For example, *Klebsiella pneumoniae* is usually resistant to ampicillin; *Enterobacter* spp. to ampicillin and many cephalosporins; enterococci to cephalosporins and quinolones; and *Pseudomonas aeruginosa* to pencilin, ampicillin, cephalosporins, and other groups. The β-hemolytic streptococci remain susceptible to penicillin and the anaerobes to metronidazole, but increasing numbers of isolates of many other species have acquired resistance to agents to which they were initially innately susceptible.

Free-living environmental bacteria are of low virulence for humans but are often inherently resistant to common antimicrobials. This is probably because they are adapted to live in soil and water where they are exposed to naturally occurring antimicrobial substances. Environmental species with inherent antimicrobial resistance include various *Pseudomonas* spp., *Acinetobacter, Burkholderia, Stenotrophomonas,* and *Ralstonia*. Although they rarely infect healthy individuals, these microorganisms may contaminate hospital environments and equipment and then colonize and infect compromised patients, producing antibiotic-resistant opportunistic infection.

Naturally sensitive bacteria may acquire antibiotic resistance caused by a number of mechanisms, with the most common probably being the production of drug-destroying enzymes (*3,*4). This is the typical mechanism by which microorganisms such as *Staphylococcus aureus* and *Escherichia coli* and other gram-negative bacteria acquire resistance to ampicillin, aminoglycosides, and chloramphenicol. There may be alterations in the permeability of the cell wall, preventing antibiotics from reaching their target sites, or there may be increased antibiotic efflux, resulting in the same effect. This is the common mechanism of tetracycline resistance and is one of the ways in which microorganisms such as *P. aeruginosa* may acquire broad-range resistance to several aminoglycosides and other agents simultaneously. Alterations in target sites prevent antibiotics from binding to their sites of action. Changes in the affinities of penicillin-binding proteins result in methicillin resistance in staphylococci, penicillin resistance in pneumococci, and ampicillin resistance in enterococci. Alterations in ribosomal-binding sites may produce acquired resistance to rifampin, fusidic acid and the macrolides, and alteration of DNA gyrase is the common mechanism of quinolone resistance. Alterations (or substitutions) of enzymes in metabolic pathways are responsible for resistance to sulfonamides and trimethoprim that block bacterial folate metabolism.

Acquired resistance may emerge by genetic mutation, which occurs relatively frequently in rapidly multiplying microorganisms or by acquisition of resistance genes

from other bacteria. The horizontal spread of resistance genes among bacteria by plasmid transfer is sometimes called "infectious resistance." The transmission of DNA between bacteria may occur by bacteriophage transduction (as in the transmission of penicillinase-mediated penicillin-resistance in *S. aureus*), conjugation (the common mechanism of transfer between gram-negative species), or transformation. Transformation was previously regarded as a relatively unimportant mechanism of resistance transfer in clinical bacteria, but there is increasing evidence for its importance in the emergence of resistance in gram-positive microorganisms. Although the host range of many plasmids is restricted and gram-positive and gram-negative microorganisms tend not to share resistance genes, plasmids can be exchanged between different bacterial species. For example, most ampicillin resistance in *Haemophilus influenzae* is mediated by a β-lactamase that probably originated from *E. coli*.

Resistance genes may be encoded on a variety of transferable elements, including transposons and integrons that can insert into both chromosomes and plasmids. The combination of several insertion elements may create large multiple resistance-gene packages *(5)*. Integrons encoding multiple antimicrobial resistances are now widespread in *Enterobacteriaceae* in both hospitals and the community *(6,7)*. There is continuous horizontal transfer of these resistance genes between and within species, and acquisition of multiple resistances favors the proliferation of certain cross-infecting microorganisms in hospitals *(8)*. Some species of both good and opportunistic pathogens appear to have a special ability to accumulate multiple resistance genes and become increasingly MDR. Examples of successful MDR healthcare-associated pathogens include *S. aureus* and coagulase-negative staphylococci (especially methicillin-resistant strains), *Enterococcus faecium* (especially glycopeptide-resistant strains), *K. pneumoniae, Acinetobacter baumannii,* and *P. aeruginosa*.

Antibiotic Use and Antibiotic Resistance

Hospital patients often have compromised host defenses due to treatment or underlying disease and are therefore at risk of acquiring infection with both virulent and opportunistic pathogens. Since antibiotic use is concentrated in hospitals, both types of pathogen are more likely to survive and proliferate in the hospital environment and colonize patients if they are resistant to common antimicrobials. Antibiotic therapy tends to suppress innately sensitive commensal bacteria and encourage their replacement with resistant microorganisms. Initially, the more resistant members of generally sensitive species are selected (a shift within a species to a population with increased resistance), and then the inherently resistant genera emerge (a shift to colonization with more resistant species). Patients who receive multiple courses of antibiotics commonly become colonized by increasingly resistant microorganisms, often suffering sequential infections with bacteria such as *Klebsiella*, *P. aeruginosa*, enterococci and *Acinetobacter,* and finally with antibacterial resistant fungi such as *Candida* spp. The tendency for antibiotic use to promote the emergence of resistant pathogens is called "antibiotic pressure" and is an inevitable evolutionary process. Despite methodological difficulties, there are many reports of resistance rising during increased antibiotic use and falling after a reduction in use (9).

A change in the pattern of serious healthcare-associated infection after the introduction of antibiotics was first noted by Finland and his colleagues in 1959 *(10)*. Between 1935 and 1957, antibiotic-sensitive gram-positive pathogens were replaced by penicillin-resistant *S. aureus* and multi-resistant gram-negative bacteria such as *E. coli*, *Klebsiella*, and *Proteus* spp. Once the emergence of resistant opportunistic pathogens had been recognized, new, more effective drugs were developed for their treatment. The worldwide problem of the multiresistant "hospital staphylococcus" in the 1960s diminished after the introduction of methicillin and other penicillinase-stable penicillins *(11)*; outbreaks of gentamicin-resistant *Klebsiella* and other gram-negative microorganisms seen in the 1970s waned in the 1980s with the use of newer aminoglycosides and cephalosporins.

After the 1980s, the pattern changed again with a dramatic increase in healthcare-associated infections with multiply resistant gram-positive bacteria (1,*12*). Methicillin-resistant *S. aureus* (MRSA), resistant to all β-lactams and to many other previously effective agents, has emerged as a worldwide cause of healthcare-associated infections and outbreaks associated with serious morbidity and mortality *(13–15)*. Coagulase-negative staphylococci are increasingly common healthcare-associated pathogens, partly because they too are often resistant to methicillin and other agents but also because many strains produce an extracellular slime (16,*17*) that enables them to colonize the intravascular and other plastic prostheses that are increasingly used in modern medicine. Finally, many antibiotics used for gram-negative healthcare-associated infections, including ampicillin, the aminoglycosides, cephalosporins and quinolones, are ineffective against enterococci, which have also emerged as important causes of healthcare-associated infection *(18)*.

This is, of course, a continuing dynamic situation. Resistant gram-positive bacteria remain a major feature of healthcare-associated infection but MDR gram-negative bacteria continue as important healthcare-associated pathogens, especially with the emergence of extended-spectrum β-lactamase (ESBL)-producing and multiply resistant strains of *K. pneumoniae*, *Enterobacter, Serratia*, and, most recently, *E. coli* (19). Broad-spectrum antibiotic use encourages the proliferation of antibiotic-resistant and toxigenic strains of *Clostridium difficile* in the bowel that cause diarrhea and pseudomembranous colitis. There has recently been an increase in community and healthcare-associated infections with *C. difficile* associated with the worldwide dissemination of highly virulent strains (20). Thus, healthcare-associated infection is now microbiologically heterogeneous, often being caused simultaneously by several different species of MDR gram-positive and gram-negative bacteria. Table 86-1 shows the distribution of healthcare-associated pathogens reported in the United States in 2003 *(21)*.

Table 86-2 shows the rates of antibiotic resistance in bacterial isolates from hospitals taking part in the U.S. National Nosocomial Infections Surveillance (NNIS) system from 1992 to 2004 *(22)*. Antibiotic resistance rates

TABLE 86-1

Percentage of Bacterial Isolates Associated with Healthcare-Associated Infection of Different Types in Intensive Care Units Reported to the National Nosocomial Infections Surveillance System, 2003

Pathogen	*Pneumo (n = 4,365)*	*BSI (n = 2,351)*	*SSI (n = 2,984)*	*UTI (n = 4,109)*
Gram-negative				
Escherichia coli	5.0	3.3	6.5	26.0
Klebsiella pneumonia	7.2	4.2	3.0	9.8
Enterobacter spp.	10.0	4.4	9.0	6.9
Serratia marcescens	4.7	2.3	2.0	1.6
Pseudomonas spp.	18.1	3.4	9.5	16.3
Acinetobacter spp.	6.9	2.4	2.1	1.6
Other	14.1	3.8	9.8	10.7
Gram-positive				
Coagulase-negative staphylococci	1.8	42.9	15.9	4.9
Staphylococcus aureus	27.8	14.3	22.5	3.6
Enterococci	1.3	14.5	13.9	17.4
Other	3.2	4.5	5.8	1.2

Pneumo, pneumonia; BSI, bloodstream infection; SSI, surgical site infection; UTI, urinary tract infection. (From Gaynes R, Edwards JR; the National Nosocomial Infections Surveillance System. Overview of nosocomial infections caused by gram-negative bacilli. *Clin Infect Dis* 2005;41:848–854.)

were highest in ICUs, followed by non-ICU wards, and then outpatients, reflecting the levels of compromise, antimicrobial courses, and length of hospitalization of the patients in these three areas. ICUs had especially high rates of methicillin resistance in both coagulase-negative and coagulase-positive staphylococci, high rates of quinolone and carbapenem resistance in *P. aeruginosa*, and high rates of resistance to third-generation cephalosporins in *Enterobacter* spp.

Table 86-3 shows results from the NNIS system comparing resistance rates in US ICUs for various pathogens isolated in 1994 to 1998 and 1999 *(22,23)*. During this period, there was a dramatic increase in resistance rates for several important healthcare-associated pathogens. In particular, there was a 47% increase in vancomycin resistance in enterococci, a 43% increase in methicillin resistance in *S. aureus*, and an increase in resistance in *P. aeruginosa* of 35% and 49% to imipenem and the quinolones, respectively.

The European Antimicrobial Resistance Surveillance System (EARSS) has been reporting on antimicrobial resistance rates in invasive (mainly bloodstream) isolates from European countries since 1999. In 2008, the EARSS network comprised almost 900 microbiological laboratories serving more than 1,500 hospitals in 33 countries and provided susceptibility data on more than 700,000 invasive isolates *(24)*. The annual reports from this organization give good data on European trends and can be used to illustrate the generally growing problem of antimicrobial resistance in clinically important bacteria while emphasizing significant regional and geographical differences. EARSS data on resistance trends are discussed under the individual pathogens, later in this chapter.

THE CLINICAL AND ECONOMIC IMPACT OF ANTIMICROBIAL RESISTANCE

Increasing antimicrobial resistance and multiple resistance results in increasing difficulties in the treatment of bacterial infections. Resistance leads to inappropriate empirical therapy; delay in starting effective treatment; and the use of less effective, more toxic, and more expensive drugs *(25)*.

Evaluation of the effect of resistance on outcomes and costs is difficult, because the risks of acquiring resistant infection—such as prior antimicrobial therapy, prolonged hospital stay, and admission to intensive care—are themselves associated with poor prognoses. Nevertheless, when adjusted for other risks, mortality rates and length of hospital stay are generally at least twice as great for patients infected with resistant bacteria as it is for those infected with susceptible strains of the same species (*26,27,*28,*29*).

In serious infections due to *Enterobacteriaceae*, resistance to third-generation cephalosporins (which is nearly always associated with multidrug resistance) tends to worsen clinical outcome *(30–33)*. A meta-analysis of bacteremia caused by ESBL-producing *Enterobacteriaceae (34)* showed significantly increased crude mortality and significantly increased incidence of delay in effective therapy. Mortality rates were higher for infections with imipenem-resistant (*K. pneumoniae* carbapenemase [KPC]–producing) *Enterobacter* spp. (11/33) than with susceptible

TABLE 86-2

Pooled Means of the Distribution of Antimicrobial Resistance Rates (%) by All ICUs Combined, Non-ICU Inpatient Units and by Outpatients, January 1998 through June 2004

Antibiotic Resistant Pathogen	*ICU*	*Non-ICU*	*Outpatients*
MRSA	52.9	46.0	31.1
Methicillin-resistant CNS	76.6	65.7	50.2
Vancomycin-resistant *Enterococcus* spp.	13.9	12.0	4.6
Ciprofloxacin-resistant *P. aeruginosa*	34.8	27.7	23.4
Imipenem-resistant *P. aeruginosa*	19.1	12.3	7.0
Ceftazidime-resistant *P. aeruginosa*	13.9	8.8	4.6
Cef3-resistant *Enterobacter* spp.	27.7	21.0	9.6
Carbapenem-resistant *Enterobacter* spp.	0.7	1.0	0.5
Cef3-resistant *Klebsiella pneumoniae*	6.2	5.8	1.8
Cef3-resistant *Escherichia coli*	1.3	1.5	0.6
Quinolone-resistant *E. coli*	7.3	8.2	3.6
Penicillin-resistant pneumococci	18.9	18.2	16.8
Ceftriaxone-resistant pneumococci	7.5	7.6	4.8

MRSA, methicillin-resistant *S. aureus*; Cef3, third-generation cephalosporin; CNS, coagulase-negative staphylococcus.
(From National Nosocomial Infections Surveillance. NNIS report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470–485.)

TABLE 86-3

Mean Resistance Rates in Selected Pathogens Associated with Healthcare-Associated Infections in ICU Patients, January–May 1999 Compared with the 5 Years 1994–1998 and January–December 2003 Compared with the 5 Years 1998–2002

	% Increase in Resistance	
Antimicrobial/Pathogen	*1999 vs. 1994–1998*	*2003 vs. 1998–2002*
Vancomycin/enterococci	47%	12%
Methicillin/ *Staphylococcus aureus*	43%	11%
Methicillin/coagulase-negative staphylococci	2%	1%
3rd Cephalosporin/*E. coli*	23%	0%
3rd Cephalosporin/ *K. pneumoniae*	–1%	47%
Imipenem/*P. aeruginosa*	35%	15%
Quinolone/*P. aeruginosa*	49%	9%
3rd Cephalosporin/ *P. aeruginosa*	<1%	20%
3rd Cephalosporin/ *Enterobacter* spp.	3%	-6%

3rd, third generation.
(From National Nosocomial Infections Surveillance. NNIS report, data summary from January 1990-May 1999, issued June 1999. *Am J Infect Control* 1999;27:520–532; National Nosocomial Infections Surveillance. NNIS report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004;32:470–485.)

strains (3/33) *(35)* and 14-day mortality was 9/19 patients with bacteremia due to KPC-producing *K. pneumoniae (36)*. However, a lack of controlled studies limits the assessment of causality in all these studies.

The impact of drug resistance on the outcome of *P. aeruginosa* infection has been investigated in a few studies, but the results are not consistent. This may be in part because it is often difficult to distinguish *P. aeruginosa* colonization from infection and also because invasive disease and bacteremia tend to occur in highly compromised patients with underlying poor prognosis *(37–40)*.

Individual studies of *S. aureus* infections have shown variable results, but meta-analyses show that infections with MRSA have worse outcomes than those due to methicillin-sensitive *S. aureus* (MSSA) strains. For example, MRSA bacteremias have twice the mortality of those caused by MSSA *(41),* and MRSA surgical site infections have significantly greater 90-day mortality, length of hospitalization, and hospital charges *(42)*.

Serious enterococcal infection, especially bacteremia, is associated with severe underlying disease, which itself has a poor prognosis. Some studies find no independent effect of vancomycin resistance on outcomes of enterococcal infections *(43,44)*; others show a significantly worse outcome (measured as treatment failure, attributable mortality, prolonged hospital stay, recurrent bacteremia, endocarditis, ICU admission, surgical intervention, and increased healthcare costs) *(45–49)*.

The general effect of antimicrobial resistance has been assessed by considering outcomes with "appropriate" or "inappropriate" therapy. Therapy is inappropriate when it is ineffective *in vitro* against the infecting microorganism or not given promptly by a suitable route (50). Failure to provide prompt, effective antimicrobial therapy may result in treatment failure and death. There is, for example, a significant association between inappropriate treatment and clinical outcome in bacteremia and ventilator-associated pneumonia *(51–54)*.

Delayed response alone is associated with increased morbidity, prolonged hospital stay, additional investigations, procedures and treatments, and increased complications, which, in conditions such as meningitis or bone and joint infection, may result in severe disability. This is costly. Additional costs and lost bed days are incurred by the need to control the spread of antimicrobial-resistant microorganisms within hospitals. Thus, even apart from mortality and morbidity, antimicrobial resistance is hugely expensive in terms of its socioeconomic impact on patients and on the cost-effectiveness of healthcare delivery.

MULTIRESISTANT PROBLEM MICROORGANISMS

Gram-Negative Bacteria

Escherichia coli *E. coli* is the commonest cause of hospital-acquired gram-negative urinary tract infection (UTI) and septicemia. *E. coli* is relatively fastidious in its nutritional requirements and does not survive well in the environment and, until recently, did not tend to cause cross-infection or person-to-person spread. For these reasons, most healthcare-associated *E. coli* infections are endogenous, arising from commensal bowel flora of the affected patient. The species is naturally susceptible to ampicillin but now about 50% to 60% of both healthcare-associated and community isolates are resistant, usually by the production of β-lactamases, enzymes that bind and destroy β-lactam antibiotics. The most common type of β-lactamase in *E. coli* is TEM-1, accounting for about 80% of such resistance *(55–57)*. TEM-1 is encoded on transferable plasmids and has disseminated throughout the world since its discovery in 1965 *(58)*. Some strains of *Enterobacteriaceae*, including *E. coli*, produce TEM-2—a similar enzyme that differs from TEM-1 only in a single amino acid and confers similar phenotypic resistance. Although ampicillin is now unreliable for the treatment of *E. coli* infection, other drugs usually remain effective, including cephalosporins, quinolones, and aminoglycosides. *E. coli* can also be treated by the combination of a β-lactam with a β-lactamase inhibitor, such as amoxicillin/clavulanic acid (co-amoxiclav) and ampicillin/sulbactam. The β-lactamase inhibitors prevent the action of TEM-1 or TEM-2 and restore the activity of the β-lactams. This combination may be ineffective, because some *E. coli* strains can produce excessive amounts of TEM-1 that swamp the effect of the β-lactamase inhibitor *(59,60)* or are resistant to it *(57)*.

Mutations in TEM-1 and TEM-2 have resulted in new ESBLs that can break down newer cephalosporins, and thus, render *E. coli* resistant to them. These ESBLs are named TEM-3, TEM-4, etc., and >100 of them have been reported *(3,61,)*. They are often plasmid-borne and are associated with aminoglycoside and other resistances encoded on the same plasmid. However, until recently, *E. coli* has remained generally antibiotic-sensitive and relatively easy to treat and has not caused much cross-infection or spread within hospitals or the community.

This situation changed with the emergence of *E. coli*–producing CTX-M ESBLs in the 1990s. CTX-M–producing *Enterobacteriaceae* first appeared in South America but have now become distributed worldwide *(62,63)*. Compared with other ESBLs, CTX-M enzymes are more active against cefotaxime than against other third-generation cephalosporins. They appear to have originated from the *Kluyvera* spp. of environmental bacteria, and more than 50 different types have been identified. They are associated with plasmids and transposons and have disseminated widely among the *Enterobacteriaceae*.

In addition to resistance to penicillins and cephalosporins, CTX-M–producing *E. coli* are usually also resistant to other previously active agents such as the aminoglycosides and quinolones. Furthermore, these new MDR *E. coli* appear to be highly transmissible both in the community and in hospitals and have disseminated worldwide. Most isolates are clonally unrelated, but large single strain community outbreaks occur *(64)*. Increasing asymptomatic fecal carriage raises the possibility of spread by food sources and international travel.

This world pandemic of CTX-M–producing *E. coli* has resulted in a new epidemiology for MDR coliforms (19,*65*). Opportunistic healthcare-associated outbreaks with mainly single clones of SHV- and TEM-type ESBL-producing *K. pneumoniae* have been replaced by sporadic and epidemic community infections with heterogenous clones of more virulent MDR CTX-M–producing *E. coli*. Spread occurs among healthy elderly people at home and in long-term care facilities; admission of these groups to hospital or care homes may result in healthcare-associated outbreaks with consequent further dissemination. Infections tend to occur in the elderly, although younger healthy patients may also be involved. The common presentation is UTI (sometimes complicated by bacteremia) in catheterized, elderly, community, or newly admitted hospital patients. The features of the new community MDR *E. coli* infections compared with the older MDR KES healthcare-associated infections have been reviewed by Pitout and Laupland (19) and are summarized in Table 86-4.

The U.K. Health Protection Agency reviewed *E. coli* bacteremias reported from hospitals in England, Wales, and Northern Ireland in 2008 *(66)*. There were about 22,000 such bacteremias in 2007. Resistance to third-generation cephalosporins in *E. coli* blood isolates increased from about 2% in 2001 to 12% in 2007 (Fig. 86-1); resistance to ciprofloxacin rose from 1% to 23%; and resistance to gentamicin rose from 1% to 8.5%. Resistance to carbapenems was rare and was ≤0.2% in 2007. There were far fewer *Klebsiella* bacteremias—about 6,000 in 2007—and among these, resistance to third-generation cephalosporins was about 14% (up from 4% in 1994); to ciprofloxacin, about 15%; and to gentamicin, about 10%. (Resistance to carbapenems was not reported.) Thus, in 2007, multidrug resistance in UK hospital blood isolates of *E. coli* was similar to or higher than in *Klebsiella*, and there were many more of them compared with *Klebsiella*.

Klebsiella, Enterobacter, and Serratia spp. *Klebsiella, Enterobacter*, and *Serratia* spp. are common opportunistic gram-negative pathogens that have similar epidemiologies and clinical presentations. They are all inherently resistant to ampicillin, and *Enterobacter* spp. and *Serratia* spp. are resistant to first-generation cephalosporins. These *Enterobacteriaceae* have a great facility for acquiring and disseminating resistance plasmids and *Enterobacter* spp. may develop chromosomally mediated resistance to second- and third-generation cephalosporins *(67,68)*.

Enterobacter spp. possess an inducible chromosomally encoded class I β-lactamase that is normally suppressed by a repressor gene and is produced in large amounts only after exposure to certain β-lactams. Full resistance to second- and third-generation cephalosporins results when stably derepressed mutants appear that express the class I β-lactamase constitutively. These mutants are selected by cephalosporin therapy and produce the β-lactamase continuously.

TABLE 86-4

Characteristics of Infections Caused by Extended-Spectrum β-Lactamase–Producing Bacteria

	Older Klebsiella spp. etc.	*Newer Escherichia Coli*
Virulence/place	Less virulent/HAI	More virulent/Community and HAI
Type of ESBL	SHV and TEM types	CTX-M (especially CTX-M15)
Infection	UTI, respiratory, intra-abdominal, blood	Usually UTIs, but also blood, gastroenteritis
Resistances	All β-lactams; usually quinolones and cotrimoxazole; usually aminoglycosides	All β-lactams; usually quinolones and cotrimoxazole; often aminoglycosides
Molecular epidemiology	Most often clonally related	Usually not clonally related, but clonal outbreaks described worldwide, including UK
Risk factors	Longer hospital stay; severity of illness; time in ICU; ventilation; urinary or vascular. Catheterization; previous exposure to antibiotics (especially cephalosporins)	Repeat UTIs/underlying renal pathology; previous antibiotics including cephalosporins and quinolones; previous hospitalization; nursing home residents; older people; diabetes; liver pathology

HAI, healthcare-associated infection; UTI, urinary tract infection.
(From Pitout JD, Laupland KB. Extended-spectrum β-lactamase-producing *Enterobacteriaceae*: an emerging public-health concern. *Lancet Infect Dis* 2008;8:159–166.)

To a greater or lesser extent, all three of these species colonize the human bowel and patient's skin and may spread from person to person via staff members' hands. They may then go on to colonize the urinary and respiratory tracts of patients treated with β-lactams and may produce bacteremia in the compromised host. They are relatively free-living and can also survive and multiply in nutritionally poor wet environments at room temperature. Because of this, they may contaminate food, enteral feeds, and infusion fluids, leading to widespread common-source outbreaks.

K. pneumoniae is the most frequently isolated member of this group and the most virulent. It is naturally resistant to ampicillin, usually by the production of SHV-1, a β-lactamase similar to TEM-1 and TEM-2, which may be encoded on either the chromosome or, less commonly, on a transferable plasmid *(69)*. The carriage rate for healthy people is low but increases in hospitalized patients, especially during prolonged hospitalization or antibiotic therapy.

During the 1970s, there were frequent reports of hospital outbreaks of gentamicin-resistant *K. pneumoniae*, sometimes associated with significant mortality when highly compromised patients were involved *(70,71)*. The microorganisms often spread between hospitals and into the community. They became endemic in some hospitals and were sometimes associated with the simultaneous appearance of multiple resistances in other strains of *Klebsiella* and in other species of *Enterobacteriaceae (72,73)*. In these cases, *K. pneumoniae* appeared to be acting as an engine of resistance dissemination, especially resistance to aminoglycosides *(74)*.

Once the epidemiology of resistant *Klebsiella* infection was understood, and following the introduction of newer cephalosporins, these outbreaks became much less common. However, strains of *K. pneumoniae* (and also *Klebsiella ozaenae*) then appeared that are resistant to third-generation cephalosporins by the production of ESBLs and can spread to produce hospital outbreaks (*61,75–78*). The ESBLs are usually the result of mutations in the genes encoding TEM-1, TEM-2, or SHV-1. They are encoded on plasmids that can transfer to other species, and they are often associated with other multiple resistances, including

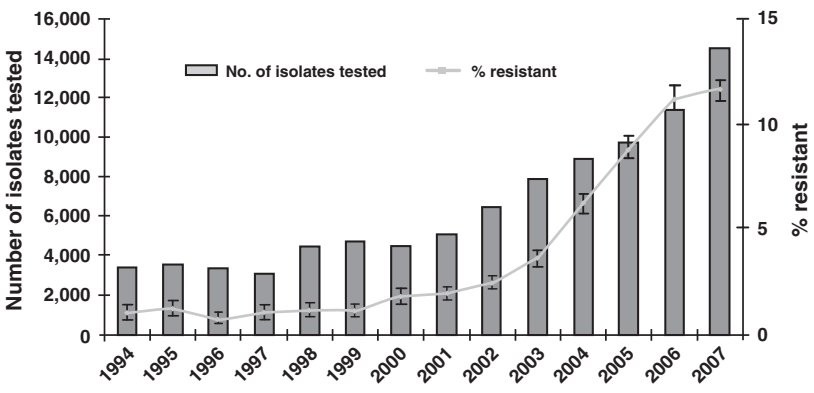

FIGURE 86-1 Resistance to ceftazidime in *E. coli* from bacteremias in England, Wales, and Northern Ireland, 1994–2007. (From Health Protection Agency. *Antimicrobial resistance and prescribing in England, Wales and Northern Ireland, 2008*. London, UK: Health Protection Agency, 2008.)

resistance to aminoglycosides *(79)*. Although ESBL-producing strains are usually susceptible to β-lactam-β-lactamase-inhibitor combinations such as amoxicillin/clavulanate and ampicillin/sulbactam, healthcare-associated isolates may be resistant by hyperproduction of the ESBL *(76,80)*. These multiresistant strains may also acquire resistance to quinolones by mutation. Thus, recent isolates are often resistant to all the common β-lactams, aminoglycosides, and quinolones and are reliably susceptible only to the carbapenems. Outbreaks with these new multiresistant *Klebsiella* spp. have an epidemiology similar to that of the gentamicin-resistant *Klebsiella* outbreaks of the 1970s.

MDR *Klebsiella* spp. are now widespread, and some strains have also picked up the CTX-M type ESBLs that have recently emerged in *E. coli*. For all these *Enterobacteriaceae*, the treatment of last resort are the carbapenems. The recent emergence of carbapenem resistance is therefore a matter of concern.

Carbapenem resistance in *Enterobacteriaceae* can be mediated by a variety of mechanisms, including permeability/efflux changes, hyperproduction of *ampC* β-lactamases or ESBLs, or production of specific carbapenemases. A range of different carbapenemases have been reported, most of them rare or uncommon. They include Ambler class B metallo-β-lactamases such as verona imipenemase and imipenemase; class D OXA-48 β-lactamase, mostly in *K. pneumoniae* from Turkey, Lebanon, and Belgium; class A clavulanic-acid-inhibited carbapenemases; chromosomally encoded non-metallo-β-lactamases of *Serratia* spp. and plasmid-mediated KPCs *(81)*.

In Europe, carbapenem-resistant *Enterobacteriaceae* are rare (except in Greece), but KPC-producing bacteria are now widespread in certain parts of China, Israel, Greece, South America, and the United States (*36,*82).

In 2009 a new metallo-beta-lactamase gene, NDM-1 (New Dehli metallo-beta-lactamase-1), conferring resistance to carbapenems, was identified in *K. pneumoniae* isolates from India (82a). Since then, it has become apparent that NDM-1 is widely distributed in coliforms in parts of India, including the gut flora of healthy people, sewage and the environment and has disseminated internationally (82b,82c,82d). Although the number of clinical infections with NDM-1-producing Gram-negative bacteria is small, the threat of these potentially untreatable infections is very serious.

The carbapenems remain the agents of last resort for the treatment of infections with *Enterobacteriaceae* and other MDR gram-negative bacteria. By analogy with CTX-M producing *E. coli,* there is a serious risk of worldwide spread of pan-drug-resistant carbapenemase-producing bacteria. Prudent antibiotic use combined with very strict infection prevention and control is essential to prevent further spread of these potentially dangerous microorganisms. All high-risk units should ensure continuous good practice and effective surveillance and have plans in place to deal with these pathogens when they arise and international cooperation is needed for worldwide control.

Resistance Rates in European Isolates of Enterobacteriaceae Antimicrobial resistance and multi-resistance have increased dramatically among European bloodstream isolates of *E. coli* in the last few years *(24)*. Resistance to ampicillin/amoxicillin ranges from 32% to 78%, and aminopenicillins are therefore no longer appropriate for empirical therapy. Although 14 of 33 European countries reported <5% resistance against third-generation cephalosporins, resistance rates to these agents have increased in 19 countries since 2004. In 2008, two east European countries reported rates above 25% (Bulgaria, 29%; and Turkey, 42%). EARSS does not identify resistance mechanisms, but the continuing rise in resistance to third-generation cephalosporins is likely to be due to ESBL production. Only four European countries reported resistance rates to fluoroquinolones of <10%; 16 had rates between 10% and 25%, 10 had rates >25%, and 3 had rates >35% (Italy, 38%; Cyprus, 45%; and Turkey, 52%). Aminoglycoside resistance is also common: only six European countries reported rates of <5%, 16 had rates of 5% to 10%, and in southern and eastern Europe, most countries reported rates of 10% or more, with the highest rates being reported by Bulgaria (31%) and Turkey (35%). Overall, in 2008, although 47% of all European bloodstream isolates of *E. coli* remained susceptible to aminopenicillins, third-generation cephalosporins, fluoroquinolones, and aminoglycosides, 8% were resistant to two of these classes, 3% to three, and 3% to four *(24)*. Data on carbapenem resistance in *E. coli* were not collected by the European Antimicrobial Resistance Surveillance System (EARSS) in 2008.

Antimicrobial resistance in bloodstream isolates of *K. pneumoniae* also varies widely. In 2008, many northern European countries had resistance rates of <5% to third-generation cephalosporins, fluoroquinolones, and aminoglycosides; however, high rates of resistance and multiple resistance to these agents, sometimes >50%, were seen in central and southeastern European countries. EARSS noted that carbapenem resistance was generally uncommon in European bloodstream isolates of *K. pneumoniae*: most countries reported no resistance and seven had rates of 1% to 5%. However, three countries had much higher rates: Cyprus, 10%; Israel, 19% (among 350 isolates); and Greece, 37% (among 1,074 isolates) (see also Chapter 34).

Pseudomonas and Pseudomonas-Like spp. These are nonfermenting, aerobic, gram-negative bacteria, which are widely distributed in nature, are nonfastidious in their nutritional requirements, and can survive and multiply in many wet environmental sites, often at ambient or low temperatures. They also readily colonize the mucous membranes of compromised patients who have been treated with multiple courses of antibiotics. Although they have little pathogenicity for normal individuals, they are resistant to many common antimicrobials and disinfectants and flourish as environmental opportunistic pathogens in intensive care and similar units.

Although many species of *Pseudomonas* and *Pseudomonas*-like microorganisms have been isolated from clinical material, the ones that cause most problems of antibiotic-resistant healthcare-associated infection are *P. aeruginosa*, *Stenotrophomonas* (formerly *Xanthomonas* or *Pseudomonas*) *maltophilia*, *Burkholderia* (formerly *Pseudomonas*) *cepacia,* and *Ralstonia* (formerly *Pseudomonas or Burkholderia*) *pickettii*. *Achromobacter xylosoxidans* is a nonfermenting gram-negative bacillus that behaves like *Pseudomonas* and causes similar healthcare-associated infections.

P. aeruginosa is the most common pseudomonad isolated from clinical specimens and the most frequent species causing invasive infection. It accounts for about 10% of all healthcare-associated infections and is roughly the third most common cause of healthcare-associated

gram-negative bacteremia after *E. coli* and *K. pneumoniae*. It is a normal commensal of humans, colonizing skin, nose, throat, and stool in a widely varying number (0–40%) of healthy subjects (83).

Many studies have shown that several different types may be in circulation during an apparent outbreak, and although person-to-person spread does occur, endogenous infection is common *(84–86)*. Carriage of clinically undetectable resistant *P. aeruginosa* may be common in healthy persons, and this resistant population may emerge under antibiotic pressure in hospitals to cause environmental colonization and endogenous infection.

P. aeruginosa is inherently resistant to most penicillins and cephalosporins, tetracyclines, chloramphenicol, sulfonamides, and nalidixic acid. It is naturally susceptible to the aminoglycosides, antipseudomonal penicillins and cephalosporins, quinolones, and carbapenems. However, acquired antibiotic resistance in *P. aeruginosa* is common. The microorganism can exchange antibiotic resistance plasmids with other gram-negative bacilli while colonizing patients *(87)*, but acquired resistance to aminoglycosides and other agents is probably more often the result of changes in membrane permeability *(88)*. Resistance to fluoroquinolones (due to mutations in DNA gyrase, membrane permeability, or both) has emerged relatively rapidly in *P. aeruginosa,* and now about a third or more of healthcare-associated isolates are resistant *(23,89,90)* (Table 86-2). This microorganism can develop resistance to ceftazidime by mutation to constitutive production of chromosomal class I β-lactamase *(68,91)*. It may also, though less readily, develop resistance to carbapenems such as imipenem and meropenem, usually by changes in membrane permeability (4,*92,93*). In the NNIS studies for the periods from 1994 to 1998 and 1999, resistance to quinolones and carbapenems in ICU isolates of *P. aeruginosa* increased by 49% and 35%, respectively, and resistance to third-generation cephalosporins (ceftazidime) increased by 20% between 1998 and 2003 (Table 86-3).

Acinetobacter baumannii *Acinetobacter* spp. are nonfermenting gram-negative coccobacilli, found widely distributed as free-living saprophytes in soil and water. They also colonize the skin and mucous membranes in about 25% of healthy people (94). The most frequently isolated *Acinetobacter*—the one most likely to acquire multiple antibiotic resistance and the most common cause of healthcare-associated outbreaks—is *A. baumannii*. Healthcare-associated outbreaks originate from contaminated environmental sources or follow hand transmission from the skin of colonized patients *(95,96)*. These microorganisms can also survive for long periods on dry surfaces *(97,98)* and can probably be transmitted via dust and fomites *(99)*. Most clinical isolates represent colonization rather than infection *(96)*, but serious and sometimes fatal infections occur in compromised patients, including septicemia, endocarditis, meningitis, and pneumonia *(100,101)*.

In the early 1970s, *Acinetobacter* spp. were usually susceptible to many common antimicrobials, including gentamicin and the cephalosporins, and they were relatively uncommon healthcare-associated pathogens *(100)*. By the mid-1980s, however, healthcare-associated outbreaks with multiply resistant *Acinetobacter* strains were being frequently reported (94). Many healthcare-associated strains are now resistant to the aminoglycosides and to older and newer cephalosporins, and some have developed resistance to the quinolones *(102,103)* and carbapenems *(104)*. The ability of *A. baumannii* to acquire multiple resistances, as well as to survive on skin and in the environment, undoubtedly contributes to its success as a healthcare-associated pathogen (see also Chapter 35).

Gram-Positive Bacteria

Staphylococcus aureus *S. aureus* is usually the second most common bacterial isolate in hospital laboratories after *E. coli* and is associated with wound infections and septicemia. Surface isolates often represent colonization, but invasive infection causes high morbidity and may be fatal. *S. aureus* is naturally susceptible to many classes of antimicrobials, including penicillins, cephalosporins, macrolides, sulfonamides, trimethoprim, tetracyclines, chloramphenicol, lincosamines, aminoglycosides, quinolones, and glycopeptides, but it has a great ability to develop resistance to many of these drugs simultaneously. Antibiotic resistance facilitates the survival and spread of these microorganisms in the hospital environment, and multiresistant strains are often responsible for large and serious outbreaks of healthcare-associated infection. Since the 1950s, many different resistance problems have been encountered *(11,105)*. Penicillin resistance due to the production of plasmid-mediated penicillinase appeared in *S. aureus* soon after penicillin was introduced, and now most strains are resistant. During the 1950s, multiresistant strains of *S. aureus* began to appear, and large epidemics of healthcare-associated infection with microorganisms resistant to penicillin, tetracycline, erythromycin, chloramphenicol, and other drugs were seen throughout the world. Many of these outbreaks were caused by virulent microorganisms of phage type 80/81, a group that became known as "the hospital staphylococcus" *(106,107)*. The healthcare-associated staphylococcus was greatly feared, because infections were often untreatable, and outbreaks were associated with high mortality rates. In the 1970s, some hospitals experienced outbreaks with gentamicin-resistant *S. aureus,* but the incidence of healthcare-associated infection with multiply resistant staphylococci gradually declined. The exact reasons for this are unclear, but the decline was associated with the introduction in the 1960s of the penicillinase-stable semisynthetic penicillins, methicillin, nafcillin, oxacillin, and cloxacillin (which are active against penicillinase-producing staphylococci); an apparent loss of virulence in the phage type 80/81 strains; and improvements in infection control.

Strains of MRSA were noted soon after methicillin was introduced into clinical practice *(108)*, but they were generally rare until the 1980s despite widespread use of methicillin, cloxacillin, and related drugs. In the late 1970s, however, MRSA emerged as a major pathogen of hospital infection in most countries and regions of the world *(15)*. In both the United States and Europe, around 30% to 50% of hospital isolates of *S. aureus* are now methicillin-resistant *(24,90)* (Table 86-5), although in the Netherlands and Scandinavia, rates are 3% or lower.

In the EARSS surveillance data for 2008, 21% of all (~32,000) invasive *S. aureus* isolates from 33 European countries were resistant to methicillin. However, MRSA

TABLE 86-5

Prevalence (%) of Methicillin Resistance in European Bloodstream Isolates of *S. aureus* 2001–2008

	2001	*2004*	*2008*		*2001*	*2005*	*2008*
Austria	8	14	8	Denmark	<1	1	3
Belgium	23	33	21	Finland	<1	3	3
Cyprus	n/a	49	46	Netherlands	<1	1	<1
France	33	29	24	Norway	<1	<1	<1
Germany	16	20	19	Sweden	<1	<1	<1
Greece	39	44	41				
Hungary	5	17	23				
Ireland	42	41	33				
Italy	41	40	34				
Portugal	32	46	53				
Romania	n/a	72	33				
Spain	23	26	27				
Turkey	n/a	40	38				
UK	44	44	31				

(From European Antimicrobial Resistance Surveillance System. *Annual report 2008*. Bilthoven, The Netherlands: EARSS, 2009.)

rates varied from <1% in the north (in the Netherlands and the Nordic countries) to over 50% in some southern European countries. The EARSS reports show that MRSA rates generally increased in most European countries between 2001 and 2004, but since then, they have fallen significantly in several countries (Table 86-5), possibly as the result of improved control measures. The Netherlands and Nordic countries continue to have strikingly low rates of MRSA but have increased (although only from <1% to 3%) in Denmark, possibly because of the emergence of the pig-associated community strain of MRSA.

Methicillin resistance is mediated primarily by the production of an abnormal PBP called PBP-2a or PBP-2′ *(109)*. β-Lactam antibiotics bind to normal bacterial PBPs and inhibit their activity, preventing proper formation of cell wall peptidoglycan and leading to cell death by osmotic lysis. PBP-2a binds poorly with most β-lactams and can fulfill the functions of the so-called essential PBPs 1, 2, and 3. Microorganisms producing PBP-2a are, thus, resistant to most available β-lactams, including methicillin and the isoxazolyl penicillins. Although they may appear susceptible to some β-lactams *in vitro*, the agents so far tested are clinically ineffective and should not be used for therapy.

The production of PBP-2a is encoded by the *mecA* gene located on the chromosome. This gene appears to have been derived from coagulase-negative staphylococci—hospital strains of which many are now frequently methicillin-resistant *(110)*. Recent genetic studies suggest that MRSA has repeatedly emerged from MSSA at different times in different parts of the world (*111,*112).

MRSA strains are resistant to methicillin, oxacillin, and other penicillinase-stable β-lactams, including the carbapenems, and to several other classes of antibiotic. Following the rapid emergence of resistance to quinolones, many strains of MRSA remain reliably susceptible only to the glycopeptides vancomycin and teicoplanin, the oxazolidinone linezolid and the lipopeptide daptomycin. Because of the current importance of vancomycin and teicoplanin in the treatment of severe MRSA sepsis, the emergence of glycopeptide resistance in MRSA is greatly feared. Unfortunately, several types of glycopeptide resistance have emerged in MRSA in recent years.

The glycopeptides are normally slowly bactericidal for *S. aureus*. However, some recent isolates of MRSA exhibit glycopeptide tolerance; that is, they are inhibited by normal concentrations of these agents but are not killed *(113,114)*. Tolerance has been associated with treatment failures, but its exact clinical significance is unclear. Glycopeptide tolerance is not routinely tested, and tolerant strains usually go undetected.

There have been reports of *S. aureus* strains with reduced vancomycin susceptibility from Japan, North America, and Europe (115*,116,117*). These strains have non-plasmid-mediated low-level or intermediate resistance to vancomycin, with vancomycin minimum inhibitory concentrations (MICs) of 8 μg/mL and have been associated with treatment failures. They have been designated "vancomycin-intermediate *S. aureus*" (VISA). In a given population of these strains, the majority have vancomycin MICs of 2 to 4 μg/mL, but there is a subpopulation with MICs of 5 to 9 μg/mL that may emerge under glycopeptide pressure. The mechanism of vancomycin-resistance in these microorganisms has not been fully elucidated but may result from increased amounts of normal D-Ala-D-Ala residues in the cell wall, which "absorb" therapeutic concentrations of vancomycin (118). These VISA strains appear to be rare and their true clinical significance is uncertain. As with glycopeptide tolerance, VISA strains are not routinely identified in the laboratory but may be identified retrospectively after treatment failure *(119)*.

High-level, inducible, transferable resistance to both vancomycin and teicoplanin is now seen quite commonly

in enterococci (vancomycin-resistant enterococci, VRE) and is encoded by a series of genes, including *vanA* (see below). This *vanA* resistance is usually plasmid-borne and was transferred to *S. aureus* in the laboratory in 1992 *(120)*. Ten years later, two clinical isolates of MRSA that contained the *vanA* gene and had vancomycin MICs of >128 μg/mL and teicoplanin MICs of 32 μg/mL were reported from the United States *(121)*. Such strains are still exceptionally rare; by 2009, only 12 had been reported worldwide *(122)*. However, since both MRSA and VRE are widespread in hospitals throughout the world, there is continuing fear that fully glycopeptide-resistant MRSA will become more common in the future. It is essential to avoid any unnecessary use of glycopeptides that might encourage the emergence of such strains, to maintain vigilant surveillance for their appearance, and to strictly isolate any cases that do occur to prevent further spread.

Within hospitals, the sources of cross-infection with MRSA are usually infected or asymptomatic patients who may be colonized in the nose, pharynx, rectum, wounds, and chronic skin lesions. Nasal carriage by staff members is usually low, on the order of 1% to 8%, but staff members may transfer MRSA between patients via hand contact, either directly from patient to patient or via fomites *(123)*. Although MRSA may be spread by airborne transmission, this appears to be less common than with MSSA. The risk of colonization and infection with MRSA increases with the length of hospitalization, the severity of the underlying disease, the number of operations or manipulations, and previous exposure to antibiotics, especially cephalosporins and aminoglycosides *(124,125)*. Although some types of MRSA appear sporadically and rarely cause outbreaks, epidemic strains spread rapidly in hospitals and may become endemic.

Topical mupirocin is widely used for the clearance of nasal carriers of MRSA during outbreaks *(126)*. Susceptible strains have MICs of <1 μg/mL, and the ointment contains 20,000 μg/mL. Resistance to mupirocin is uncommon, but rates tend to be higher in patients given prolonged treatment such as those in dermatology clinics and during outbreaks of mupirocin-resistant strains. Mupirocin acts by inhibiting bacterial isoleucyl-tRNA synthetase, and resistance appears to be mediated by the production of modified enzymes. Isolates showing low-level resistance have a single chromosomally encoded modified synthetase, whereas those with high-level resistance also have a second enzyme encoded on a plasmid *(127,128)*. Staphylococci can be trained to low levels of mupirocin resistance (MICs < 64 μg/mL) *in vitro*, and similar low-level resistance may emerge during therapy. The clinical significance of such resistance is uncertain, since topical mupirocin concentrations are very much higher than these MICs, and carriage of low-level resistant strains can be eradicated with normal mupirocin therapy. More important are isolates showing high-level resistance (MICs > 1,024 μg/mL), which cannot be cleared by mupirocin therapy *(129)*. This type of resistance may be carried on a conjugative plasmid or transposon and can transfer to other microorganisms *(130)*. Since mupirocin is so useful in the management of *S. aureus* outbreaks, the use of this agent should be carefully controlled to preserve its effectiveness.

MRSA strains are usually brought into hospitals by asymptomatic carriers—either patients or staff members. An important control measure is to screen patients admitted from other hospitals and keep them in isolation until they are shown not to be carriers. Similarly, new staff members who have recently worked at other hospitals (including agency staff members) should not be allowed to work until they have been shown to be free of MRSA. It is also good practice to inform other hospitals if infected or colonized patients are to be transferred to them.

Until recently, MRSA infections presenting outside of hospitals were caused by MRSA strains acquired during previous hospital or healthcare contact *(131)*. (Healthcare-associated MRSA, HA-MRSA) True community-acquired or community-associated MRSA (CA-MRSA) caused by strains distinct from HA-MRSA in patients without prior healthcare contact began to emerge in the 1990s (132). These CA-MRSA clones appear to have emerged by the acquisition of the SCC*mec* cassette by community strains of MSSA. Although HA-MRSA strains tend to cause infection in hospitalized, compromised, elderly patients, often with a history of surgery or indwelling devices, CA-MRSA, like community strains of MSSA, affect younger, healthy people and can spread readily in community settings and hospitals. Unlike HA-MRSA, but like the MSSA strains they are derived from, CA-MRSA are often virulent, causing primary skin infections and invasive sepsis in healthy people. CA-MRSA are characteristically susceptible to most non-β-lactam antimicrobial agents, contain SCC*mec* types IV or V, and produce the Panton-Valentine leukocidin toxin (PVL), a putative virulence factor. Although the role of PVL is debated, PVL-positive CA-MRSA has been associated with severe skin sepsis and fatal necrotizing pneumonia (*133,*134). Nevertheless, not all CA-MRSA produce PVL; some strains have become multiply antibiotic resistant, and CA-MRSA is increasingly the cause of hospital outbreaks (135).

The prevalence of CA-MRSA is particularly high in the United States, where CA-MRSA is now the most common cause of both hospital and community *S. aureus* infections in certain cities. European CA-MRSA prevalence rates are low but increasing. The United States is dominated by a single successful clone, the PVL-positive USA300, but CA-MRSA strains from most other parts of the world are characterized by clonal diversity with only about half expressing PVL *(136)*.

The shuttling of CA-MRSA between hospital and community may result in more frequent MRSA infections in the community, more severe MRSA infections in hospitalized patients, the spread of MRSA to previously spared hospital specialties such as pediatrics and obstetrics, more frequent MRSA infections in less-compromised patients and in healthcare workers, and the emergence of multiply resistant CA-MRSA strains. This new MRSA epidemiology will require new control measures, both in hospitals and in the community (see also Chapters 28 and 29).

Coagulase-Negative Staphylococci There are many species of coagulase-negative staphylococci, of which the most common to be isolated from clinical material is *Staphylococcus epidermidis*. At one time, coagulase-negative staphylococci were regarded as insignificant pathogens of humans, but they are now recognized as important causes of infection in hospitalized and compromised patients. Many of these microorganisms are multiply antibiotic-resistant

(137) and can produce an extracellular "slime" that allows them to stick to plastic prostheses and survive on foreign surfaces within a protective biofilm (16,*17,138*). As a result, infections with coagulase-negative staphylococci are being seen with increasing frequency in compromised patients. These include bacteremia (associated with intravascular catheters and vascular grafts), endocarditis (prosthetic heart valves), meningitis (ventricular shunts), peritonitis (peritoneal dialysis catheters), and infection of joint prostheses. Coagulase-negative staphylococci are now common isolates from blood cultures, usually associated with vascular lines, especially indwelling and long-term ones such as Hickman lines *(138)*.

About half the strains isolated in hospitals show multiple antibiotic resistance, including resistance to methicillin (and other β-lactams) and gentamicin. Methicillin-resistant strains tend to be more multiply resistant than methicillin-sensitive ones. Healthy individuals are normally colonized by relatively sensitive microorganisms, primarily *S. epidermidis*. After admission to the hospital, and especially after exposure to multiple courses of antibiotics or surgical prophylaxis, patients become colonized with multiply resistant strains and with other more resistant coagulase-negative species such as *Staphylococcus hemolyticus (139)*. Resistance in coagulase-negative staphylococci appears to be increasing, probably under the pressure of antibiotic use *(140)*. Sensitive staphylococci may receive plasmid-borne resistance factors from other microorganisms during contact on the skin surface, and there is evidence that coagulase-negative staphylococci may be a reservoir of resistance genes that can be transferred to *S. aureus (141,142)*.

Because of extensive multiple resistance in coagulase-negative staphylococci, the glycopeptides vancomycin and teicoplanin are often used for therapy and prophylaxis in high-risk patients. Low-level resistance to glycopeptides has appeared in hospital isolates of coagulase-negative staphylococci, and such resistance can be produced by exposure to increasing drug concentrations *in vitro*. Teicoplanin resistance is easier to produce than vancomycin resistance, and MICs are higher *(143)*. Similar low-level teicoplanin-resistant, vancomycin-sensitive strains are being increasingly isolated from clinical specimens *(144–146)*. There is some evidence that *S. hemolyticus* is more likely to exhibit teicoplanin resistance than are other coagulase-negative species but not all studies have shown this.

Molecular methods have revealed clusters of hospital infection with indistinguishable strains of coagulase-negative staphylococci *(147–150)*. In most instances, however, the sources and routes of transmission of the outbreak strains are unclear. In general, however, infection with coagulase-negative staphylococci should be regarded as endogenous unless clustering of unusually resistant isolates is noted. Colonization and infection with resistant strains are more likely with prolonged hospitalization and multiple courses of antibiotic therapy. Eradication of bloodstream infection will usually require the removal of the colonized catheter or prosthesis (see also Chapter 30).

Enterococci Enterococci are found in the stools of most normal people and sometimes in other sites such as the mouth and vagina. *Enterococcus faecalis* and *Enterococcus faecium* predominate, with *E. faecalis* usually being the most common; other species are uncommon causes of human infection. The enterococci typically cause endogenous infections, most commonly of the urinary tract, but also of the abdomen and pelvis, where they are usually mixed with other bowel flora. They are relatively poor pathogens but may go on to cause invasive disease in compromised patients, causing cholangitis, septicemia, endocarditis, and meningitis *(151)*. Multiresistant strains of enterococci cause hospital outbreaks in which they colonize the bowels of asymptomatic patients and are transferred between patients on staff members' hands *(151,152)*.

The enterococci are typically susceptible to ampicillin/amoxicillin but intrinsically relatively resistant to benzylpenicillin and other β-lactams such as cloxacillin, the cephalosporins, and the carbapenems. They are also usually resistant to trimethoprim and the sulfonamides, the quinolones, low levels of aminoglycosides, and low levels of clindamycin. Furthermore, these microorganisms have a remarkable ability to acquire new resistances to ampicillin/amoxicillin and other drugs that might be used against gram-positive bacteria, including chloramphenicol, erythromycin, tetracycline, high levels of aminoglycosides and clindamycin, and now, the glycopeptides vancomycin and teicoplanin. *E. faecium* is inherently more resistant to penicillin and ampicillin than *E. faecalis*, probably due to changes in the affinity of the enterococcal PBPs.

Transferable β-lactamase–mediated ampicillin resistance has been reported in *E. faecalis,* but although such strains have caused several large hospital outbreaks *(153,154)*, they are usually rare in clinical material.

Because the enterococci are intrinsically resistant to the most commonly used antimicrobials, they have become increasingly important as causes of infection and superinfection in hospitalized patients. Enterococci are now the third most common cause of healthcare-associated infections, being responsible for 10% to 12% of all healthcare-associated infections, 10% to 20% of HA UTI, and 5% to 10% of HA bacteremias *(155)*. Because of their great ability to acquire multiple resistances, the enterococci are one of the few bacterial groups that can become resistant to most available antibiotics.

Glycopeptide-Resistant Enterococci Glycopeptides inhibit the synthesis of gram-positive cell walls by binding to the amide bond of the D-alanyl-D-alanine terminal sequences of the muramyl pentapeptide of the elongating peptidoglycan polymer. The large glycopeptide molecules then impede the action of both the polymerase that extends the peptidoglycan backbone and the transpeptidase that cross-links the growing chain to the existing cell wall *(156,157)*.

Most clinically important gram-positive bacteria are naturally susceptible to the glycopeptides vancomycin and teicoplanin. Vancomycin resistance can be divided into low-level (MICs of 8–32 μg/mL) and high-level (MICs > 64 μg/mL). Acquired glycopeptide resistance is rare but is most frequently seen in enterococci, which exhibit at least four resistance phenotypes *(158)*: (a) v*anA*, high-level transferable resistance to both vancomycin and teicoplanin, associated with the production of a 38- to 40-kDa membrane protein, (b) *vanB*, inducible low-level resistance

to vancomycin alone that, in some strains, is associated with a 39.5-kDa membrane protein, (c) v*anC*, constitutive low-level vancomycin resistance seen in some strains of *Enterococcus gallinarum*, and (d) *vanD*, described in only a few strains of *E. faecium*, with constitutive resistance to vancomycin (MICs ~64 μg/mL) and to low-levels of teicoplanin (MICs ~4 μg/mL). *Enterococcus casseliflavus/Enterococcus flavescens* appear to have intrinsic low-level resistance unrelated to that of the other phenotypes.

The v*anA* phenotype of high-level resistance to both vancomycin and teicoplanin is usually encoded on a transferable plasmid and is the most serious clinical problem. v*anA* strains have vancomycin MICs of 64 to more than 1,024 μg/mL and teicoplanin MICs that are usually one or two times lower than this. The *vanA* gene encodes an abnormal D-Ala-D-Ala ligase, which results in the replacement of the normal D-Ala-D-Ala termini of peptidoglycan precursors by D-Ala-D-Lactate, which cannot bind glycopeptides *(157,158)*. The successful production of the *vanA* glycopeptide resistance phenotype is dependent on the cooperative activity of the products of seven genes, which are usually contained in a transposon and usually encoded on a plasmid. The mechanisms and genetics of the other vancomycin resistance phenotypes have not been so well elucidated, but they all seem to result from the production of altered ligases. The *vanA* gene is variably transferable by conjugation or transformation *in vitro* to other gram-positive bacteria, including *S. aureus (120)*, but it has not, until recently, been passed to other genera naturally. However, as described above, there were reports from the United States in 2002 of two unrelated clinical isolates of MRSA that had acquired the *vanA* gene, presumably from enterococci *(121)*. Only a handful of similar events have since been reported and continuing surveillance will reveal whether such strains will increase in prevalence in the future.

Vancomycin has been used for several decades, but acquired resistance was rare until a multiple strain outbreak of vancomycin- and teicoplanin-resistant enterococci appeared in London in 1986 *(159)*. Since then, such strains have been seen throughout the world. They are common in the United States, where the NNIS survey found a 20-fold increase in healthcare-associated VRE isolates during the period 1989 to 1993 *(160)* and a 47% increase in ICU isolates from 1994 to 1998 and in 1999 *(23)*. In US ICUs, about 12% of hospital isolates of enterococci are VRE. They are much less common in Europe.

In the EARSS surveillance data for 2008 *(24)*, no invasive vancomycin-resistant *E. faecium* were seen in 10/33 countries. However, three countries reported vancomycin resistance rates in *E. faecium* isolates of more than 25%, namely, Greece (28%), Ireland (35%), and the United Kingdom (28%). In several European countries, VRE rates have been declining, possibly as the result of improved control measures. The worldwide emergence of VRE has been associated with the spread of a major hospital-adapted clonal lineage (clonal complex 17: CC17) of *E. faecium* with a background of high-level aminoglycoside resistance *(161)*.

Although the origin of the vancomycin-resistance transposons is obscure, the emergence of this resistance has occurred during a time when the glycopeptides have been increasingly used for the treatment of multiresistant staphylococci, enterococci, and *C. difficile*–associated diarrhea *(162)*. Furthermore, outbreaks of healthcare-associated VRE are most common in renal, liver, and hematology departments and in ICUs where glycopeptide therapy is common.

A further source of glycopeptide "pressure" is the use of the antibiotic avoparcin in animal husbandry. Avoparcin is a glycopeptide related to vancomycin that is not used in human therapy but is added in small amounts to animal feed in Europe. Several studies suggest that in farms where avoparcin additives are used animal and human bowels become colonized with *vanA* type VRE, and frozen chickens in supermarkets may be a source of VRE for people unexposed to hospitals or glycopeptides *(163,164)*. After admission to hospital, treatment with glycopeptides may select these microorganisms from the bowel with resulting healthcare-associated infection *(165)*. As a result of these studies, several European countries have now banned avoparcin feed supplements, but this issue remains controversial. Avoparcin is not used in the United States, which has the greatest incidence of VRE and where transmission appears to be mainly healthcare-associated. The reasons for the differences in the epidemiology of VRE between Europe and the United States have not been fully elucidated *(166,167)* (see also Chapter 33).

Multiply Resistant Pneumococci *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia, the second most common cause of meningitis, the third most common cause of septicemia, and an important pathogen of otitis media. All of these are predominantly community-acquired infections. Until recently, the pneumococcus was fully sensitive to benzylpenicillin and not often considered an important hospital pathogen. However, the pneumococcus does cause hospital cross-infection *(168)*, and hospital outbreaks with multiply resistant strains (which are more readily recognized) are being reported with increasing frequency. Transmission is presumably by droplet spread, and ideally, infected patients should be nursed in side rooms.

S. pneumoniae frequently acquires resistance to tetracycline and sometimes to sulfonamides, erythromycin, lincomycin, or chloramphenicol. Pneumococci are normally relatively resistant to aminoglycosides (MICs of streptomycin 8 μg/mL), but some strains show high-level resistance (>2,000 μg/mL). Penicillin resistance was first reported in 1967 from Papua, New Guinea and, since then, has been seen with increasing frequency in many countries. Multiple resistance is an increasing problem, the most commonly seen patterns being resistance to penicillin and tetracycline and resistance to penicillin, tetracycline, and chloramphenicol.

Sensitive strains of pneumococci have penicillin MICs of 0.006 to 0.008 μg/mL. The first penicillin-resistant isolates showed low-level resistance with MICs of 0.1 to 1.0 μg/mL, but in 1977, pneumococci were isolated in South Africa showing high-level resistance with penicillin MICs of >1 μg/mL *(169)*. Penicillin resistance results from the stepwise acquisition of multiple genetic changes that produce various alterations in pneumococcal PBPs *(170)*. The variant sequences inserted into the PBP genes appear to have been derived by transformation from oral streptococcal species *(171)*. Although many penicillin-resistant isolates

of pneumococci are sensitive to newer β-lactams such as cefotaxime, some strains are resistant to these drugs by producing simultaneous changes in more than one penicillin-binding protein. Penicillin resistance in pneumococci may not be detected by routine sensitivity-testing methods, and for disc testing, a 1 mg oxacillin disk is recommended *(172)*.

The geographic variation in the distribution of resistant strains of pneumococci is considerable, even between different cities in the same country. In the EARSS surveillance data for 2008 *(24)*, 10% of all (>11,000) invasive *S. pneumoniae* isolates reported by 32 European countries were nonsusceptible to penicillin. Most northern countries had nonsusceptibility rates below 5%, but Finland (11%) and Ireland (23%) had relatively high rates. Rates of >25% were reported from southern and eastern Europe, including France (30%), Hungary (27%), and Turkey (34%). Other countries had even higher rates but with small numbers of isolates. In the US NNIS surveillance data up to 2004, penicillin resistance rates in healthcare-associated isolates were around 19% for both ICU and non-ICU patients (Table 86-2).

Since the early 1980s, many reports have appeared of hospital outbreaks of penicillin-resistant pneumococci *(173–176)*. These outbreaks often involve children or the elderly in day-care or chronic care centers. In these age groups, nasal carriage is common, and during outbreaks, other patients, staff members, and family members may become rapidly colonized by resistant pneumococci after casual contact with affected patients. Carriage may persist for several months, and the microorganisms may then disseminate further within the community.

Respiratory infections with strains of pneumococci showing low-level penicillin resistance can be treated with high doses of penicillin. Meningitis and infections with high-level resistant strains have been successfully treated with vancomycin or third-generation cephalosporins such as cefotaxime or ceftriaxone *(177,178)*. However, resistance to third-generation cephalosporins has increased dramatically in some areas *(179),* and there have been failures with these regimes in meningitis; a combination of vancomycin with cephalosporins, meropenem, or rifampin have been recommended *(180)*. Treatment with other antistaphylococcal agents such as erythromycin, chloramphenicol, lincomycin, or rifampin should be guided by the results of sensitivity testing.

Clostridium difficile *C. difficile is* a special type of antibiotic-resistant healthcare-associated pathogen. *C. difficile* is an anaerobic spore-forming bacillus that is widely distributed in the environment and colonizes the bowel asymptomatically in some people; it is resistant to several common antimicrobials. Antibiotic therapy tends to disrupt the normal sensitive bowel flora and allows antibiotic-resistant *C. difficile* to proliferate. Some classes of antibiotics, especially cephalosporins and quinolones, appear also to encourage the microorganism to sporulate and produce toxin. Toxigenic strains produce two toxins A and B *(181)* that act on the bowel mucosa to produce *C. difficile*–associated disease (CDAD). This ranges from mild, reversible diarrhea to pseudomembranous colitis, toxic megacolon, and fatal bowel perforation.

CDAD may occur as sporadic cases when carrier patients enter hospital and are started on broad-spectrum antibiotics. However, cross-infection from diarrheal CDAD patients to others may occur following contamination of staff hands or the hospital environment with spores. *C. difficile* is now the most common cause of healthcare-associated diarrhea *(181)*.

Since January 2004, English hospital trusts have been required to report cases of CDAD in inpatients older than 65 years. There was an increase in the numbers of reported cases of CDAD from 44,448 in 2004 to 51,690 in 2005 *(182)*. Increasing CDAD has been associated with significant and increasing mortality: the number of death certificates mentioning *C. difficile* in England and Wales increased from 975 in 1999 to 1,214 in 2001 and to 3,807 in 2005 *(183)*.

In addition to the continuing increase in endemic *C. difficile* infections, there have been recent reports from Canada, the United States, and Europe of large, often multicenter, hospital outbreaks of CDAD, associated with high rates of morbidity and mortality (20,*184,185,*186). These outbreaks have been caused by a new virulent and highly transmissible strain of *C. difficile*, referred to variously as toxinotype III, North American pulse field gel electrophoresis type 1, and PCR-ribotype 027 (NAP1/027) (186). This strain appears to be a hyperproducer of toxin and elaborates a binary toxin as well as toxins A and B. *C. difficile causing* CDAD is thus another environmental, opportunistic MDR pathogen that is encouraged by antimicrobial use, is spread by poor hygienic practice, and has increased dramatically in recent years (see also Chapter 37).

CONCLUDING REMARKS

Antimicrobial resistance, often multiple, has spared few healthcare-associated pathogens and is increasing inexorably. Even by the early 1990s, several authorities had warned that the emergence of essentially untreatable multiresistant healthcare-associated pathogens signified a crisis for antimicrobial therapy and heralded the end of the antibiotic era ((4): *The crisis in antibiotic resistance*; *(187)*: *Resistance to antimicrobial drugs — A worldwide calamity;* (1): *Epidemiology of drug resistance: implications for a post-antimicrobial era*). The situation has since deteriorated further and has been aggravated by the lack of new antimicrobials in the pharmaceutical pipeline *(188)*. The Infectious Diseases Society of America has produced a policy paper in response to this crisis entitled *Bad bugs, no drugs. As antibiotic discovery stagnates….a public health crisis brews* (189), and the European Academies Science Advisory Council and the European Society of Clinical Microbiology and Infectious Diseases have voiced similar concerns (*190,*191).

The lesson that should have been learned and taken to heart is that increasing antimicrobial use is associated with increasing antimicrobial resistance. The management and control of resistant infections in hospitals will depend more on the control of hospital infection and of unnecessary antimicrobial therapy than on the availability of yet more powerful antibiotics.

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CHAPTER 87

Antimicrobial Stewardship

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In the 20th century, the discovery of penicillin was regarded as one of the major medical advances that stimulated "the antibiotic revolution" (1). While transforming the prognosis of infections, by the middle of the last millennium, over 80% of patients diagnosed with acute bronchitis received antibiotics—a shift in public and professional behavior that was not supported by evidence of clinical benefit (2). Therefore, an increase in antimicrobial resistance was an inevitable, evolutionary consequence of the increased exposure of bacteria to antimicrobials *(3)*. Resistance is now a global public health problem that impacts clinical practice (1,2). Despite this problem, the perception among clinicians regarding the relevance of resistance to their clinical practice remains challenging. For example, a recent survey of 149 junior hospital doctors from France and Scotland showed that although 95% regarded resistance as a national problem, only 63% rated the problem as important in their own daily practice *(4)*. These results are consistent with other studies *(5–7)*, which show that only a minority of staff are aware of effective methods for reducing antimicrobial resistance.

Patients and the public have also an important role in reducing collateral damage from antibiotics *(8)*. In a large UK household survey, 79% of 7,120 respondents were aware that antibiotic resistance is a problem in British hospitals, but 38% of respondents did not know that antibiotics do not work against most coughs or colds, and 43% did not know that antibiotics can kill the bacteria that normally live on the skin and in the gut. Therefore, the education of clinicians and the public about resistance is important. The focus, however, should be on changing behavior rather than simply increasing knowledge about antibiotics or resistance. A recent analysis (9) of the value and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries concluded that hard scientific evidence for a cause–effect relationship is lacking because of multiple potential confounders, their multifaceted nature, and relatively poor availability of data. However, despite this, the results of several campaigns suggest they had a positive effect on the use of antibiotics, although whether this was related to change in the behavior of physicians, patients, or both was not made clear (9). While we wait for better designed interventions, one European campaign is worthy of attention. The European Parliament initiated an annual European Antibiotic Awareness Campaign in 2008, targeted at increasing awareness of the general public about the prudent use of antibiotics in 2008 and improving antibiotic use in primary care in 2009. The campaign for 2010 will focus on hospital prescriptions. The campaign materials include a focus on key unequivocal messages, logos, slogans, and media-related material such as toolkits and television coverage. Key success factors were good cooperation and process for building the campaign, strong political and stakeholder support, and the development of campaign materials based on scientific evidence (10).

WHAT IS ANTIMICROBIAL STEWARDSHIP?

In Europe in 2008, 16 countries had developed a national strategy to contain antimicrobial resistance, and 9 countries had an action plan *(11)*. If we are to preserve antibiotics as a valuable and precious resource and extend their useful life, a core component of most of these strategies is antimicrobial stewardship (ABS), which has been defined as a set of measures or interventions delivered by a multidisciplinary team working in healthcare institutions to optimize antimicrobial use among patients in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use including ecological effects such as resistance and *Clostridium difficile* infections (CDI) (12–14). There are also formidable hospital and society costs associated with antimicrobial-resistant infections (ARI). In a recent study of 1391 hospitalised patients 188 (13.5%) had a antimicrobial resistant infection (ARI). The medical costs attributable to the ARI ranged from $18,588 to $29,069 and excess duration of hospital stay and attributable mortality of 6.4 to 12.7 days and 6.5% respectively. The total costs to this patient cohort were $13.35 million in 2008. This study eloquently identifies the potential beneficial fiscal impact of good ABS programs and their cost-effectiveness (15).

At the heart of any stewardship program is an antimicrobial management (AMT) or stewardship (AST) team—terms commonly used for the multidisciplinary team. In this program, each member is given specific roles, which collectively take responsibility for the implementation of local policies. The critical value and role of the pharmacist as part of this team has recently been reviewed (16).

To be effective, the team must have full support from hospital leadership, work closely with infection control teams, and provide regular feedback to individual clinicians and clinical teams about their compliance with policies.

Stewardship programs are composed of organizational structures and action plans for implementing ABS. While many such programs have a hospital focus, they are also of relevance and importance to primary care (17). Targets for ABS include appropriate antibiotic selection, dosing, route, and duration of therapy. ABS needs to be combined with infection prevention measures and environmental decontamination to limit the emergence and transmission of antimicrobial resistance; this trio of measures will address the so-called holy trinity of resistance development and spread (18). This trinity recognizes that to minimize the development of resistance there must be a collaboration between ABS, infection control programs, and environmental service departments.

BOX 87-1

National Antimicrobial Prescribing Indicators Introduced by Scottish Government in 2009

Hospital-based empirical prescribing: Antibiotic prescriptions are compliant with the local antimicrobial policy, **and** the rationale for treatment is recorded in the clinical case notes in ≥95% of sampled cases.

Surgical antibiotic prophylaxis: Duration of surgical antibiotic prophylaxis is ≥24 h%, **and** it is compliant with local antimicrobial prescribing policy in ≥95% of sampled cases.

Primary care empirical prescribing: Seasonal variation in quinolone use (winter months vs. summer months) is ≤5%, calculated from PRISMS data held by NHS Boards.

(From Scottish Antimicrobial Prescribing Group. Available at *http://www.scottishmedicines.org.uk/smc/6616.html* (cited May, 2010).)

PRIMARY CARE ANTIMICROBIAL STEWARDSHIP

The focus of this review is primarily hospital stewardship programs. However, one should not underestimate the need for similar programs in the community, particularly long-term care facilities and the veterinary sector. They need to be developed and implemented strategically in conjunction and collaboration with hospital programs. There are many emerging examples of successful stewardship programs addressing primary care. Programs from Belgium (19), France (20), and Sweden (21,*22*) among others, are worthy of note. In France, a sustained national reduction in antibiotic use has been associated with a reduction in the proportion of penicillin-nonsusceptible *Streptococcus pneumoniae* in France *(23)*. More recently, in Israel a national restriction of ciprofloxacin use was associated with an immediate, marked reduction in ciprofloxacin resistance in gram-negative bacteria isolated from urine by 1.16% for each decrease of 1,000 DDDs (defined daily doses) in ciprofloxacin use (24). Of these successful national initiatives, very few have been linked with improved patient clinical outcomes, which is a long-term ambition of these interventions.

One example of a more cohesive national stewardship program that integrates community and hospital stewardship and has a focus on CDI, an important adverse ecological outcome, is emerging from Scotland. Hospital-based studies have shown that the introduction of conservative antibiotic policies in hospitals aligned with strict infection control was associated with a reduction in CDI (25,26). In Scotland, this was one of the key factors that stimulated a national stewardship program with one aim: to reduce *C. difficile*–associated diarrhea (CDAD). In 2009, the Scottish government announced a new health efficiency and access to treatment target for *C. difficile*–associated disease by the National Health Service (NHS) Scotland. This was defined as being "to reduce the **rate** of CDAD among patients aged 65 and over by at least 30% by 31 March 2011." The target will measure the rate of CDAD reported from acute hospitals, nonacute hospitals, and community settings per 1,000 occupied bed days in Scotland (27). Recognizing the key relationship between poor-quality antibiotic prescription, particularly cephalosporins and quinolones, and CDAD, the Scottish government and Scottish Antimicrobial Prescribing Group (SAPG) have agreed upon and set three supporting antimicrobial prescribing targets, in addition to infection control measures, that support and encourage hospitals and communities to achieve this CDAD target. The target related to community prescribing is seasonal variation in quinolone use (summer months vs. winter months). This indicator is now a set target of <5% variation for all health regions (NHS Health Boards) within Scotland *(28)*. This is 1 of 12 quality indicators to evaluate the impact of primary care ABS interventions that have been developed by the European Surveillance of Antimicrobial Consumption Group *(29)*. The indicators are either measurable from routinely available data or can be measured sustainably by clinical teams. Other targets related to hospital prescribing have also been set and are summarized in Box 87-1. In Scotland, national data on the primary care quinolones indicator is currently being analyzed, but data from the author's region, NHS Tayside, one of the health regions in Scotland, show that consumption has fallen by 2 prescriptions per 1,000 residents per month in the past year (D. Nathwani, personal communication). Assuming seven DDDs per prescription, this equates to a decrease of at least 3,000 DDDs per month in NHS Tayside's population of 350,000 people, which should be enough to reduce ciprofloxacin resistance in *E. coli* by 1% (24). Analysis of trends in antibiotic resistance will follow the analysis of the national impact of the primary care quinolone prescribing indicator.

The models of the various stewardship programs employed in the community need to reflect not only the clear differences in community and hospital-care provision but also national and regional sociocultural and economic differences in healthcare provision (30).

HOSPITAL ANTIMICROBIAL STEWARDSHIP

In the United States and Europe, a variety of organizations have proposed a framework and governing principles for hospital antimicrobial stewardship (H-ABS)

(2,14,17). This will help to support the development, implementation, and evaluation of existing and new programs within North America and Europe. However, their value in other countries may be more limited due to resourcing and sociocultural differences. For example, in India and Sri Lanka, 66% of community prescriptions include an antimicrobial, and in Bangladesh and Egypt, antibiotic use accounts for 54% and 61%, respectively, of all hospital prescriptions *(31)*. The potential value of ABS in such countries and its current role have recently been reviewed *(32)*. Therefore, a more global perspective, including cost-effectiveness of stewardship in developing countries, is also urgently required in keeping with the World Health Organization's aspirations *(33)*.

HOSPITAL ANTIMICROBIAL STEWARDSHIP GUIDANCE

In 2005 and 2008, MacDougall and Polk (12) and Owens (18) have comprehensively reviewed ABS programs in healthcare systems. It is not the intention of this review to detail the key studies identified in these and subsequent studies but rather to highlight systematic evaluations of recent literature and summarize their key findings.

The first systematic review of the literature was undertaken by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). The published guidelines (14) for developing an institutional program to enhance antimicrfobial stewardship provide a range of recommendations and the supporting evidence for the effectiveness of a range of strategies. Whilst the guidance is primarily from a US healthcare and hospital perspective, many of the recommendations are broadly applicable to most countries and settings. These recommendations are supported by the evidence base for the range of tools or interventions used in stewardship programs and are tabled (Table 87-1). These guidelines use the IDSA–United States Public Health Service grading system for ranking clinical guidelines *(34)*.

The Cochrane Effective Practice and Organization of Care (EPOC)Group acceptd three designs for the evaluation of interventions: clinical trials, controlled before-and-after studies, and interrupted time-series (ITS) analysis (35). Guidelines on the application of these designs to the evaluation of interventions to reduce infection have been published (36) together with guidance on statistical analysis (37,38). All of these sources agree that an uncontrolled before-and-after study is not a valid study design (35–38). Less than 50% of articles published in 2004 to 2006 about interventions to improve hospital antimicrobial prescribing (39) met these minimum standards set by the Cochrane EPOC Group, which is an issue that scientific journals need to address to improve the quality of their publications.

This Cochrane collaboration systematic review and meta-analysis of ABS interventions in the community (40) and hospital (39) is probably a more robust analysis since the quality of studies and evidence reviewed were subject to the strict criteria mentioned above. In these reviews, the most common method for the evaluation of interventions was an ITS in hospitals (55% of studies) compared with 28% randomized controlled trials. ITS design also had the lowest risk of bias compared with other study designs.

The design of the various inpatient-based studies, the type and target for the intervention, and the outcome measures are summarized in Table 87-2 (39). Eighty-one (76%) of one hundred and six interventions relating to prescriptions in hospital inpatients (39) were associated with statistically significant improvement in the primary outcome. Nineteen (18%) of the hospital interventions aimed at increasing the intensity of antibiotic treatment, and only eight (8%) studies targeted the decision to prescribe—often an important source of poor prescribing. The most common target for intervention was the choice of drug (80%).

Computerized decision support is a promising method for reducing the number of patients that receive unnecessary antibiotics (41), and one study has shown the potential for this approach in hospital care *(42)*. Forty-seven (44%) of the interventions included a restrictive component, which limited the choice of antibiotic to professionals. This supports one of the two key recommendations in the IDSA and SHEA guidelines (14): formulary restriction or a requirement for preapproval for a specific drug, or both. This is commonly called a "front-end program," where antimicrobials are made accessible through a formulary or approval process.

The two most common persuasive interventions used in hospitals were the distribution of educational materials and reminders. In the Cochrane review (39), only 10% of hospital interventions used audit and feedback—commonly called the "back-end" program where antimicrobial use is reviewed after therapy has been initiated and recommendations are made with regard to their appropriateness. The relatively small number of studies evaluating the impact of audits with intervention and feedback is interesting as this intervention is regarded as fundamental to effective ABS in the IDSA and SHEA guidance (14).

The conclusions from this and other Cochrane reviews (*43,44,*45) is that the most successful interventions are those that involve professionals who are catalysts for change in both the development and dissemination phases and who provide concurrent feedback about implementation. However, this approach requires a considerable investment of time by these professionals as well as a need for information systems that are capable of providing concurrent feedback. Simply providing prescribers with educational information may be relatively unsuccessful, but this approach also requires considerably fewer resources, and so it could be a more cost-effective method for achieving change. Relevant educational material is increasingly available but is of variable quality. A review (46) of the availability and quality of a range of Web-based educational material relating to ABSs in healthcare institutions revealed a wealth of material but also showed significant variability in terms of design and ease of navigation, the amount and scope of information, the availability of material in different languages, and the ability to download the material. The available resources had a US and European bias, but most included guidance, current news, and educational teaching material. The prudent antibiotic user website PAUSE (http//www.pause.online.org.uk) is particularly useful for undergraduate students but can be adapted for postgraduate use. It is

TABLE 87-1

Infectious Diseases Society of America's Recommendations for Specific Antimicrobial Stewardship Measures

Strategy	*Recommendation (Strength and Grade of Recommendation)*
1. Resourced multidisciplinary AMT or AST	A-111
2. Collaboration between AST, hospital infection control, pharmacy, and other relevant stakeholders	A-111
3. Hospital leadership support and engagement	A-111
4. Agreement between key stakeholders of authority, compensation and outcomes of program	A-111
5. Hospital organizational and administrative support	A-111
6A. Prospective audit with intervention and feedback	A1
6B. Formulary restriction and preauthorization to reduce use and cost	A11
Formulary restriction and preauthorization to reduce long-term resistance	B11-111
Education	A-111
Enhance knowledge	B-11
Education impact on changing prescribing behavior	
Guidelines and clinical pathways improve antibiotic use	A-1
Guidelines and clinical pathways implemented through education and feedback on antibiotic use and outcomes	A-111
Antibiotic cycling	C-11
Antimicrobial order forms	B-11
Combination therapy to prevent resistance	C-11
Combination therapy to increase breadth of cover	A-11
Streamlining or deescalation of therapy	A-11
Dose optimization	A-11
Intravenous (parenteral) to oral conversion to reduce length of hospital stay and costs	A-1
Healthcare information technology to improve the decision-making process:	A-111
Electroinic medical records	B-11
Computer physician order entry	B-11
Clinical decision support	
Effect of computer-based surveillance on tracking resistance patterns, identification of nosocomial infections and drug adverse events	B-11
Value of clinical microbiology to provide specific data on resistance and epidemiology of outbreaks	A-111
Value of process and outcome measures to determine impact of antimicrobial stewardship on antimicrobial use and resistance patterns	B-111

Note: Core strategies. A-1 means good evidence to support a recommendation for use based on evidence from one or more properly randomized controlled trials *(34)*. For a majority of the recommendations, the quality of evidence is not very high (i.e., A or B; 2 or 3). (Adapted from Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis* 2007;44:159–177.)

recommended by the European Society for Microbiology and Infectious Diseases [ESCMID].

The Cochrane reviews (39) also concluded that hospital-based restrictive interventions were associated with a greater immediate impact than persuasive interventions. However, the impact of persuasive and restrictive interventions was similar after 6 months, and after 12 months, there was a suggestion that persuasive interventions had greater impact (39). Despite this, a recent survey *(47)* of 190 junior and 250 specialist medical staff, of which 164 responded, 85% had a positive attitude to an antibiotic approval (restrictive) program as this approach made teams think carefully about antibiotic choice. 91% also believed the advice given was helpful and educational (88%). Only 10% believed this process undervalued their intuition and experience, and 19% believed it infringed upon their autonomy.

Whilst guidelines and systematic review evidence is helpful, they do not often help differentiate, for policymakers working in "real-world" settings, the most effective interventions to implement based on clinical and cost-effectiveness grounds. Perhaps the next logical step in guideline development for stewardship may be to use the GRADE approach *(48)*. This approach may help patients, clinicians and policymakers better understand the implications of adopting guideline recommendations of variable strength. The GRADE approach encompasses recommendations based on a balance between the desirable and undesirable effects of an intervention, the quality of evidence, the value and

TABLE 87-2

Comparison of Evaluations of Interventions to Improve Antimicrobial Prescribing for Hospital Inpatients[a]

Comparison	*Hospital Inpatients*	
Design	***Number***	***%[a]***
Controlled before and after study	15	14
Controlled clinical trial	3	3
Randomized clinical trial	30	28
Interrupted time series	58	55
Target		
Under treatment of infection	19	18
Decision to prescribe	8	8
Choice of drug	89	84
Timing	9	8
Duration of treatment	17	16
Intervention		
Persuasive, professional	56	53
Restrictive, healthcare system	47	44
Structural	7	7
Single component	63	59
Multifaceted	44	42
Outcome		
Antimicrobial use	88	83
Financial savings	33	31
Clinical outcome	32	30
Microbial outcomes	31	29
Cost of design and implementation of the intervention	13	12
Total studies	**106**	

[a]Some studies had more than one target or outcome.
(From Davey P, Brown E, Fenelon L, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev (Online)* 2005:CD003543.)

preferences of key stakeholders, and cost (or resource) allocation. This makes the decision-making process of what intervention(s) to adopt more "real world"–informed and transparent but accepts that, ultimately, successful implementation of all or some of these measures will be dependent on local need, organization, available resources, and priorities. The Cochrane systematic reviews (39), for example, identified significant gaps in the evidence base relating to cost-effectiveness. Thirty-one percent of hospital-care studies estimated the financial savings from a reduction in the use of target drugs, but only twelve percent of studies included information about the cost of design and implementation of the intervention, which is essential to the overall assessment of cost-effectiveness.

Whilst these reviews do inform the development and implementation of a stewardship program, local involvement and planning with all key agencies to seek consensus and ownership at a provincial and/or regional level is crucial. A recent example of reaching local consensus for a particular region has been the Ontario, Canada, Antimicrobial Stewardship Project *(49)*. The recommendations of a consensus conference indentified priority intervention for Ontario hospitals. This group acknowledged key drivers for successful stewardship and identified the core elements of the program and the required marketing strategy to support the implementation of a program within their region. The consensus conference identified the following core generic messages that would be relevant for most programs globally:

1. ABS programs are, first and foremost, patient safety and quality of care initiatives. They are also cost-effective across healthcare systems. The World Health Organization recognizes antibiotic resistance as third in priority on a list of patient safety challenges.
2. ABS programs and interventions are needed at provincial, regional, and local levels and should require accreditation by a national relevant body.
3. Implementation of programs need organizational and clinical leadership, performance accountability, and should be supported by dedicated and sustained resources, a multidisciplinary team of experts, information technology, education and training, measurement capability, and marketing strategy.
4. Existing and new networks and resources should be used or developed to support the effective implementation of ABS programs.

For those seeking a more European perspective, a recent European Union workshop in 2009 developed a conceptual framework for the implementation of ABS in the European Union (17). It aims to define the structural and organizational requirements so as to optimize antibiotic use in hospitalized patients. This framework recognizes: (a) the relevance of community care, (b) the importance of further research on the comparative clinical and cost-effectiveness of a range of interventions, (c) the need to strengthen the legal basis and core funding of ABS programs, and (d) the need to ensure that ABS is a core component of quality improvement and patient safety promotion initiatives. In Scotland, for example, healthcare-associated infections (HAIs) and ABS are now key components of the Scottish Patient Safety Program, a national quality improvement health initiative *(50)*. This program is immersed in the Institute of Health Care Improvement Methodology *(51)* to support achieving safe and reliable healthcare (52). At the heart of achieving improvement in HAI is teamworking, organizational change, and an improvement model where change is driven and evaluated through rapid tests of change called the Plan-Do-Study-Act (PDSA) cycle. The PDSA cycle is shorthand for testing a change by developing a plan to test the change (plan), carrying out the test (do), observing and learning from the consequences (study), and determining what modifications should be made to the test (act) *(53)*. The Institute for Healthcare Improvement has also developed the concept of care bundles to help healthcare providers improve the reliability of delivery of essential healthcare processes *(54)*. This has emerged from the acknowledgement that healthcare delivery is too dependent on individual clinicians' knowledge, motivation, and skills, with the result that only approximately 50% of patients receive the recommended care *(55)*. One explanation is that processes in healthcare are rarely designed to meet specific, articulated reliability goals *(55,56)*. A care bundle is a small set of practices that have been

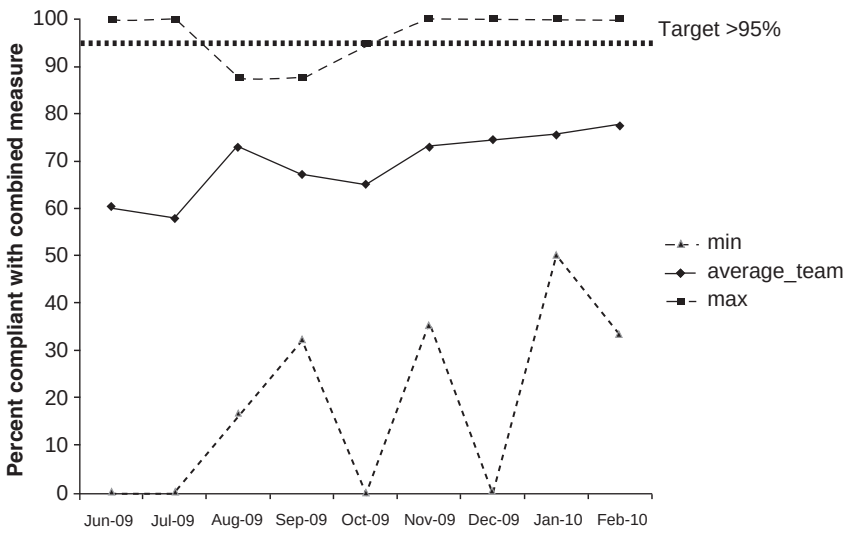
individually proven to improve patient outcomes and, when implemented together, are expected to result in a better outcome than when implemented individually *(54)*. The impact of a bundle depends both on the evidence that supports the recommended care processes and on the implementation and spread of its recommendations. Their value in infection prevention and management has recently been reviewed (57).

Implementation of Antimicrobial Stewardship Programs

Despite the publication of national ABS guidance, many surveys show that their recommendations have not been widely adopted or routinely implemented. For example, in the United Kingdom in 1994, only 62% of 427 UK hospitals had a policy for antibiotic therapy and 75% had an antibiotic formulary *(58)*. Following interventions by the Department of Health to pursue any hospitals that did not have a formal prescription policy, a further survey of acute healthcare trust in England in 2004 to 2005 revealed that an antimicrobial policy was in place in 89% of responding trusts (109/123) *(59)*. This is an improvement on the previous survey result, but it is disappointing that 11% of responding hospitals had not taken the essential first step of writing an antibiotic policy. In the United States, 100% of 47 hospitals surveyed in 2000 had an antibiotic formulary *(60)*. However, only 47% had written policies for surgical prophylaxis—a key area of antibiotic misuse *(61)*. On a more encouraging note, a recent 2010 nationwide self-reporting survey from Belgian hospitals (62) of the national implementation of AMTs in hospitals revealed >90% adoption of stewardship interventions such as a formulary, practice guidelines for antibiotic therapy and surgical prophylaxis, and analysis of consumption data. All hospitals had an active AMT and many had appropriate interactions with the infection control teams and hospital management. This study also emphasizes the key role of AMTs in H-ABS. The survey is available electronically on the JAC website (http://jac.oxfordjournals.org/) and may be useful for developed countries wishing to gauge the maturity of stewardship programs within their hospitals.

Efficacy of Antimicrobial Stewardship Programs

The reviews by MacDougall and Polk in 2006 (12) and Lesprit and Brun-Buisson in 2008 *(63)* have summarized the evidence base and flaws with studies that have aimed to measure the impact of stewardship programs. The Cochrane reviews (39) identified that 32 (30%) of the hospital-based studies included reliable data about clinical outcomes. In only 12 of these studies was the intervention either wholly ($n = 8$) or partially ($n = 4$) designed to increase the intensity of antibiotic treatment. Clinical outcomes were measured in only 20 (23%) of 87 studies that aimed solely to reduce the intensity of antibiotic treatment. These latter studies do provide some reassurance that there were no unintended



Boards involved	3	3	5	7	9	10	12	13	14
Hospital units	15	12	14	23	27	31	34	37	42
Number units>95%	0	1	0	0	1	3	5	5	5
% units >95%	0%	8%	0%	0%	4%	10%	15%	14%	12%

FIGURE 87-1 Compliance with a combined measure of empirical antimicrobial prescribing in 14 NHS Boards in Scotland. The combined measure has two components: is the indication for treatment in the notes and is the treatment compliant with hospital policy? Data are collected from medical, surgical, and care of the elderly admission units. Data shown are as posted on April 20, 2010.

adverse clinical consequences of this reduction. Thirty-one (29%) hospital studies provided reliable data about microbial outcomes, and 24 interventions were associated with significant improvement. Studies with microbial outcomes are subject to additional risks of bias (39).

How Should Compliance with Antibiotic Stewardship Programs be Monitored?

One of the key components of ABS programs is an antibiotic policy or guideline for empiric treatment of infection or sepsis, disease-specific guidelines, and surgical prophylaxis. Measuring compliance with these policies is a common target for measuring compliance with stewardship programs. Hospitals fortunate enough to have sophisticated information systems may be able to use these to monitor compliance with policies *(64)*. However, this remains the exception rather than the rule. Less sophisticated information systems can still provide valuable information, but there is often no substitute for the manual collection of data *(65)*. This is not necessarily as daunting as it may seem. A 1-day prevalence survey of an entire hospital can be achieved in a few hours and may be a useful tool to detect deviations from guidelines and to provide physicians with educational feedback. The European Surveillance of Antimicrobial Consumption project has adapted a Web-based tool developed in Sweden for antibiotic surveillance (66) and has successfully used it for comparative surveillance of hospitals in 20 European countries (67). A variety of staff can be involved in auditing policies, including trainee nurses, pharmacists, doctors, and medical students *(68)*. Participation in data collection is an educational experience, and the information can be used to agree upon care bundles of three or four essential processes of care that must be completed and documented for every patient to monitor antibiotic compliance and review infection management *(69)*.

A more target- or performance-driven approach is to set nationally agreed compliance targets for key components of antibiotic prescribing in hospitals. In Scotland, for example, the two hospital prescribing indicators for acute hospital admission, empirical prescribing and surgical prophylaxis, were chosen to measure compliance with local antimicrobial policies. The SAPG had previously recommended a review of all hospital antimicrobials to restrict agents associated with CDI *(70)*. Compliance with this policy would, therefore, provide an assurance that these agents were not being used. Data for the combined (compliance with policy and recording in the medical case notes) hospital empirical prescribing measures show steady improvement in the average from June 2009, despite the fact that the number of participating hospital units has increased from 15 to 42 (Fig. 87-1). In the data from December 2009 to March 2010, at least 10% of hospital units have achieved the target of 95% reliability for the recording of diagnoses in notes and compliance with the local antibiotic policy.

CONCLUSIONS

Antibiotic stewardship must be integrated with infection prevention and control and environmental decontamination. Pivotal to this is the regular collation, analysis, interpretation, and feedback of data about antibiotic use, resistance, and clinical outcomes of infection at a local and national level.

A review of current evidence suggests that the evidence base for antibiotic stewardship should be strengthened by supporting evaluations that meet the minimum method criteria for inclusion in a Cochrane systematic review. Similarly, the cost-effectiveness of these interventions require further study with methodological rigor.

AMTs need to be supported both legally and fiscally with strong local and national leadership and alignment with quality improvement and patient safety programs. There is also a growing evidence base for effective behavioral and structural interventions and modern educational interventions to support antibiotic stewardship.

ACKNOWLEDGMENTS

I would like to thank my colleague Peter Davey for his immense contributions to ABSs and his guidance and support in helping me write this review. I also acknowledge the contributions of members of the SAPG and have their permission to share some of their data.

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SECTION XIV
The Literature in Healthcare Epidemiology and Infection Control

CHAPTER 88

A Methodologically Focused Review of the Literature in Healthcare Epidemiology and Infection Control

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The use of appropriate epidemiologic methods in experimental design and data analysis is recognized as an important aspect of generating sound scientific evidence in healthcare research. This chapter discusses methodologies relevant to epidemiologic, outcome, and intervention studies, as they are applied to problems of healthcare-associated infections. We stress common pitfalls and focus particularly on limitations of the published literature in healthcare epidemiology. Although the quality of studies in this field has improved over the last decade, many study reports still remain inadequate and lack methodological rigor.

Although many of the basic ideas of healthcare epidemiology can be traced back to Semmelweis *(1)*, the formal application of epidemiologic methods in infection control received a substantial boost during the 1970s and 1980s, with the publication of a number of methodologically oriented articles that brought innovation to the field (*2,3*,4,*5*). These influential, seminal articles covered topics such as the relationship between prevalence and incidence, matched cohort study design, confounding, and effect modification. Based on the assumption that healthcare-associated infections have causal and preventive factors that can be identified through systematic investigation, these articles demonstrated convincingly that epidemiologic methods add important knowledge to reduce the rates of healthcare-associated infections. Thus, the conceptual framework was laid for many interventional and observational studies in the field.

This chapter is based on this seminal body of work and brings to the readers' attention newer methodologies and principles. Recent advances in the conceptual underpinnings of epidemiology and selection of statistical models that facilitate causal inference may not have garnered widespread attention by Infection Preventionists and healthcare epidemiologists. Using selected articles as examples, the quality of methods in the infection control literature is discussed and opportunities for improvement are highlighted. By necessity, our review of articles and choice of topics is selective. The criticisms and suggestions, which complement the information presented in Chapters 1 to 4, are intended to be constructive. Some of our arguments may even challenge conventional wisdom and, in the process, stimulate a fresh perspective on the literature in infection control and healthcare epidemiology.

The chapter is organized into five sections based on specific recommendations for improving the quality of observational research in infection control and translating that research into action:

1. Use terminology clearly and precisely.
2. Search for and destroy confounding (as much as possible).
3. Recognize selection bias in all of its guises.
4. Account for timing of exposures and time at risk.
5. Develop guidelines according to explicit rules.

Diligent adherence by authors to these recommendations will facilitate clarity, completeness, and transparency of reporting of observational research in our field. Note that this chapter does not include recommendations for designing, conducting, and analyzing clinical trials and intervention

studies with a quasi-experimental design. The limitations and challenges of the latter study design have been underscored in recent years (6,7). Several approaches may help optimize the design of such quasi-experimental studies (i.e., "before and after" intervention studies) *(8)*. The ORION Statement published in 2007 provides standards for the design of high-quality quasi-experimental studies and outbreak reports (9). In particular, univariate and multivariate time-series analyses may complement conventional analytical methods and could be useful to study intervention effects in quasi-experimental studies. For instance, time-series methods have been applied for quasi-experimental study designs in which rates of antibiotic-resistant infections are ascertained before and after an intervention *(10,11)*. However, uncertainties still remain regarding the use of time-series analysis as an appropriate research methodology for analyzing the effect of infection control interventions and antibiotic policies on the epidemiology of multidrug-resistant microorganisms *(12)*.

RECOMMENDATION 1: USE TERMINOLOGY CLEARLY AND PRECISELY

Fundamental to scientific reasoning is the correct use of terminology. Several expressions used in healthcare epidemiology are misnomers, well embedded in everyday use. Table 88-1 summarizes several commonly misused terms and suggests more accurate terms.

Confusion in Classification of Study Design and Use of Terms *Case* and *Control*

Misnomers regarding terminology appear to be particularly common in conjunction with studies that examine outcomes of infections and other adverse events. If patients with a healthcare-associated infection are being compared to patients without healthcare-associated infection with respect to an outcome such as length of stay, mortality, or medical costs, a *cohort study* is being conducted, assuming that patients are selected on the basis of the presence or absence of infection. The infection constitutes the exposure. Similarly, studies in which outcomes of patients with a resistant microorganism are compared with outcomes of patients with the susceptible form of the microorganism are following a cohort design. If exposed and nonexposed subjects are matched on other criteria, such as age and severity of illness, the study is a *matched cohort study*. The distinction between matched cohort and matched case–control studies is not just a semantic one. In a matched case–control study, it is necessary to perform a matched analysis if the matching factors are associated with exposure, even if they are not associated with the outcome, whereas in a matched cohort study, this requirement does not exist *(13)*.

Abundant examples exist in which the terms *case* and *control* are used in the context of a matched cohort study, leading to confusion about the study design *(14)*. For instance, a study *(15)* about the "attributable mortality rate" of bacteremia due to methicillin-resistant *Staphylococcus aureus* (MRSA) claimed to perform a "retrospective cohort analysis and two independent case–control analyses." As outlined above, this terminology is incorrect, since in all three analyses, outcomes were compared, and thus, the term *matched cohort studies* would have been more appropriate.

Multiple Meanings of the Term *Attributable*

Perhaps nowhere is terminology in healthcare epidemiology more confusing than in the use of the word *attributable* (*16,*17). This word is included in a myriad of epidemiologic

TABLE 88-1

Terminology: Commonly Used Problematic and Ambiguous Terms

Commonly Used Name	*More Appropriate Term*	*Explanation*
Prevalence rate	**Prevalence or prevalence proportion**	Prevalence is the proportion of a specified population with a condition or disease at a defined point in time. A rate is the magnitude of change of one entity divided by another entity. Rates have different units in the numerator and denominator. *Prevalence rate* is an example of a term in which the word "rate" is used inappropriately to mean proportion.
Matched case–control study	**Matched cohort study**	Retrospective studies assessing the impact of healthcare-associated infections are comparing outcomes (deaths, costs) as principle study measurement. Since the exposure is known (presence or absence of an infection) and the outcome unknown, it is a cohort study by definition.
Mortality rate	**Case–fatality proportion or fraction**	*Mortality rate* is often used as a synonym for the incidence proportion of deaths in a study cohort due to the disease of interest. Similar to the expression *prevalence rate*, it would be more accurate to use the terms *case–fatality proportion* or *case–fatality fraction*.
Attributable fraction	**Excess fraction**	If the term *attributable fraction* is taken to mean the fraction of disease (or deaths) in which exposure was a contributory cause of disease, strong biologic assumptions are required. In order to avoid this problem, the term *excess fraction* is preferred.

terms with meanings that vary widely. The dictionary definition of *attributable* is "ascribed to" and, in epidemiology, it is frequently taken to be synonymous with "caused by." However, there are two types of causation that are often not distinguished. During a defined follow-up period, an exposure may either shorten the interval to occurrence of disease or cause a disease case to occur that otherwise would not have occurred *(18)*. The former is an *accelerated disease case*, whereas the latter is an *excess case*. If exposure prevents disease, this may be restated to indicate that exposure either lengthens the interval to occurrence of disease or averts a case from happening that otherwise would have occurred.

The rationale for constructing formulas to measure the *attributable fraction* is that not all disease in exposed patients is necessarily due to exposure: some exposed individuals would have developed disease, even at the same time, if they had not been exposed. It is also evident that the ratio of exposed patients belonging to these two causal types, accelerated or excess cases, depends on the duration of the follow-up. It can be shown that, compared to the enumeration of excess cases, deriving an estimate of the number of accelerated cases relies on additional, more tenuous assumptions about the form of the causal relationship between exposure and disease. Hence, rather than attempting to estimate the fraction of exposed cases that are caused by exposure, it is generally preferred to restrict attention to excess cases. The occurrence of excess cases can be estimated by simply comparing the incidence proportion in exposed individuals to the incidence proportion in nonexposed individuals, assuming that confounding is absent. Due to these considerations, Greenland and Robins *(19,20)* recommend the use of the term *excess fraction* in place of *attributable fraction* when the objective is to quantify the fraction of exposed cases that are excess cases caused by exposure. They reserve the term *etiologic fraction* to indicate the proportion of exposed cases caused by exposure, including both types of causation. The *population excess fraction* is an estimate of the fraction of all cases in the population that are excess cases due to exposure. The set of terms that cover these concepts are referred to as the family of *attributable fractions (13,19)*.

In contrast to the rich literature available in the field of chronic disease epidemiology, controlled studies aiming to determine the proportion of hospital deaths attributable to healthcare-associated infection are both rare and insufficient for the calculation of stable estimates *(21)*. Furthermore, several methodological issues have to be considered, since the causal relationship between exposure to infection and death can be jeopardized by multiple confounders and biases (see example 3 below: *Excess Mortality Due to MRSA Bloodstream Infection*). Clearly, the choice of methods does matter when the excess burden of healthcare-associated infections needs to be assessed. For instance, in a recent cohort study by a French group investigating the outcome of 8,068 critically ill patients, the statistical association between intensive care unit (ICU)-acquired infection and mortality tended to be less pronounced in findings based on the population excess fraction than in study findings based on estimates of relative risk (17).

RECOMMENDATION 2: SEARCH FOR AND DESTROY CONFOUNDING

This section discusses the central challenge in epidemiology, namely, how to reduce confounding. Informative examples from the published literature in infection control that have relevance to key aspects of the problem of confounding have been selected for pedagogic purposes. Prior to evaluating the quality of the methods used in these investigations, we provide an in-depth explanation of why confounding is important and how it arises. There are four research questions covered by the chosen articles, reworded here to be as explicit as possible:

1. Does prolonged postoperative antimicrobial use increase the risk of healthcare-associated bloodstream infection (BSI) compared to short postoperative antimicrobial prophylaxis?
2. How much does inadequate antimicrobial treatment of BSI in critically ill patients heighten the risk of death compared with adequate antimicrobial treatment?
3. Among patients with BSIs due to *S. aureus*, does methicillin-resistance increase the risk of death compared to methicillin-susceptible infection?
4. Does perioperative antimicrobial prophylaxis decrease the risk of surgical site infection (SSI) after clean surgery compared to no prophylaxis?

Background

The surgeon who explains that the reason his or her patients have a higher infection rate is that he or she operates on sicker patients demonstrates an informal grasp of the concept of confounding. However, when it is necessary to conduct and analyze an epidemiologic investigation, this intuitive understanding of confounding reveals its limitations. We begin by offering two core principles that may run somewhat counter to conventional wisdom:

1. It is not possible to use *statistical criteria alone* to recognize confounding or to determine whether it has been removed.
2. Confounding is identifiable only in the context of a *causal model (22)*.

Confounding is present when there is discordance between the *true causal effect* of an exposure on the outcome in a target population and the *measured association* between exposure and disease *(23)*. Thus, an exploration of confounding starts with an exposition on causation. What is meant by *true causal effect*?

Causation is best understood in terms of the question: What would have happened if the exposure had not occurred? Stated another way, the causal effect of exposure in exposed individuals is represented by the difference between their actual disease status and what would have happened if everything else had been the same up until the time of exposure, but that they had then not been exposed or exposed to a different degree in the latter scenario *(23)*. Under this formulation, causation is defined on the basis of a comparison between outcomes under mutually exclusive conditions: exposed and unexposed or, alternatively, varied levels of exposure. However, in any single patient, only one of these conditions is observed. In the absence

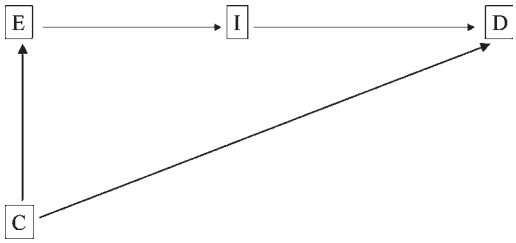

FIGURE 88-1 Graphical representation of causal relationships illustrated by *directed acyclic graphs*. An exposure (E) has both direct and indirect effects on disease (D). The indirect effects are mediated by an intermediate variable (I). A confounding factor (C) is a cause of both the exposure (E) and the disease (D).

of time machines to replay experience under dissimilar exposure conditions, a straightforward way to directly measure causal effects is not available. When exposure is randomly allocated, it is possible to derive an estimate of the unconfounded, average causal effect of exposure, with a random error correlated with sample size. In the absence of random allocation of exposure, causal inference relies on untestable beliefs regarding causal relationships and unmeasured confounders *(24)*.

It is useful to depict assumptions about causal relationships in a graphical format to identify potential sources of confounding. The causal effects of exposure on disease may be visualized as arrows aiming from exposure to disease (Fig. 88-1). These arrows represent the postulated causal mechanisms or pathways by which exposure affects the outcome or disease. Causal pathways that link exposure (E) and disease (D) may be direct or indirect. An indirect pathway is characterized by the presence of an "intermediate variable" (I) that mediates a causal effect, whereas a direct effect lacks an intermediate variable. The causal null hypothesis is the assumption that there are no indirect or direct causal pathways pointing from exposure to disease. Graphical representations of causal relationships are called *directed acyclic graphs* (25,*26*).

Confounding arises when direct or indirect causes of exposure are also direct or indirect causes of disease status. When exposure is a type of treatment and confounding is due to factors that influence treatment selection, the term *confounding by indication* is sometimes used *(27,28)*. Causes of exposure can be visualized as arrows pointing toward exposure. If these inputs into exposure also have outputs connecting to disease through paths that do not include exposure, noncausal pathways from exposure to disease exist. The labeling of a pathway as noncausal is done from the perspective of exposure and disease. If research questions pertain to multiple exposures, the postulated connections between each factor of interest and disease may, in turn, be divided into causal or noncausal pathways. Noncausal pathways create an association between exposure and disease, one that is not a consequence of exposure, hence the need to block the noncausal pathways if the goal is to estimate the true causal effects of exposure. Factors located within these noncausal pathways are usually associated both with exposure and disease, although in any given study these associations may themselves be obscured by confounding, and therefore, not manifested (*23,*29).

Successful randomization eliminates confounding by breaking the causal inputs into exposure or treatment. It makes the exposure or treatment actually received independent of what would have happened had exposure been absent or altered. This principle, which is surprisingly difficult to grasp, is another way to define the absence of confounding. The goal of epidemiology is to attempt to accomplish this feat with respect to measured confounders, using appropriate design and analytic strategies (29).

Perhaps what poses the most difficulty to individuals conducting epidemiologic research and readers of the literature is the myriad of statistical techniques available to analyze data. These statistical methods are not reviewed in detail here. Detailed recommendations for conducting methodologically sound multivariable analyses of observational studies have been summarized elsewhere (30,31). Rather, our goal is to emphasize the distinction between the statistical evaluation of association and the identification of confounding. Contrary to widespread belief, the *p*-value is not a useful test of confounding. Even the comparison of crude and adjusted measures of association is an inadequate approach by itself to detect confounding. Depending on the causal model, the adjusted measure of association may be more or less confounded than the crude measure. The judgment of whether an adjusted association is less confounded than a crude association relies on assumptions about the causal relationships between exposure, outcome, and the adjustment variables *(32)*.

Example 1: Prolonged Antimicrobial Prophylaxis

The first step toward reducing confounding in observational research on causal effects is to recognize its potential existence and to obtain measurements on potential confounders or to account for potential confounding during the design phase of the study. Sometimes these initial steps are omitted, as the following example illustrates.

Many investigators have examined the effect of antimicrobials on the subsequent occurrence of infection. Under certain conditions, systemic antibiotic use may decrease the risk of healthcare-associated infection. This has been demonstrated in clinical trials on ventilator-associated pneumonia (VAP) *(33,34)*. An opposite effect of antimicrobial prophylaxis was suggested in a study that found that the duration of antimicrobial prophylaxis after major surgery was associated with a significantly increased risk of healthcare-associated BSI *(35)*. The authors of this study observed six cases of BSI among 180 patients receiving short antibiotic prophylaxis, compared with 16 cases of BSI in 94 patients with extended antibiotic prophylaxis (crude odds ratio [OR], 5.9). These results were published without any consideration of the possibility of confounding.

In an observational study we conducted on the relationship between duration of antimicrobial prophylaxis and infections *(36)*, we found a strong association between prolonged antibiotic prophylaxis and subsequent healthcare-associated BSI in the crude analysis. A total of 2,641 patients undergoing cardiac surgery were included in the study, divided into those in whom antimicrobial prophylaxis was short (<48 hours) and those in whom antibiotic prophylaxis was prolonged (>48 hours) *(36)*. The unadjusted analysis revealed an OR of 3.3, based on the

occurrence of 27 cases of healthcare-associated BSI (1.8%) after 1,478 procedures using short antibiotic prophylaxis compared with 65 cases of healthcare-associated BSI (5.7%) after 1,139 operations with prolonged antibiotic prophylaxis. The problem with this crude analysis was that the length of follow-up and ICU stay affected the likelihood of receiving prolonged antimicrobial prophylaxis.

Using survival analysis methods removed confounding related to differences in the length of follow-up; the apparent association appeared smaller (hazard ratio [HR], 1.7) based on Cox proportional hazards regression. Seventy-seven percent of cases of healthcare-associated BSI occurred in patients who stayed longer than 4 days in the ICU. Similarly, extended antibiotic prophylaxis was correlated with longer ICU stay. After stratifying for length of ICU stay, prolonged antibiotic prophylaxis was not associated with a significantly increased risk of BSI (HR, 1.4). In an additional analysis, we showed that prolonged antibiotic prophylaxis did not decrease the incidence of SSI; however, it increased the risk of isolation of resistant gram-negative bacteria and vancomycin-resistant enterococci (VRE) (37). In summary, these results demonstrate confounding of the crude association between prolonged antibiotic prophylaxis and healthcare-associated BSI by differences in follow-up and length of ICU stay *(36)*.

Example 2: Inadequate Antimicrobial Therapy

Frequently, investigators do attempt to address confounding but use analytic methods that are suboptimal. A common error is to identify confounders primarily on the basis of the statistical significance of the association between the outcome and potential confounders. This strategy is inappropriate when the purpose of the regression model is to estimate the magnitude of the causal effect of an exposure on an outcome.

As an example, consider studies that have examined the impact of inadequate antimicrobial treatment of infection on patient outcomes *(38–41)*. This is a research question that is not amenable to direct testing in a randomized trial, since it would be unethical to willingly expose patients to inappropriate treatment. To answer the question, therefore, we have to rely on observational studies. On the face of it, it is highly likely that inadequate antimicrobial therapy does have some negative effect on outcome in critically ill patients. The key objective of an observational study, then, is to remove as much of the confounding as possible so as to obtain an unbiased estimate of the magnitude of effect of inadequate therapy. In one such widely cited study of patients in the ICU with BSI, therapy was defined as inadequate if the antimicrobials being given to the patient were ineffective against the causative pathogen at the time that identification and susceptibility results were reported by the clinical microbiologic laboratory *(42)*. The crude relative risk for mortality after inadequate therapy compared with adequate therapy equaled 2.2, corresponding to a crude OR of 4.1 *(42)*. The "adjusted" effect estimate of inadequate antimicrobial treatment of BSI on hospital mortality had an OR of 6.9, after including the use of vasopressors, age, organ dysfunctions, and severity of illness, along with inadequate therapy, in a multivariable logistic regression model.

A major limitation with this analysis was that the factors included in the logistic regression model were only those found to be significantly associated with mortality. A stepwise variable selection approach was used with a *p*-value of .05 as the limit for the acceptance or removal of new terms. The problem is that this method does not remove confounding by factors not selected in the model. Many characteristics were identified that distinguished patients with inappropriate and appropriate antimicrobial use, such as time in the hospital prior to BSI, prior use of antimicrobials, and serum albumin. Presumably, these were factors that directly or indirectly influenced the probability that treatment was inadequate or were proxies for such factors. Some of these factors were also associated with the outcome but not always to a statistically significant degree. Not including these factors in the model likely contributed to an exaggerated estimate of effect *(42)*.

All observational research is limited by the possibility of residual confounding due to unmeasured variables, but given a postulated causal model and a set of measured variables, some analytic strategies are less prone to confounding than others (25). The key point is that confounders do not have to be statistically significantly associated with the outcome to be confounders. As stated in the background section, the results of statistical hypothesis testing are tangential to the recognition of confounding. To some extent, the notion that confounders should be significantly associated with the outcome reflects the belief that the only "true" associations are ones that are statistically significant. Instead of focusing on statistical significance, the analysis should be directed toward a careful consideration of the potential sources of confounding and deriving the least-biased estimate of the true causal effect.

A frequently overlooked problem with conventional regression models is that they impose assumptions regarding the form of the relationship between the additional model factors and the outcome and between these additional factors and the exposure, which, if incorrect, may increase confounding *(43)*. The association parameter derived from the regression model provides an estimate of the unconfounded causal effect of exposure only when all of the assumptions of the multivariable model are correct. In addition, automated variable selection methods completely ignore the relationship between the putative confounders and the exposure. If the factors selected into the model are affected by exposure, their inclusion may also be deleterious with respect to confounding. This problem is discussed in more detail below.

Traditional stratification methods have an advantage over regression models because they involve fewer assumptions, but they lead to sparse numbers within strata when multiple confounders are present (44). Newer analytic strategies have been developed that overcome some of these types of problems and allow improved causal inference. These more robust methods start with a specification of the exposure of interest and build on an explicit structural model of causal relationships *(45)*. Another recent advance in epidemiology is the use of simulation to increase the flexibility of sensitivity analyses of confounding and other types of bias *(46,47)*.

One analytic method that has gained widespread application is the use of propensity scores, particularly for point exposures that are dichotomous or categorical *(28)*. The propensity score is the probability of exposure or treatment

based on factors that influence treatment, and thus, lies between 0 and 1 *(48)*. A multivariable logistic regression model is typically used to estimate this probability, and most commonly, the propensity score is used as either a matching or stratification variable to remove confounding by indication due to measured factors *(49)*. The propensity score method relies on assumptions about the form of the relationship between the confounder and exposure but is less susceptible than traditional models to bias by misspecification of the relationship between the confounders and the outcome *(50)*.

Example 3: Excess Mortality Due to MRSA Bloodstream Infection

Including a variable for adjustment sometimes increases confounding rather than reduces it. This happens when the adjuster is a consequence of the exposure of the interest and either lies on one of the causal paths between exposure and the outcome or is also an effect of the outcome *(51)*.

A number of investigators have compared outcomes in patients with resistant and susceptible infection *(40,52,53)*. In such studies, it is especially crucial to precisely specify the causal hypothesis of interest. Often, it pertains to the virulence of the microorganism: Do infections due to the resistant form of the microorganism have worse, similar, or better outcomes than infections due to the susceptible form of the microorganism? One such study measured mortality following BSI, comparing infections due to MRSA and to methicillin-susceptible *S. aureus (54)*. One of the control variables included in the logistic regression model was the presence of shock, presumably measured at the time of detection of BSI. The problem is that one path by which methicillin resistance may raise the mortality rate is in increasing the risk of shock. Controlling for shock produces bias toward the null in the estimate of the effect of methicillin resistance by blocking one of the causal pathways linking the exposure and outcome. More suitable adjusters would be measures of the severity of illness, such as an APACHE score, taken prior to the onset of symptoms and signs of infection *(55,56)*.

On the other hand, if the study goals were to address the question whether inadequate therapy of methicillin resistance caused an increase in mortality compared to adequate therapy of methicillin-resistant or methicillin-susceptible infection, shock at the time of detection of infection, prior to initiation of therapy, would be an appropriate adjuster. In this situation, shock is no longer causally downstream of the exposure of interest.

Example 4: Antimicrobial Prophylaxis in Clean Surgery

The final example is of a publication in which confounding was addressed in an appropriate fashion *(57)*. The purpose of the study was to evaluate the effect of antimicrobial prophylaxis on SSI after clean surgery. Control variables included in the analysis were factors that possibly influenced both the decision to prescribe antibiotic prophylaxis and the outcome of interest (SSI in clean surgery). The observational study, of patients undergoing herniorrhaphy or selected breast surgery procedures, was done in conjunction with a randomized clinical trial of perioperative antibiotic prophylaxis *(58)*. Patients were included in the observational cohort if they did not participate in the clinical trial. Thirty-four percent of patients (1,077/3,202) received prophylaxis at the discretion of the surgeon; 86 SSIs (2.7%) were identified. The unadjusted OR for infection comparing prophylaxis recipients with nonrecipients was 0.85 (26/1,077 vs. 60/2,125). The OR after adjustment for duration of surgery and type of procedure was substantially lower, at 0.59, indicating a 41% reduction in the odds of SSI following prophylaxis. Additional adjustment for age, body mass index, the presence of drains, diabetes, and exposure to corticosteroids did not change the magnitude of this effect meaningfully. The conclusion of the investigators was that the clinical criteria individual surgeons were using to decide which patients should receive prophylaxis were successfully targeting patients within the clean surgery group who were at higher risk for infection. Thus, this study confirmed results from the randomized study *(58)* and showed that, after correct adjustment for confounders, prophylactic antibiotics were beneficial in the nonrandomized patients.

RECOMMENDATION 3: RECOGNIZE SELECTION BIAS IN ALL OF ITS GUISES

Selection bias occurs when the selection of study subjects induces a noncausal association between exposure and disease. Thus, the end result is similar to confounding: it leads to distortion of the measured association between exposure and disease away from the true causal effect *(59,60)*.

For a variety of reasons, selection bias tends to be more common in case–control studies than cohort studies, although this need not be the case if the case–control study is rigorously conducted *(59,60)*. In the case–control study, subjects are chosen for inclusion according to case status (e.g., presence or absence of a resistant microorganism). The key principle is that controls should be an unbiased sample of the source population with respect to exposure. Just as in a cohort study, it is necessary to delineate the source population or study base—individuals who would be classified as cases if they developed the disease, or alternatively, the person–time experience during which there is eligibility to become a case. The failure to select subjects independently of exposure status distorts the causal relationship between exposure and disease. If subject selection is influenced by a factor that is associated with exposure, the consequence is selection bias. The result is that distribution of exposure in controls will differ in a systematic way from that of the entire study base. The sampled exposed and unexposed individuals will no longer be comparable with respect to disease incidence; a noncausal exposure–disease association is induced.

Antimicrobial Use and Risk of Infection with Resistant Microorganisms

Case–control studies on antibiotic-resistant microorganisms typically aim to determine risk factors (e.g., specific antimicrobial agents) causally related to colonization or infection with resistant pathogens *(61–63)*. The choice of appropriate controls is central to the validity of results in those studies (64,*65–67*).

We will look at studies of antimicrobial risk factors for infection with VRE, which have been plagued by suboptimal selection of controls (64). If the exposure of interest in a case–control study of VRE acquisition is vancomycin use, then controls should be selected that are representative of vancomycin exposure in the entire cohort of

hospitalized patients. Controls should not be intentionally limited to certain wards where vancomycin use is low since this would falsely overestimate the OR obtained for vancomycin. Often, for convenience reasons, patients with vancomycin-susceptible enterococci (VSE) are selected as the control group. The reason the choice of patients with susceptible microorganisms as the control group leads to a biased estimate of relative risk is that a distorted estimate of exposure frequency in the source population is obtained. The selection bias introduced by using control patients with susceptible microorganisms is likely to have the strongest impact on estimating the effect of exposure to antibiotics that are active against susceptible (but not resistant) microorganisms, which is often the exposure of greatest interest. The reason for this particular bias is that treatment with active antibiotics likely inhibits the growth of susceptible microorganisms, therefore making this exposure less frequent among patients who are culture-positive for susceptible microorganisms than among patients in the source population *(65)*.

Thus, vancomycin therapy may be identified as an individual risk factor not because it is a risk factor for the development of VRE but because fewer patients in the VSE comparison group received vancomycin. Vancomycin may be causal only with respect to its killing effect on VSE, not to its effect of enhancing the risk of VRE acquisition *(68)*. The selection bias associated with this type of control group selection was demonstrated in a meta-analysis that aimed to assess whether vancomycin therapy was a risk factor for the development of VRE *(69)*. Studies that used a control group of patients with VSE identified vancomycin therapy as a risk factor (pooled OR, 10.7), whereas studies that used a second control group (no patients with VRE and not limited to patients with VSE—therefore, similar to the base population of hospital admissions) revealed a far weaker association (OR, 2.7). This weaker association was then eliminated when the analysis was limited to studies that also controlled for time at risk prior to the outcome *(69)*.

Another situation in which selection bias may be a problem results from the use of clinical cultures to identify patients with a resistant microorganism. If the exposure influences the performance of the test used to identify the resistant microorganism or is itself influenced by a factor that affects culturing, the consequence is selection bias. In studies of resistant microorganisms, when the exposure of interest is antimicrobial use, factors that may influence both future culturing practices and prescribing of antimicrobials are the initial symptoms and signs of infection. Adjusting for the clinical manifestations of infection and other indications for antimicrobial use can remove this selection bias.

RECOMMENDATION 4: ACCOUNT FOR TIMING OF EXPOSURE AND TIME AT RISK

Time at Risk

There are two common ways that time is misunderstood or mishandled in epidemiology studies within the field of infection control. One pertains to the concept of *time at risk* and the other to time-varying exposures. The key role of time in the occurrence and detection of disease is worth emphasizing. First, time at risk serves as the stage on which other causes act. For instance, the longer the patient is hospitalized, the greater the opportunity for the patient to experience the use of invasive medical devices that are causes of healthcare-associated infection and the higher is the cumulative probability of occurrence of a healthcare-associated infection. Second, even for those causes that are experienced at a single point of time—for instance, ingestion of food contaminated by *Listeria*—time is important because of the induction period. If the follow-up time is shorter than the maximum interval from exposure to onset of symptoms (incubation period), the case may not be detected *(70)*. Third, time at risk itself may act as an intermediate variable, mediating the effects of other causes of disease. One of the indirect pathways by which high illness severity leads to higher infection risk is by increasing the length of hospital stay *(71)*. Fourth, exposures may not be constant during the period of risk; accounting for time-varying exposures poses additional problems discussed in more detail below.

Consider what actually constitutes the time at risk for healthcare-associated infections, using the situation in which only the initial infection is studied. An individual's time at risk for a healthcare-associated BSI begins when he or she is admitted to the hospital and ends at the time of occurrence of the first BSI or at discharge. More precisely, information about the presumed incubation period may be used to modify the start and stop times of this interval. The first 48 hours after hospitalization is "immortal time" in the sense that, by the usual case definition, events with onset during that interval are excluded. Conversely, infections detected up to a certain number of days after discharge may be included as cases, and so the follow-up time may extend for a brief period postdischarge *(72)*. Notwithstanding these subtleties, the time at risk is approximately the hospital length of stay for individuals who do not experience a BSI and the interval from admission to occurrence of the infection for those that do.

When the time at risk varies substantially from individual to individual, the incidence rate, denominated by person–time experience, is the appropriate measure of disease frequency. This concept is widely understood in infection control and forms the basis for measures of disease frequency such as number of catheter-related infections per 1,000 catheter days (*73,*74). However, the implication of variation in time at risk for the choice of the target measure of effect is less often recognized. Generally, if there is a need for adjustment on time-at-risk, the target parameter of an epidemiologic analysis should be person–time based, usually the incidence rate ratio or HR *(75,76)*. Analyses of data from case–control or cohort studies using logistic regression often neglect this issue *(77,78)*. Sometimes in such analyses, the time at risk is treated as a conventional risk factor *(79,80)*. Although this approach may be less biased than not accounting for time at risk at all, it neglects the distinction between time at risk and other types of confounders *(81)*. A related limitation is to use hospital length of stay for all patients, regardless of case status, as the adjustment variable *(82)*. A comparable type of inaccuracy is to calculate incidence densities using total person–time instead of person–time-at-risk *(83)*.

Time-Varying Exposures and Matched Cohort Studies

The analytic techniques that account for variation in time at risk are particularly valuable when exposures change over time. An exposure is considered time varying when its value changes in a meaningful way during follow-up. In outcome studies of healthcare-associated infections or other adverse events, in which the aim is to estimate the causal effect of infection on endpoints such as mortality or costs, the infection is a time-varying exposure (84). Infected patients are deemed exposed after onset of the infection. Prior to infection, patients are unexposed, as are patients who never experience infection. The interval from the start of follow-up to the onset of infection differs from patient to patient.

The most commonly used method to estimate excess morbidity and mortality caused by healthcare-associated infection or other adverse events is to perform a matched cohort study in which patients with the adverse event are matched to one or more reference patients who did not experience the adverse event *(52,85,86)*. Infected and uninfected patients are usually matched for age, the underlying disease, and additional variables that may have contributed to excess morbidity and extra length of hospital stay (Fig. 88-2).

This study design has several limitations because of the time-varying nature of the exposure. One source of bias occurs when infected and uninfected patients are compared with regard to *total* hospital costs or *total* hospital length of stay *(87–90)*. For infected patients, only those costs incurred after the occurrence of the healthcare-associated infection are possibly secondary to infection. Prior to the occurrence of infection, patients are unexposed. The association between preinfection outcome and infection is entirely noncausal from the perspective of measuring the excess burden of infection. Therefore, combining preinfection outcomes with postinfection outcomes dramatically amplifies confounding.

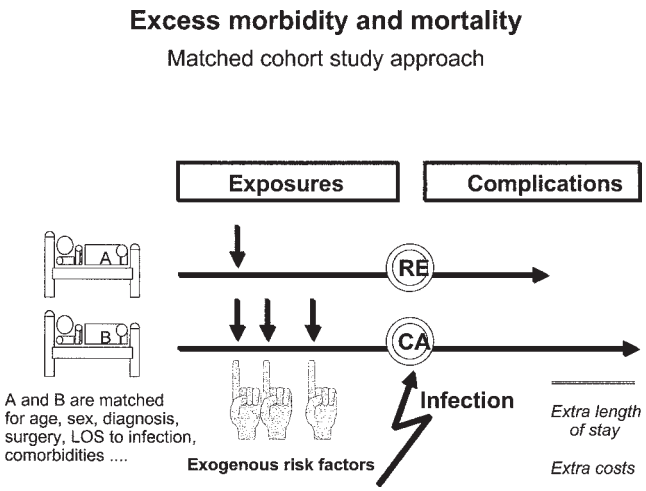

FIGURE 88-2 A schematic design of a matched cohort study. *Arrows* indicate exposure to risk factors for infection after admission. Patient A is considered an uninfected reference patient (RE) for "case" patient B (CA) who developed healthcare-associated infection indicated by the *broken arrow*. (Courtesy of Didier Pittet.)

Modifying the analysis such that average postinfection length of stay in infected patients is compared with average total length of stay in noninfected patients does not completely remove confounding by time *(91)*. Bias persists even in matched cohort studies in which noninfected patients are selected to have a hospital length of stay at least as long as the interval to infection in the corresponding infected patient, irrespective of differences in the severity of illness *(85)*. The reason for this bias is that conditioning on presence or absence of infection induces an association between the time to infection and time to discharge *(92)*.

Several recent studies have demonstrated the effect of this bias (*86,93–95,*96). Outcome analyses that did not account for the time prior to the occurrence of the infection or adverse event yielded different results than studies that did account for the time prior to the infection. As shown in Table 88-2, there is an important difference in excess length of stay between conventional matching approaches and methods that adequately model the timing of events. Schulgen et al. *(97)* tested different methods and showed that the use of unmatched or matched comparisons between noninfected and infected patients led to an overestimation of the excess length of stay due to SSI or healthcare-associated pneumonia compared to analyses based on a structural formulation of transitions between different states (Table 88-2). Similarly, Asensio and Torres *(98)* found that regression models yielded lower estimates of the excess length of stay and cost due to healthcare-associated infection than a matched-pair comparison. Likewise, Nguile-Makao et al. *(86)* observed that a multistate model that appropriately handled VAP as a time-dependent event produced lower values of the attributable mortality of VAP than a matched cohort analysis.

Another approach to estimating cost and length of stay effects of adverse events is to apply survival models, in which the adverse event is incorporated as a time-dependent variable *(99)*. This strategy can be applied to costs as well as length of stay *(91)*. Even when the time-varying nature of the exposure is accounted for, it is still necessary to adequately adjust for traditional confounders those factors that both increase the risk of infection and affect the outcome of interest. For instance, Soufir et al. *(100)* investigated the excess risk of death due to catheter-related bloodstream infection (CR-BSI) in a cohort of critically ill patients. The crude case–fatality ratio was 50% and 21% in patients with and without CR-BSI, respectively. The statistical method of adjustment was based on Cox proportional hazards regression, with the inclusion of matching variables and prognostic factors for mortality. CR-BSI remained associated with mortality following adjustment for prognostic factors at ICU admission (HR, 2.0; $p = .03$). However, after controlling for severity scores calculated 1 week before CR-BSI, the increased mortality was no longer significant in the Cox model (HR, 1.4; $p = .27$).

In summary, healthcare-associated infections unquestionably have substantial effects on morbidity and mortality. However, the matched cohort study design produces bias in the estimation of the effects of healthcare-associated infection on length of stay and costs. Cost effects or excess length of stay are likely to be overestimated if the interval to onset of healthcare-associated infection is not properly accounted for in the study design or analysis (84). Finally,

TABLE 88-2

Estimated Duration of Extra Stay in Days Per Infected Patient and 95% Confidence Interval for Two Studies on the Effect of Surgical Site Infection (Study I) and on Healthcare-Associated Pneumonia (Study II)

	Postoperative Wound Infection (Study I)		*Healthcare-Associated Pneumonia (Study II)*	
Approach	*Estimated Extra Hospital Stay*	95% CI	*Estimated Extra Stay in ICU*	95% CI
Two-group comparison	20.7	18.4–23.0	14.4	10.7–18.2
Confounder matching	16.9[a]	12.9–20.9	12.3	9.7–14.9
Confounder and time matching	11.4[b]	7.1–15.7	8.2	5.9–10.5
Method 1	9.8	5.7–13.8	3.4	0.8–6.0
Method 2	11.5	8.9–14.0	4.0	1.5–6.1

[a]Matching for age, sex, diagnosis, and degree of contamination of wound.
[b]Matching for age, sex, diagnosis, degree of contamination of wound, and time to infection.
Study I used a Markov transition state model and study II used a structural nested failure time model. Both studies account for the time from admission to healthcare-associated infection in the estimation of the effect of healthcare-associated infection on subsequent length of stay.
(Adapted from Schulgen G, Kropec A, Kappstein I, et al. Estimation of extra hospital stay attributable to nosocomial infections: heterogeneity and timing of events. *J Clin Epidemiol* 2000;53(4):409–417.)

appropriate statistical methods are important in analysis of excess costs associated with healthcare-associated infections, because informed decisions and policy developments may depend on them. Additionally, exaggeration of excess costs may lead to unintentional errors in the economic analysis of intervention programs (101).

RECOMMENDATION 5: DEVELOP GUIDELINES ACCORDING TO EXPLICIT RULES

Translating research in infection control into practice guidelines involves as the first step a rigorous review of evidence. Although expert opinion is a critical component of the development of recommendations and guidelines, it is important, whenever possible, to use results of the highest quality studies possible as the basis for infection control policy *(8)*. This is crucial, because many practices in infection prevention and control of multiresistant microorganisms have not been validated by controlled clinical trials. Unfortunately, there are many important questions in infection control for which we may never obtain data from randomized trials because of limitations in funding, lack of feasibility, and ethical dilemmas.

Methodological Quality of Guidelines in Infection Control

Guidelines are widely used and cited, because they attempt to summarize and critically appraise currently available evidence and give recommendations for daily practice *(102,103)*. By contrast, individual trials are often conflicting or nondefinitive because of their small sample size or other methodological limitations. Many guidelines rely on reviews that were either previously published or created by guideline developers. Systematic reviews can aid in guideline development because they involve selecting, critically appraising, and summarizing the results of primary research. The more rigorous the review method used and the higher the quality of the primary research that is synthesized, the more evidence-based the practice guideline is likely to be *(104)*. Conversely, the quality of a review is compromised if a comprehensive search is not made to ensure that all potentially relevant articles are considered for inclusion, if the selection of studies is not reproducible or is open to bias, if the methodological quality of the primary studies is not evaluated, or if possible reasons for the variability in results are not explored *(105)*. Table 88-3 summarizes the most commonly used levels of evidence of preventive or therapeutic interventions and the grading scale for recommendations made in practice guidelines.

Many guidelines in the infection control and clinical infectious disease literature are not following the highest possible methodological standards for the development of guidelines, as suggested by the Cochrane review group *(106)*. For instance, the draft of the new guideline on preventing catheter-related infections to be published in 2010 omitted eight category 1A recommendations that were listed in the old 2002 version of this document but were not mentioned anymore in the new version. The Center for Disease Control and Prevention's hand-hygiene guideline *(107)*, an otherwise exemplary appraisal of the evidence, also did not include a detailed description of the systematic review process. Finally, an analysis presented at the Infectious Diseases Society of America's 47th annual meeting revealed that most of the society's treatment guidelines are based on expert opinion, nonrandomized trials, and case studies. Only approximately 15% of the guidelines are supported by randomized controlled trials, considered the highest level of evidence. Nonetheless, more than 40% of the guidelines' recommendations were classified as class A, the strongest level of treatment recommendation (Dong Lee et al. from the Division of Infectious Diseases

TABLE 88-3

Levels of Evidence and Grades of Recommendations for Preventive or Therapeutic Interventions

Quality of evidence

I Evidence obtained from at least one properly randomized clinical trial with high power

II-1 Evidence obtained from clinical trials with low power or without randomization

II-2 Evidence obtained from well-designed cohort or case–control studies

II-3 Evidence obtained from studies using historical cohort comparisons

III Descriptive case series without controls or opinions of respected authorities

Strength of recommendation

A Good evidence to support a recommendation

B Fair evidence to support a recommendation

C Insufficient evidence to recommend for or against a recommendation

D Fair evidence to withhold a recommendation

E Good evidence to withhold a recommendation

(Adapted from the rating scale used by the U.S. Preventive Services Task Force.)

at Drexel University College of Medicine in Philadelphia, Pennsylvania. Infectious Diseases Society of America's 47th annual meeting: Abstract 1324, presented November 1, 2009). Overall, many guidelines in this field leave uncertain the study selection criteria, data extraction process, and quality of the included studies. To improve the quality of evidence, investigators assembling consensus guidelines should add more systematic information about the search methods, data sources, study selection criteria, and details about study designs, interventions, settings, and the quality of studies included in their recommendations *(108)*.

CONCLUSION

We have critically assessed selected articles from the healthcare epidemiology and infection control literature to highlight methodological limitations and areas in need of improvement. We hope that this review will act as a stimulus to further research, based on sound methodological tools, and that the resulting body of work will advance new hypotheses for the prevention of healthcare-associated infections. Assuming that healthcare-associated infections have causal and preventive factors that can be identified through systematic investigation of different populations, epidemiology has the potential to contribute substantially to the understanding of the effectiveness of infection control measures and to act as a driver of practice change. As in any scientific endeavor, the fundamental challenge in healthcare epidemiology is to ask the important questions and then select the right methods to answer them. The availability of systematic epidemiologic methods for use in infection control provides an opportunity for more complete prevention of healthcare-associated infections in the next millennium.

ACKNOWLEDGMENTS

We thank Michael Rubin and Marc Lipsitch for helpful comments on an earlier version of this chapter.

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SECTION XV

Organization and Implementation of Infection Control Programs

CHAPTER 89

Surveillance of Healthcare-Associated Infections

Katherine Allen-Bridson, Gloria C. Morrell, and Teresa C. Horan

Surveillance is the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know. Surveillance of nosocomial or, as they are now known, healthcare-associated infections (HAIs) is a significant component of efforts to reduce and eventually eliminate HAIs in healthcare settings, including hospitals, long-term care facilities, and ambulatory surgical care centers *(1)*. In the 1970s, the Study on the Efficacy of Nosocomial Infection Control found that if hospitals adopted intensive surveillance and multifaceted prevention and control programs, nearly one-third of HAIs could be prevented (2). Later, the Centers for Disease Control and Prevention (CDC) recommended infection surveillance as a way to evaluate the success of control measures (*3,*4). In addition, surveillance of HAIs may provide data that are useful for recognizing emerging trends and contributing factors, such as procedures and new technologies that reduce HAIs. Increasingly, HAI surveillance data is being used by both regulatory agencies such as The Centers for Medicare and Medicaid Services (CMS) and The Joint Commission (JC), to assess the quality of care in the healthcare setting as well as by state health department HAI programs to assist in and to disseminate infection prevention activities.

NATIONAL HEALTHCARE SAFETY NETWORK

Throughout this chapter, CDC's National Healthcare Safety Network (NHSN) system is used to illustrate essential components of HAI surveillance. The NHSN is a secure, Internet-based surveillance system that integrates patient and healthcare personnel safety (HPS) surveillance systems. Three former CDC surveillance systems, including the National Nosocomial Infections Surveillance System (NNIS), National Surveillance System for Healthcare Workers, and the Dialysis Surveillance Network, were combined to form the NHSN.

The NHSN enables healthcare facilities to collect and use data about HAIs, adherence to clinical practices known to prevent HAIs, the incidence or prevalence of multidrug-resistant microorganisms (MDROs) within their organizations, trends and coverage of HPS and vaccination, and adverse events related to the transfusion of blood and blood products.

Since the inception of the NNIS system in 1970, CDC's primary goals for HAI surveillance have been to describe the epidemiology of HAI, provide national-level HAI comparative rates for hospitals and other healthcare systems, and promote methodologically sound surveillance in healthcare systems *(5,6)*. The NHSN includes four components, each concerned with an aspect of HAI control and prevention: patient safety, HPS, biovigilance, and e-surveillance.

The patient safety component of NHSN includes surveillance methods to identify and track device-associated infections, procedure-associated infections, antimicrobial use, MDROs, *Clostridium difficile* incidence and prevalence, and influenza vaccination of inpatient populations during the influenza season. Most of the modules require that a trained infection preventionist (IP) conduct active, patient-based, prospective surveillance of events and their corresponding denominator data.

The HPS component of NHSN includes methods to track and manage blood and body fluid exposures and influenza vaccinations of healthcare workers. The biovigilance component includes the collection of adverse event data to improve outcomes in the use of blood products, organs, tissues, and cellular therapies. The hemovigilance module is designed for monitoring adverse reactions and quality control incidents related to blood transfusion.

The e-surveillance component of NHSN is a work in progress and aims to make more extensive use of electronic data stored in healthcare application databases for the surveillance of HAIs and antimicrobial use and resistance (AUR). These efforts focus on standards-based solutions for conveying healthcare data and validation processes to confirm that the data received at CDC accurately reflect the data transmitted by healthcare facilities. Access to electronic information is of critical importance to healthcare as well as other segments such as science, business, and industry. Innovative methods of HAI surveillance require using new electronic tools to obtain healthcare information. The National Health Information Infrastructure (NHII) was created by executive order of President George W. Bush in April 2004 to develop a comprehensive network of interoperable systems to promote access to healthcare information and decision support *(7)*. Although the NHII supported ongoing research, adapting electronic data and new communication methods to acquire surveillance data of HAIs has been a slow and complex effort *(7)*. Increasing the use of electronic health record (EHR) systems and other tools will help automate data collection tasks previously performed manually *(8)*. Financial incentives up to $24 billion are available as a result of the U.S. Health Information Technology for Economic and Clinical Health Act (HITECH), a component of the American Recovery and Reinvestment Act of 2009. HITECH funding is expected to accelerate progress in EHRs deployment (9,10). Although new data-mining methods expedite surveillance efforts, until they are validated for sensitivity and specificity, they do not replace traditional practices of surveillance for infection that must continue to be conducted (11). However data are collected, surveillance measures must be accurate, comparable, and reflect the particular area of healthcare being monitored *(12,13)*. To ensure that data collected will support decision making, the healthcare facility should focus on its most critical and large-scale problems and use surveillance methodology that adheres to sound epidemiologic principles (11). A brief synopsis of the NHSN patient safety component modules follow (14). For complete and up-to-date information about the NHSN surveillance system components and criteria, access www.cdc.gov/nhsn/.

Procedure-Associated Module

Protocols in this module offer guidance relating to surgical site infection (SSI) and postprocedure pneumonia (PPP) monitoring. PPP events are monitored only for inpatient operative procedures and only during the patient's stay (i.e., postdischarge surveillance methods are not used for PPP).

Device-Associated Module

The use of medical instruments increases the risk of developing an HAI, and most patients admitted for care are exposed to a medical device in the course of their treatment. These devices include, but are not limited to, vascular and urinary catheters and respiratory ventilators. NHSN enables facilities to monitor infectious complications associated with the use of these devices and also related processes that might increase infection risk, such as central-line insertion practices (CLIPs).

Antimicrobial Use and Resistance Module

As part of their facility's antimicrobial stewardship efforts, the AUR module helps healthcare facilities electronically capture antimicrobial use and microorganism resistance to antimicrobials and analyze and report that data.

Multidrug-Resistant Microorganism and *Clostridium Difficile* Infection Module

The MDRO and *C. difficile* infection (CDI) module helps facilities meet criteria and metrics outlined in several organizational guidelines to control and measure the spread of MDROs and CDIs within their healthcare system. The module includes required and optional surveillance activities that can be tailored to the needs of the facility. In addition, process measures such as adherence to Contact Precautions when caring for patients known to be infected or colonized with an MDRO or *C. difficile,* as well as active surveillance testing for MDROs can be monitored. Finally, facilities may also measure the incidence and prevalence of positive cultures of these microorganisms in their patients.

Vaccination Module

Inpatient hospitalizations provide opportunities for routine influenza and infectious disease vaccinations in accordance with published recommendations. The vaccination module provides a means to monitor the success of efforts to capitalize on these opportunities.

PURPOSES OF SURVEILLANCE

A healthcare facility should have clear goals before implementing a program, and these goals must be reviewed and updated frequently using a tool such as an infection control annual risk assessment. This assessment should identify new infection risks resulting from evolving patient populations and facility priorities *(15)*. Examples include the introduction of new high-risk medical interventions, an increasingly immunocompromised patient population, and changing pathogens or antibiotic resistance. It is vital to identify and state goals or purposes of surveillance before designing a system and starting surveillance (11,*16,*17).

Establishing Endemic Rates to Inform Prevention Strategy

Most HAIs are endemic, that is, not part of recognized outbreaks *(18)*. A basic purpose of surveillance is to quantify endemic baseline HAI rates; 91% of hospitals reported using surveillance data for this purpose *(19)*. Baseline infection rates provide facilities with objective knowledge of the ongoing infection risks in their patients, and calculating these metrics is a first step toward infection prevention *(19)* (*see Data Analysis*). Determining endemic rates helps advance activities to improve quality of care. Failure to use surveillance data or evidence-based results to guide

prevention efforts is misguided and costly, compromising patient care and unduly burdening today's vulnerable healthcare system.

Identifying Outbreaks

Once endemic rates are established, focusing on deviations from the baseline may lead to identification of infectious outbreaks. The benefits of maintaining routine surveillance must be weighed against its heavy resource burdens. Outbreaks of HAIs are often identified more quickly by astute clinicians or laboratory personnel rather than by IP analysis of surveillance data. This lack of timeliness often limits infection prevention personnel's use of routine surveillance in identifying outbreaks in a hospital. Automatic computerized tracking mechanisms found in infection prevention and laboratory-based software and new, innovative surveillance techniques have the potential to quickly identify outbreaks and unusual or rare laboratory findings requiring immediate follow-up (*8,13,20,*21).

Evaluating Control Measures

After a problem has been identified through surveillance and control measures have been initiated, monitoring is needed to ensure that the problem has been controlled or eliminated. Alternatively, monitoring may show that some control measures are actually ineffective or unnecessary. For example, daily changing of respiratory ventilator breathing circuits was instituted and believed to help prevent ventilator-associated pneumonia (VAP). However, surveillance data have proven this intervention to be a costly and ineffective method of lowering VAP rates *(22,23)*. After the initial success of instituting control measures, it is also necessary to counteract complacency and not revert to preintervention routines. Monitoring efforts require vigilance and constancy in the collection and evaluation of surveillance data and the dissemination of findings to participants (24,*25*).

Collaborating with New and Existing Partners

During the past decade, individuals, consumer groups, legislative and regulatory agencies, and payors have heightened awareness of the problem of HAIs. Many state legislatures have instituted requirements for public disclosure of HAI rates, and many of these mandates require the use of the NHSN for facility reporting and state acquisition of HAI data. As a result, new state HAI programs have been developed and new relationships forged between these agencies, healthcare facilities, consumer groups, and federal HAI surveillance and prevention groups. States then have the information needed to inform the development of statewide initiatives to tackle HAI issues. Measures are also underway to link pay for performance with prevention of HAIs in acute care settings *(26)*, both of which require collection of HAI data. Because of this increased focus, the Healthcare Infection Control Practices Advisory Committee developed a guidance document on public reporting of HAIs *(27)*.

Many regulatory and accreditation organizations have interest in the measurement and prevention of HAIs. That interest has influenced how infection prevention programs develop policy and carry out their surveillance and infection reporting duties. Regulatory agencies within the U.S. Department of Health and Human Services, CMS, and the leading private sector accrediting body, the Joint Commission *(28,29)* are tasked with ensuring quality healthcare delivery to Medicare and Medicaid recipients. Since 1992, hospitals accredited by the Joint Commission have been required to use surveillance to bring about change in the risk of infection to patients *(30)*. There is renewed and heightened focus on patient safety related to prevention of infection and transparency of mechanisms. CMS changed the rules for the hospital Inpatient Prospective Payment System for fiscal year 2011, authorizing a higher annual payment for hospitals reporting central line–associated bloodstream infection (CLABSI) rates with the other measures required under the Inpatient Prospective Payment System *(31)*. SSI rate reporting will be required, beginning in 2012. This process gives hospitals a financial incentive to report the quality of their services and allows CMS access to data to help consumers make more informed decisions about their healthcare.

The CDC's Division of Healthcare Quality Promotion (DHQP) has been charged to collaborate in the healthcare, computer, business, and government sectors to create the expertise, information, and tools necessary to implement processes and prevention strategies to reduce and prevent HAIs. One of DHQP's partners, the National Quality Forum, is responsible for endorsing measures of healthcare quality—including HAI measures—that can be used for public reporting and quality improvement *(29)*. State agencies are also partnering with DHQP, and many agencies have instituted regulatory controls by enacting laws that mandate public reporting of HAIs *(32,33)*. In addition to participating in other infection prevention initiatives and research studies, healthcare facilities are also engaged with DHQP to implement strategies to reduce and prevent HAIs. The infrastructure needed by healthcare facilities to participate and report these prevention measures however, is sometimes not available (24,*34–36*).

Comparing Infection Rates among Healthcare Facilities and External Groups

Establishing the priorities of an infection control program is a difficult and ever-changing task. Surveillance allows a healthcare facility to compare their HAI rates with rates of other facilities. Interfacility rate comparison identifies outcomes that are most in need of improvement and identifies places where the finite resources of an infection control program should be directed. A healthcare facility's high infection rate, as compared with other facilities, may signal an investigation of a potential problem. In recent years, there has been a greater focus on external comparisons of facilities and groups to other facilities and groups as well as comparisons to aggregates such as the NHSN. Mandatory reporting systems that will be used for interfacility comparisons should be based on established public health science *(3,27)*. This type of comparison requires accurate data collection and appropriate risk adjustment of HAI outcomes. To adequately adjust infection data, patients' intrinsic and extrinsic risks for infection must be examined (*see Comparing Risk-Adjusted HAI Data*). Progress has been achieved in suitable risk adjustment, but more data on specific risk factors are still needed *(12)*. A facility's overall HAI rate is not a valid measure of the efficacy of the infection prevention program *(37–42)*, does not take underlying risk differences

into account, and should not be used for interhospital comparison. The standardized infection ratio (SIR) (*see Standardized Infection Ratio*), incorporating methodologically sound risk adjustment of HAI outcomes, is the preferred summary statistic to use for interhospital comparison.

Ensuring data accuracy is another challenge for healthcare facilities and the organizations responsible for aggregating their data. The independent determination of data accuracy or validation is an essential activity for organizations aggregating data from multiple collectors *(13)*. Aggregating organizations should examine a facility's data and screen for unusual patterns or other indications of inaccuracies. This should include reporting data back to the hospital to confirm that data received matches data sent. Determining the accuracy of the data includes confirming HAI case-finding methodology using three measures: sensitivity, positive predictive value (PPV), and specificity. Sensitivity is the percentage of all true infections that are reported. PPV is the percentage of reported infections deemed to be true infections. Specificity is the reported number of patients without HAI divided by the true number of patients without HAI *(43)*. Using an independently trained observer to ascertain the sensitivity, PPV, and specificity of HAI case-finding will strengthen the credibility of the surveillance system, help identify the means to adjust rates for facilities with rates that vary, and enhance the overall strength of the surveillance system.

Although determining the sensitivity, PPV, and specificity of all facilities validates the credibility of the multifacility surveillance system or aggregate group, determining the variation in sensitivity and specificity among facilities in a multifacility system may be an even more critical measure of credibility. Surveillance rarely achieves 100% accuracy. However, if one hospital finds HAIs among only 30% of its patients compared with a second hospital, which finds HAIs among 90% of its patients, the disparity in infection rates may be caused entirely by differences in case-finding sensitivity.

Determining sensitivity and specificity is difficult and resource-intensive. Fortunately, the NNIS evaluation study suggested that IPs generally report HAI data accurately. Low sensitivity (underreporting of infections), which ranged from 59% to 85% for the four major sites of HAI—bloodstream, pneumonia, urinary tract, and surgical—was a more serious problem compared with reporting of other measures. PPV ranged from 72% to 92% for these sites, and specificity ranged from 97.7% to 98.7% *(44)*. Because of the increase in state-based mandatory reporting of HAIs, there has been a corresponding increase in assessing data for inaccuracies and conducting formal validation studies *(45–49)*. Additionally, federal funds have been allocated for this purpose *(50)*.

ATTRIBUTES OF A SURVEILLANCE PROGRAM

A successful surveillance program uses thorough epidemiological principles in its planning. The data collected must be useful and complete. Attributes of a successful surveillance program are as follows:

- Accuracy
- Timeliness
- Usefulness
- Consistency
- Practicality

Accuracy

Effective surveillance must produce accurate data. Inaccurate data can result in wasted effort, resources, and personnel time, as well as the initiation of inappropriate, potentially harmful interventions. Using case definitions advances the accurate collection of HAI surveillance. A case definition is a "set of standard criteria for deciding whether or not a person has a particular disease or health-related event" *(51)*. The use of case definitions helps validate that patients identified as having an HAI do, in fact, have an HAI. The NHSN provides and requires the use of criteria (case defintions) for all types of HAIs.

Likewise, for surveillance data to be accurate, the denominator data, defined as the number of patients who are at risk for infection that is used to calculate infection rates, must also be accurate. For example, IPs must invest time to ensure that the identified number of central-line catheter days is correct to achieve an accurate CLABSI rate. Data collection can be time-consuming, and sampling methods offer a less time-consuming alternative *(52)*. Sampling methods however, including electronic capture, must be validated by a proven method before implementation.

Gathering accurate, highly sensitive numerator data is possible only if patients are monitored for the entire period of the case definition. For instance, NHSN case definitions for SSI specify a period of 30 days to 1 year postsurgery; the extended time period allows data to be gathered on surgeries that involve surgical impacts. Limiting surveillance to 1 week would result in inaccurately low SSI rates caused by a lack of sensitivity, because it would exclude patients who developed an SSI in weeks 2 to 4 (in a surgical procedure without implant).

Decreasing length of stay (LOS) within hospitals could directly affect the SSI rate. During 1970 to 2005, the average LOS in US hospitals decreased from 7.8 to 4.8 days *(53)*. This shortened LOS requires that surveillance be adapted to identify those patients whose infection develops in the postdischarge period (i.e., postdischarge surveillance). This adaptation is especially important for operative patients. Studies have shown that the percentage of SSIs that would be missed without postdischarge surveillance ranges from a low of 7% in trauma patients to a high of 85% to 95% in cesarean section patients *(54–59)*.

Postdischarge surveillance could use one of several techniques including contacting the patient or physician by telephone or mail; the surgeon, nurse, or IP observing the patient in the clinic; and detecting SSIs on readmission *(54–59)*. Significant methodological problems can exist, however, with postdischarge surveillance, such as physicians not responding in a timely manner to the IP; patients inaccurately diagnosing infection *(60)*, and uncertainty about how to account for patients lost to follow-up. These problems are not easily addressed, and studies have mixed findings on proposed solutions. For example, education on signs and symptoms of SSI would seem to improve a patient's ability to diagnose their own SSI. In one study, however, such education actually corresponded to a reduced sensitivity and significant reduction in specificity

of SSI identification (65.2%) compared with sensitivity and specificity of SSI identification in noneducated patients (83.3%) *(59)*.

Some studies had contradictory findings. One study successfully used antimicrobial administration in discharged surgical patients as a case-finding method. The same study also found that using other methods, such as mailed questionnaires to surgeons or patients, resulted in poor sensitivity data *(61)*. Yet in another study, the significant amounts of antibiotics dispensed following surgery, especially in breast surgeries (14%), led the authors to suspect preoperative prophylaxis extended into the postdischarge period may be a threat to the predictive value of postdischarge antimicrobial data as a case-finding tool *(62)*. Clearly, postdischarge surveillance methods need refinement. Research may reveal that a variety of procedure-specific data sources and methods are needed to identify the majority of postdischarge SSIs. Until a standard method is developed and validated, the Surgical Wound Infection Task Force recommended in 1992 that facilities use a method that accommodates their resources and data needs *(63)*.

Finally, accurate data also requires precise mathematical calculations. Many HAI software programs are currently available to assist with this, including the NHSN, which calculates risk-stratified rates, frequency tables, run charts, and SIRs.

Timeliness

A sound surveillance program produces useful and timely HAI data. There are two temporal methods of surveillance: prospective and retrospective. Prospective surveillance is monitoring patients during admission for symptoms and case-definition criteria so that the infection is identified as it develops. It involves reviewing patient records and visiting patient-care units during the patients' stay. Retrospective surveillance involves looking back to identify infections after they have occurred. An example of retrospective surveillance is to identify infections using only the review of a patient's chart following discharge.

Prospective surveillance can more quickly identify clusters of infection, and therefore, facilitate prompt investigation, analysis, and response activity and may prevent the development of more cases. It can also provide increased visibility of IPs on the wards, encourage staff reporting of suspected infections, and produce timely feedback of data for quality improvement purposes. One disadvantage is that it requires greater resources than retrospective surveillance, because multiple data sources need to be accessed rather than viewing all data gathered on a single completed patient chart. Retrospective surveillance "allows for a comprehensive review of sequential events in the closed record and avoids the often time-consuming efforts of locating and reviewing charts in busy patient care areas." Retrospective surveillance is best suited for issues that "have little opportunity or need for intervention" because the identification of HAI issues may be delayed (11). NHSN participation requires prospective surveillance.

Usefulness

Because infection prevention efforts have competing priorities, limited surveillance resources are best spent on actionable issues, including those that have validated methods of improvement (e.g., bolstered standards of practice, instituted prevention bundles, or uses new or enhanced technology). Monitoring issues with no opportunity for improvement produces wasted effort, frustration, and does not support the principles of quality improvement.

Consistency

Surveillance data must be collected in a consistent manner to be useful. First, individuals and facilities must be consistent in their collection and interpretation of data. Surveillance personnel must uniformly apply case definitions (e.g., all data collectors should identify a case of VAP the same way). Consistency is achieved with uniform case definitions, surveillance methods, and data sources, as well as with targeted education of IPs. Within facilities, new case-finding staff should be mentored in correct methods and the determination of cases validated by experienced IPs. Consistency of case determinations within an infection control department should be validated routinely by cross-checking. Sharing case studies among facilities in which subject matter experts have made HAI determinations *(64)* produces greater consistency. A stable infection prevention and control department that has low rates of staff turnover encourages data consistency.

The targets of surveillance should also maintain consistency over time. Longitudinal data must be available to successfully analyze the value of prevention efforts. This does not mean that newly identified issues must be set aside. Considering that a facility's high-risk procedures and patient populations will probably experience only incremental changes over time, ongoing monitoring and collecting longitudinal data can occur simultaneously with the monitoring of newly identified issues.

Practicality

Finally, the best surveillance plan is only as good as its execution. Although plans must be based on the needs of the facility, they must also reflect the actual resources available. According to a recent survey, 44% of an IP's time is spent on surveillance activities, and a facility of 500 beds has, on average, just over 0.5 fulltime equivalents in an IP role *(65)*. Facility-wide, active, prospective surveillance in such a setting is limited and cannot be completed accurately, comprehensively, or in a timely manner.

DEVELOPING A FACILITY SURVEILLANCE PLAN

Every facility should develop a formal surveillance plan, methodologically identifying the goals, types, approaches, and methods of surveillance to be undertaken. The essential steps involved in this process are listed in Table 89-1 and are explored further in this section.

Assessing the Population

The first step in developing a surveillance plan is to perform a facility-specific risk assessment, which identifies the facility's patient populations at greatest risk of acquiring HAIs and procedures posing the greatest risk of infectious complications (11). From this information, surveillance efforts can be prioritized and valuable resources used efficiently. Both assessment and plan should be reviewed

TABLE 89-1

Essential Elements of Surveillance

- Assess the population
- Select the outcome (event) or process to survey
- Choose the surveillance method(s) keeping in mind the need for risk adjustment of data
- Monitor for the event or process
- Apply surveillance definitions during monitoring
- Analyze surveillance data
- Report and use surveillance information

(Adapted with permission from Lee TB, Baker OG, Lee JT, et al. Recommended practices for surveillance. *Am J Infect Control* 2007;35(7):427–440.)

routinely to determine changing facility needs. The following variables should be identified in the assessment and used to determine HAI risks, surveillance capabilities, and how efforts should be prioritized:

- **Patient populations served by the facility that are at high risk of infection**, such as elderly, neonatal, or immunocompromised patients (e.g., those with autoimmune disorders; oncology, burn, or trauma patients; and those on medications or treatments suppressing the immune system).
- **High-volume or high-risk operative procedures that are performed.** High-volume procedures have the potential to harm large numbers of patients if deviations from high-quality care occur (e.g., a facility that performs a large number of laminectomies each month). Infections following high-risk procedures (e.g., hip arthroplasty) could result in severe or deadly infections or permanent loss of function or quality of life.
- **Types of invasive devices that are proven to be associated with HAI development** (e.g., intravascular or indwelling urinary catheters and respiratory ventilators).
- **Resources available for use in the surveillance.** The number, skills, and education level of fulltime staff available for surveillance and the types and scope of data sources will determine surveillance capacity.
- **The need to meet state and federal mandates.** Work with local, state, and federal health departments to ensure that required HAI reporting is completed.

The Focus of Surveillance

After the facility assessment has been completed, foci of surveillance must be determined. An HAI surveillance system may be sentinel event-based, population-based, or both. Each system type has a different focus. In sentinel event-based surveillance, the focus is on sentinel infections or those that clearly indicate a failure in the facility's efforts to prevent infections and require individual investigations *(66,67)* and root-cause analysis. Because of this, denominator data and infection rates are usually not collected or generated in sentinel event-based surveillance. Because sentinel surveillance identifies only the most serious problems, it should not be the only surveillance system employed in a facility. Population-based surveillance focuses on patients with similar risks for infection (e.g., patients undergoing endoscopy in a facility). It allows for the calculation of rates of HAI using both a numerator (the number of infections) and denominator (the number of exposures to the risk or patients at risk).

Regardless of the focus of surveillance selected, a successful surveillance plan needs to be well understood by and receive the support of facility management. It must be tailored to provide the information needed to identify and address the facility's HAI risks as well as to meet any external regulatory requirements.

Types of Surveillance

Once the foci of surveillance have been identified, the next decision is which type of surveillance to use. Two questions must be answered to determine the type of surveillance: Will the surveillance be passively or actively completed, and will the metrics used be outcomes or processes? Again, the facility risk assessment should inform both of these decisions. Each type of surveillance offers advantages. Factors including intended use of the data, resources available to complete the surveillance (including personnel, financial, data, and technical), and existing regulatory mandates will determine which type of surveillance to use.

Passive versus Active In passive surveillance, people who do not have a primary surveillance role (i.e., people other than IPs) provide the routine identification and reporting of infections. For example, when an HAI is suspected, clinical healthcare personnel complete the forms and send them to the IP. Because clinical personnel's skills and knowledge are related to patient care rather than surveillance, it is not surprising that problems associated with passive surveillance include misclassification, underreporting, and lack of timeliness. Negative reporting (i.e., confirming that no infections have occurred during the surveillance period) is usually not a part of passive reporting. Because negative reporting is not included in passive reporting, IPs may incorrectly conclude that no infections have developed, causing reported HAI rates to be falsely low.

Active surveillance is the process of vigorously looking for HAIs using trained personnel, most often including IPs. In this type of surveillance, IPs seek out HAIs using various data sources and methods, discussed later, to determine whether an HAI has occurred. IPs are likely to be current with changes in surveillance definitions and able to extend the search for the source of the infection beyond the walls of the healthcare facility. IPs can work with outpatient facilities affiliated with their facility when needed to address opportunities for infection prevention identified by surveillance. An IP at hospital A can also share HAI information with an IP at neighboring hospital B when B's patient presents to hospital A with an HAI. Active surveillance frequently will include visits to patient-care units and discussions with patient-care staff. Negative reporting is a required component of active surveillance.

Passive surveillance requires fewer resources than active surveillance, may not need a dedicated IP, and requires only minimal activities of those reporting. Active surveillance is

more accurate and provides complete identification of HAIs and an increased visibility of the IP within the facility. This allows the IP to develop relationships with the staff and may result in early identification of other infection prevention and control issues.

Outcome Versus Process The type of measurement must also be decided. Is the facility interested in measuring (a) the outcomes of care (e.g., SSI) or (b) the ways in which healthcare is delivered, also known as process measurement (e.g., preoperative hair clipping instead of shaving to prevent SSI)? Outcome measurements examine the results of healthcare interventions or activities. Process measurements examine the rate at which targeted actions, such as prevention measures, occur. There has been recent and renewed interest in using process measurements in HAI surveillance, because it evaluates a facility's compliance with bundles of prevention practices. Bundles, a combination of prevention activities aimed at producing the lowest rate of infection for a given intervention (e.g., VAP bundles, CLIPs), have been operationalized to produce checklists of actions *(68)*. These actions or processes can be monitored and compliance rates calculated. Process measures have also been used for monitoring traditional infection prevention activities, such as hand washing by healthcare personnel.

Mant provides a useful overview comparing outcome with process monitoring *(69)*. According to Mant, the advantage of outcome measurement is that it provides a direct measure of an important health outcome (e.g., a healthcare facility-associated CDI rate). They summarize important data in a manner that is clear and useful. The advantages of process measures are that they are easily interpreted and more sensitively and directly measure specific aspects of healthcare. Outcomes may be influenced by a variety of factors, some of which are not related at all to the delivery of healthcare (e.g., patient characteristics, measurement issues, and chance). Mant suggests that it is preferable to use outcome measures when healthcare seems to be the major determinant rather than for those issues that are socioeconomic or not related to healthcare. Process measures better monitor specific healthcare actions that have been proven to impact patient outcomes and are sometimes endorsed by national guidelines. Measuring process *and* outcomes for a single healthcare issue produces robust surveillance data that can lead to notable improvements in patient health. For example, CLIP and CLABSI data can be studied in tandem to inform and evaluate prevention efforts.

Perspectives of Surveillance

There are two perspectives to consider when performing surveillance: (a) scope and (b) approach. Each perspective has two choices. For the scope of surveillance, a facility may choose to perform facility-wide surveillance or to target surveillance of units or specific HAI events. For the approach of surveillance, a facility may decide to utilize a patient-based approach, or they may opt for a laboratory-based approach. Each perspective and approach has its advantages and disadvantages, and a facility must determine the best perspective and approach to meet its needs.

Scope: Facility-wide Versus Targeted Facility-wide HAI surveillance (also known as total, comprehensive, or house-wide) *(70)* involves monitoring all patient care areas for all types of HAIs (e.g., urinary-tract infections, SSIs, pneumonias, skin and soft-tissue infections, etc.). If properly collected, this data can be stratified by facility ward or service. Facility-wide monitoring can be a useful approach for very small facilities, but it is extremely labor-intensive, and is therefore, not feasible for most healthcare facilities.

Facility-wide surveillance can include two types of monitoring: incidence (new cases only) or prevalence (both new and existing cases). Prevalence surveillance can be performed on a single day (point prevalence) or over several days (period prevalence). In point prevalence, each patient is visited only once, and the surveillance is usually performed by a trained team using chart review, discussion with caregivers, and/or direct assessment of patients to identify infections. A facility may choose to utilize incidence surveillance on a routine, ongoing basis for targeted units or infections, to utilize prevalence surveillance to inform on specific infection concerns as they arise, and to determine the need for infection control or prevention activities. For instance, a facility may perform continuous-incidence surveillance for CLABSIs in those units that have the largest percentage of these devices. Additionally, the identification of the possible transmission of a resistant *Acinetobacter* species in a patient-care unit may warrant a prevalence survey to determine the infection and colonization burden of this microorganism, and therefore, one aspect of risk to patients. Follow-up prevalence surveys can be used to determine the success of transmission prevention efforts. Some studies have used prevalence surveillance to estimate antimicrobial use and adherence to isolation practices and to monitor practices related to high-risk devices such as intravascular catheters *(71,72)*. One group of investigators used sequential prevalence surveys to estimate the effectiveness of their infection control program on reducing the risks of HAI *(73)*. Prevalence surveillance data have also been used to heighten the awareness of HAI problems in institutions without other surveillance methods in place and have been influential in helping to establish ongoing prospective (incidence) surveillance. Using prevalence surveillance to establish a single overall rate for the purposes of interfacility comparison is not recommended for the same reasons that generating overall rates from incidence surveillance is not recommended *(41)*.

Prevalence methods have also been used to demonstrate long-term trends in the epidemiology of HAI in an institution. This method has met with varying success. One study demonstrated these trends may be estimated from repeated prevalence surveys *(72)*. However, the interpretation of the results was complicated by the small number of patients studied and variations in the types of prevalence rates calculated. Therefore, secular trends within a facility are best derived from ongoing prospective (incidence) surveillance methods.

Prevalence surveys also can be used to determine the approximate sensitivity of a facility's ongoing prospective surveillance, that is, how well true infections are being detected *(74)*. The assumption is made that the prevalence surveyors will detect and correctly identify 100%

of infections. An estimate reflects the percentage of true infections detected by routine surveillance; this has been termed the *efficiency-of-reporting score* or *efficiency factor (74)*. The efficiency factor, which was found in one national study to be 65%, can then be used to adjust incidence rate estimates for the magnitude of underascertainment, and thus, yield a more accurate rate *(75)*. This method and all incidence surveillance methods assume perfect specificity (1.0), that is, that patients without infection are identified as not having a true infection. However, one study found that IPs had more difficulty determining when an infection was not present than when one was present *(76)*, suggesting the need to adjust infection rates by the efficiency factor. Before ongoing prospective surveillance attained widespread use in the United States, some investigators used data from prevalence surveillance performed at regular intervals or from a single study to estimate the incidence of HAI *(77,78)*. This use has not been applied widely, partly because statistical conversion is necessary (*see Data Analysis)*.

There are two primary disadvantages of prevalence surveillance. First, the small number of patients surveyed in small facilities may not provide sufficient data for identifying important differences among patient populations, for example, the difference between pneumonia rates on medical and surgical services. Second, the prevalence rate overestimates the patients' risk of infection, which is calculated as the number of active infections on the day of the visit divided by the number of beds visited. This is because situations that result in extended patient stays (such as the complication of an HAI) can extend the hospital stay, increasing the prevalence rate when compared to the incidence rate (79) (*see Defining and Calculating Rates*). Most facilities perform incidence surveillance and utilize the data to calculate routine incidence rates (e.g., unit-specific monthly VAP rates).

Surveillance strategies that resulted in more efficient use of IPs began to emerge in the late 1970s. These strategies target efforts on certain areas in the facilities (e.g., intensive care units [ICUs]), patient groups (e.g., surgical patients), or infection sites (e.g., bloodstream infections), or a combination of both. This type of surveillance is, referred to as targeted surveillance. More recently, antibiotic-resistant microorganisms have been the subject of targeted surveillance. A variation on this approach, called surveillance by objective, was used by Haley in the mid-1980s (*80*,81). In this approach, infections are prioritized for prevention efforts—the more serious the infection, the more the effort expended. In ranking infections, Haley recommended using more than just the relative frequency of occurrence. Factors to assess included morbidity and mortality, extra costs associated with the infection, and preventability *(82–84)*.

Targeted surveillance (also known as objective- or priority-based) may be either site-directed or unit-directed. Site-directed targeted surveillance focuses on detecting one or more specific sites of infection (e.g., bloodstream infections or MDROs) occurring among all admitted patients. This approach would be useful, for example, in facilities that introduce prevention bundles and would allow the measurement of the success of these activities.

Unit-directed surveillance targets specific patient locations with the highest risks of HAI (e.g., ICU and bone-marrow transplant units). Within the NNIS system, unit-directed surveillance was aimed at ICUs and high-risk nurseries *(37)*. Beginning in 2005, the NHSN offered an opportunity for facilities to participate in HAI surveillance in patient-care areas outside the ICU including patient-care wards, freestanding dialysis centers, long-term acute-care areas, and outpatient areas *(85)*. In unit-directed surveillance, patients may be monitored for the presence of all types of infection or for only particular infections (e.g., VAP) or process measures (e.g., administration of antibiotics to emergency-room patients with pneumonia, within 4 hours of presentation). Because a geographically smaller area is covered during unit-directed surveillance, theoretically, less time is needed for this type of surveillance. However, ICU-targeted surveillance can be more time-consuming, because patients in these units may have extensive medical records.

Facility-wide surveillance has the advantage of providing a comprehensive view of the facility and detecting potential clusters of infection or antibiotic resistance throughout the facility. Weber et al. (86) found that this type of surveillance in their 700-bed acute-care hospital would have identified 60% more cases of all methicillin-resistant *Staphylococcus aureu*s and vancomycin-resistant enterococci, almost 70% more respiratory infections, and 80% more CLABSIs in the facility's medical–surgical areas than using targeted surveillance alone. However, using facility-wide surveillance for other than small facilities requires an inordinate amount of staff time and is probably not driven either by findings from the facility risk-assessment or prevention goals. Accordingly, the accuracy of facility-wide surveillance has been challenged, and it is not recommended to be used for interhospital comparisons *(87)*. Risk categories for data collected using facility-wide surveillance cannot be identified, which further limits its usefulness in infection prevention activities and is among the reasons that it is not a currently recommended method of surveillance for most institutions *(41)*.

Targeted surveillance has become increasingly common, because it requires fewer resources and has the potential for yielding more meaningful results than facility-wide surveillance. Targets or objectives are chosen as a result of the facility risk assessment. A disadvantage of targeted strategies is that clusters of infection in areas not under surveillance may be missed, although Haley recommended that the IP train other facility staff to be alert for and to report unusual clustering *(16)*. Using data that is available from other sources may also allow the identification of HAIs in areas not routinely targeted. This type of data mining answers some of the challenges posed by HAI surveillance. Many facilities customize their surveillance plan by combining unit- and site-directed targeted surveillance. This combination allows monitoring of high-risk populations located in special units, as well as those undergoing high-risk invasive procedures (e.g., central-line catheterization or total hip arthroplasty).

Patient-Based versus Laboratory-Based Case finding in patient-based surveillance involves assessing risk factors and monitoring patient-care procedures and practices.

It requires ward rounds and discussions with caregivers. Laboratory-based surveillance, on the other hand, involves detecting possible HAIs solely on the basis of laboratory reports from clinical specimens. The primary disadvantage of laboratory-based surveillance is that it will miss infections that are not cultured (e.g., clinical sepsis that only presents physical signs and symptoms and is treated empirically). Important infection issues that are not subject to culture may go unrecognized when only laboratory-based surveillance is used. Patient-based surveillance is, therefore, the recommended approach and is required for participation in most NHSN modules.

A summary of the advantages and disadvantages of types of, and approaches to, surveillance can be found in Table 89-2.

DATA COLLECTION

Numerator

Defining Healthcare-Associated Infection Data collectors must be able to accurately and quickly identify infections that are healthcare-associated and consistently apply definitions and criteria (88). Uniform definitions are critical for comparing data among healthcare facilities and comparing data with an aggregated database (e.g., state or national system) *(42,63,76,89)*. The NHSN system defines an HAI as "a localized or systemic condition that results from adverse reaction to the presence of an infectious agent(s) or its toxin(s) and that was not present or incubating at the time of admission to the healthcare system" (90). For most bacterial HAIs, this means that the infection usually becomes evident 48 hours

TABLE 89-2

Advantages and Disadvantages of HAI Surveillance Types and Approaches

Type/Approach	*Advantages*	*Disadvantages*
Passive	• Requires fewer dedicated resources	• Increased potential for misclassification and underreporting • Lack of timeliness
Active	• Increased visibility of the IP may lead to increased sensitivity of surveillance	• Requires dedicated resources, increased surveillance time
Outcome	• Outcomes (e.g., rates) are of most interest to patients/staff • Measures all aspects of care • Important to measure impacts of prevention efforts	• Can be influenced by nonhealthcare delivery issues that cannot be controlled by healthcare personnel • HAI rates and their limitations can be difficult to understand
Process	• Easy to interpret • More sensitively and directly measure aspects of care • Useful for measurement of adherence to bundles of care, proven to impact patient outcomes	• Do not measure the outcome of care that is often of most interest to patients and healthcare staff
Facility-wide	• Provides rapid, inexpensive estimate of HAI magnitude in facilities • Amenable to smaller facilities • Can be useful to identify and rationalize the need for ongoing prospective surveillance	• May not detect important HAI incidence differences between patient populations if denominators are small
Targeted (priority-based)	• Is directly responsive to the findings of the facility risk assessment, targeting unique surveillance needs • Directs limited IP resources to most important surveillance areas	• Unless combined with adjunct staff looking for HAIs or other data sources, may miss clusters of infection or emerging issues in locations/populations in which surveillance is not performed
Prevalence	• Can be useful to determine an estimate of HAI experience if incidence monitoring is not available (highlight a problem) • Periodic monitoring can provide an estimate of HAI trends within facility	• May fail to detect differences in rates between populations • May overestimate the HAI experience because of extended length of stays, when compared with incidence rates
Incidence	• Can be used to calculate meaningful rates for the time period of interest only (i.e., will not include HAIs from previous time period) • Comparative rates are available (e.g., NHSN)	• None
Patient-based	• More inclusive, accurate	• More labor-intensive
Laboratory-based	• Less labor-intensive	• Fails to identify HAIs that are not cultured, resulting in falsely low rates

(i.e., the typical incubation period) or more after admission. However, because the incubation period varies with the type of pathogen and, to some extent, with the patient's underlying condition, each infection must be assessed individually for evidence that links it to the healthcare event.

Several other important factors enter into HAI definitions and the use of those definitions for HAI surveillance *(89)*. A combination of clinical findings, diagnostic test results, and the type of patient determines the presence and classification of an infection. Clinical evidence comes from direct observation of the infection site and physical assessment or review of other pertinent sources of data, such as the patient's chart (detailed later in this chapter).

CDC/NHSN surveillance definitions of and criteria for specific types of HAIs can be found in the NHSN manual on the NHSN Web site at http://www.cdc.gov/nhsn/TOC_manual.html. Criteria for two HAIs require special consideration: infections acquired in the healthcare setting but not becoming evident until after discharge and infections in a neonate resulting from passage through the birth canal. The preventability or inevitability of an infection is not a consideration when determining whether it is healthcare-associated. For example, preventing the development of healthcare-associated *C. difficile* gastroenteritis after extensive antibiotic treatment may not be possible, but these infections are defined as HAIs because they would not have occurred in the absence of healthcare (i.e., antibiotic treatment). As another example, some would argue that neonatal infections acquired during vaginal delivery are inevitable and, therefore, should not be counted as healthcare-associated. However, as noted previously, these neonatal infections (e.g., group B streptococcal bacteremias with early onset) are considered healthcare-associated, even though they can be identified as maternally acquired. The analysis of their incidence can be disseminated to obstetricians for intervention and prevention strategies.

Three types of infections are *not* considered healthcare-associated: (a) infection associated with a complication or extension of infection already present on admission but not related to previous healthcare, unless a change in pathogen or symptoms strongly suggests the acquisition of a new infection, (b) infection in an infant that is known to have been acquired transplacentally (e.g., toxoplasmosis, rubella, cytomegalovirus, or syphilis) and becomes evident at or before 48 hours after birth, and (c) reactivation of a latent infection (e.g., herpes zoster [shingles], herpes simplex, syphilis, or tuberculosis). Finally, there are two conditions that are not infections at all but are important to consider in the surveillance for HAI: (a) colonization, which is the presence of microorganisms (on skin, mucous membranes, in open wounds, or in excretions or secretions) that are not causing adverse clinical signs or symptoms, and (b) inflammation resulting from a noninfectious cause such as injury or chemical exposure.

Surveillance definitions of HAIs are not intended to guide diagnostic or therapeutic decisions. Additionally, surveillance definitions at times may not accurately describe what is clinically observed or suspected. Physicians may, for instance, believe that a bloodstream infection is secondary to an unidentified infectious process occurring within the gut and should not be identified as a CLABSI because they believe the source is the gut and not the vascular catheter. Currently within NHSN, without an infection by surveillance definition for gastrointestinal infection or gastroenteritis along with microbiologic evidence suggesting that the two are related, CLABSI surveillance definitions will require the reporting of a CLABSI. HAI surveillance requires the consideration of multiple factors. As a result, a rigorous surveillance program can miss identifying true infections and erroneously count some noninfections as infections.

Identifying Data to Collect The data collected on a patient with a HAI include demographic, infection, laboratory, and other diagnostic test data. Table 89-3 shows the most essential data to collect. Additionally, information describing important risk factors for infection should also be collected but only if the information will be analyzed and used by the facility. For example, timing, dosage, and route of administration of preoperative antibiotics may be collected if such data will be used to help understand and guide the practice of surgical prophylaxis. Information on the use of indwelling urinary catheters, central intravascular or peripheral lines, or ventilators allow for surveillance of infections associated with these devices. Where feasible, corresponding denominator data should also be collected so that risk-adjusted infection rates can be calculated (e.g., VAP rates per 1,000 ventilator days in a specific type of ICU). In the NHSN system, information on adverse outcomes of HAI is also collected, such as development of a secondary bloodstream infection and the death of a patient. Determining the relationship between infection and death is essential in understanding an important outcome of HAI.

Identifying types of risk factors associated with the operation is useful when examining infections in surgical patients. Depending on the operative procedure, these may

TABLE 89-3

Essential Data on Healthcare-Associated Infections

Demographic	Name
	Age
	Sex
	Medical record number
	Service
	Location
	Admission date
Infection	Onset date
	Site of infection
Laboratory	Pathogens
	Antibiograms
	Source
	Date
Other diagnostic	CT scan
	MRI scan
	Endoscopy
	Operative note

include operative procedure category, duration and wound class of the operation, the American Society of Anesthesiologists score, use of general anesthesia, use of an endoscopic approach, whether the procedure was performed emergently or as a result of traumatic injury to the patient, and other variables. Data collected on all surgical patients being monitored, not just on patients who develop SSIs, provide a denominator for the calculation of specific rates.

Whenever possible, the data should be entered, analyzed, and stored on a secure computer. NHSN data collection forms can be accessed at http://www.cdc.gov/nhsn/dataCollectForms.html.

Finding Data The type of patients served by the healthcare facility and the methods of documentation determine which sources of data are used to perform surveillance. The IP should have ready access to every area of the facility and the full cooperation of facility staff to perform surveillance or conduct an outbreak investigation *(91)*. Case finding usually begins with the admission department, and also includes microbiology laboratory records, patient wards, sentinel reporting systems, and other areas, which could indicate the patients' charts that need to be reviewed *(92)*.

Capitalizing on Electronic Health Records Many healthcare facilities currently use some form of EHR. Electronic data used in the capture of information for the EHR, includes capture of both administrative data in electronic form (e.g., coded discharge data for claims processing) and clinical data in electronic form, such as EHRs used for clinical recordkeeping. This technology can influence how surveillance is conducted and can save time by accessing electronically available information. Electronic alerts obtained from clinical data may suggest the presence of an HAI and prompt further investigation. Microbiology data, radiologic data, and antimicrobial prescription data are some examples of clinically obtained electronic data. Chapter 16 contains a detailed discussion of the use of EHR, and specifically as used in surveillance for HAI.

The use of administrative coding data (e.g., ICD-9-CM discharge diagnosis coding or Medicare Provider Analysis and Review data) has often been suggested as a means to decrease the manual burden of HAI surveillance. However, this method of HAI identification has been shown to be very imprecise. One study cited a 0.23 PPV when comparing ICD-9-CM code-identified HAIs with HAIs identified using traditional methods (93). Another study using ICD-9-CM codes to identify urinary-tract infections (UTIs) showed a lack of discrimination between community-acquired and HAIs *(94)*. Surveillance for hospital onset *C. difficile* or methicillin-resistant *S. aureus* infection using these types of codes was found to be inaccurate as well *(95,96)*. Jhung and Banerjee (97) identify three primary limitations of using code data: (a) diagnosis code lists can be artificially abbreviated, (b) code lists do not correspond directly to clinical syndromes, and (c) clinicians and coders do not always speak the same language. Therefore, use of electronic data requires carefully piloted studies that include rigorous validation studies to confirm the accuracy.

When a potential infection case is identified through surveillance, the event must be confirmed. The most important source for confirmation is the patient's chart, which contains results of laboratory, radiology, and pathology studies; nursing and physician's notes and consults; admission notes with admission diagnoses; history and physical examination findings; records of diagnostic and surgical interventions; temperature charts; and reports of antibiotic administration. Patient care staff, including nurses, physicians, and respiratory therapists, are excellent additional data sources and can also be trained to complete forms alerting IPs to possible HAIs *(92)*. External sources of data, from health departments or CDC, can alert the IP about the need for active surveillance for newly emerging infections.

Collecting Data Healthcare workers who regularly interact with patients or review charts may be able to provide the IP with data collection assistance. However, due to their specialized training and experience using the case definitions, the IP or medical epidemiologist should be responsible for confirming the presence or absence of an HAI.

Usually, case-finding begins with the IP screening admission lists for patients admitted with infection (either community-acquired or readmission with an HAI) and those patients whose diagnoses (e.g., diabetes or severe immunosuppressive disorders) put them at risk of acquiring an HAI. Next, a visit to the laboratory or electronic review of culture reports can help better define the list of patients whose records require review. On the ward, a quick screening of nursing care reports, temperature charts, antibiotic administration sheets, Kardexes, and conversations with nurses and physicians can expand or focus the list. The IP's regular visits to the microbiology laboratory and patient wards provide opportunities to interact with staff members and gather clues on infected patients, identify unusual patterns of infection, and provide on-the-spot infection control education. Records are reviewed for evidence of infection, usually laboratory data followed by a review of the patient's record *(98,99)*. Physicians' progress notes and nurses' notes from the patient's record are particularly helpful and should be reviewed first. When access to computerized data sources exists, the IP can perform many case-finding activities at his or her desk. However, there is no substitute for frequent visits to the laboratory and patient-care areas to help accurately complete the infection data collection forms. These visits offer the chance for the IP to hear about observations that laboratorians or clinicians have made and may identify infection prevention opportunities not gleaned from electronic data review only.

Given the increasing demands for HAI data and the significant burden that manual collection of these data places on infection prevention and control resources, automated HAI surveillance using algorithmic case detection is an area of immense interest. In this type of surveillance, an algorithm developed from preexisting surveillance definitions, and using unique business logic, captures patient data from various electronic systems within a facility to determine the presence or absence of an HAI. While promising, this method of surveillance presents several challenges, including differences in the types and amounts of available harvestable

electronic data, variances in databases used within facilities and the need for standardization of algorithms for interfacility comparisons *(100)*. One of the biggest outstanding questions is whether these automated surveillance systems will produce data that are of a sufficient quality both from a sensitivity and specificity perspective. A small study comparing manual versus algorithmic detection of VAP applied against the determination of VAP by an infectious disease physician using CDC criteria found a slightly better PPV by algorithm (95%) than by clinician identification (81%) *(101)*. Another study used electronically captured data to compare an outcome called "ventilator-associated complications" to the CDC's VAP definition. Ventilator-associated complications were defined by increases in ventilator settings following a period of stable settings. This simpler system was better able to identify hospital mortality than manual application of the CDC VAP definition *(102)*. This type of surveillance may provide answers to the question of how to collect necessary HAI data when dealing with limited human resources. Validation studies will be key to moving this process along so that the data are accepted by those using it to institute and measure prevention efforts.

Identifying Denominator Data to Collect The denominators of infection rates are a tabulation of the cohorts of patients at risk of acquiring HAIs. For comparative purposes, the traditional denominators of patients admitted to or discharged from the facility, ward, or service have largely been replaced by denominators that better reflect the differences in risks among the monitored patients, such as number of days of exposure to a device. Examples of denominators currently used in NHSN are total number of patients and patient days in the unit and total number of ventilator days, central-line days, and urinary catheter days. Surveillance for antimicrobial resistant microorganisms requires the number of admissions to the unit of study or, in the case of outpatient surveillance, the number of patient healthcare episodes. As discussed in the section on numerators, NHSN has adopted a risk-modeling approach for procedure-specific SSI rates, in part, because it better enables fair inter- and intrafacility comparisons than previous universal risk-stratification systems (*see Comparing Risk-Adjusted Data*). For information on required denominator data for NHSN participation, see the specific NHSN module www.cdc.gov/nhsn.

Finding and Collecting Data The IP should enlist the help of others in the healthcare facility to collect denominator data. Operating room staff keep detailed logs of each procedure performed and can be encouraged to send daily reports to the IP. Alternatively, if the operating room records are computerized, these data can be downloaded directly into the infection control department's computer system. Similarly, a ward clerk can be trained to take daily counts of the number of patients admitted and a charge nurse can document the number of commonly used devices associated with HAI (e.g., urinary catheters). The midnight census can be used as the source of the number of patients in the unit, and respiratory therapy charge logs can also be used for ventilator days. As stated previously, all procedures must be validated by comparison with a proven method before they can be implemented.

DATA ANALYSIS

Defining and Calculating Rates

A rate expresses the probability of the occurrence of an event. It usually takes the form $(x/y)k$, in which the numerator x is the number of times an event has occurred in a population during a specified time period; the denominator y is the total population during the same time period, including those who did and did not experience the event; and k is the base or constant (e.g., 100, 1,000, or 10,000) that expresses the rate as a whole integer. The time period must be specified and identical for the numerator and denominator for the rate to be meaningful.

Three kinds of rates are used in HAI surveillance: incidence, prevalence, and incidence density. Incidence is the number of new cases of disease that occur in a defined population during a specified period of time. For HAI incidence, it is the number of new HAIs in a given time period divided by the number of patients at risk during that time period.

Prevalence is the total number of active (existing and new) cases of the disease in a defined population either during a specified period of time (period prevalence) or at a specified point in time (point prevalence). The point prevalence HAI rate is calculated by dividing the number of active HAIs in patients surveyed by the number of patients surveyed.

Rhame described the relationship between incidence and prevalence rates of HAI as follows: $I = P[LA/(LN - INTN)]$, where I is the incidence rate, P is the prevalence rate, LA is the mean length of facility stay for all patients, LN is the mean length of facility stay for patients with one or more HAI, and INTN is the mean interval from admission to the first HAI in those patients with one or more HAIs (79,*103*). In the hospital setting, prevalence rates almost always overestimate the infection risk because the LOS of uninfected patients is usually shorter than for those with infection. This can be seen more readily by rearranging the equation as $P = I(LN - INTN)/LA$, such that prevalence equals incidence times infection duration.

Incidence density is the instantaneous rate at which disease is occurring, relative to the size of the disease-free population. Incidence density is measured in units of the number of cases of disease per person per unit of time (e.g., 1.3 CLABSI per 1,000 central-line days). Incidence density is useful when the infection rate is a linear function of the length of time a patient is exposed to a risk factor (i.e., the longer the patient is exposed, the greater is the chance of acquiring infection). For example, rate 1—number of urinary catheter–associated UTIs divided by the number of indwelling urinary catheter days—is more useful than rate 2—number of urinary catheter–associated UTIs divided by the number of patients with urinary catheters. Rate 1 controls for the length of time a patient is exposed to the risk factor—the indwelling urinary catheter—which is linearly related to the infection risk.

One other rate that is often used is the attack rate, which is a special type of incidence rate. It is usually expressed as a percentage, where $k = 100$ and is used almost exclusively for describing outbreaks of infection in which particular populations are exposed for short periods of time.

Standardized Infection Ratio

Summarizing the HAI experience across groups of patients is desirable under certain circumstances, such as when a facility wants to describe its experience in a single metric that can take into account those risk factors that have been found to be associated with differences in infection rates (*see Comparing Risk-Adjusted HAI Data*). Based on the standardized mortality ratio, which is used widely in public health to analyze mortality data *(104)*, the SIR can be used for this purpose for HAI data. The SIR is an indirect adjustment technique that uses a standard population's risk-adjusted data to determine the number of HAIs that would be expected to occur if the facility's experiences were similar to those of the standard population's *(25)*. This expected number of HAIs (*E*) is then divided into the number of infections identified or observed (*O*), and the ratio is called the SIR (i.e., SIR = *O/E*). If the value of the SIR is equal to 1, then the HAI experience of the facility is the same as that of the standard population's. If the SIR is >1, there are more HAIs in the facility than expected, and further exploration of the data are needed to determine the causes and remedy them. If the SIR is <1, there are fewer HAIs than expected, and if case finding has been accurate and complete, this can be taken as evidence that HAIs are being prevented. The SIR is gaining acceptance as a useful metric, as evidenced by its use in hospital-specific HAI data reports in states with mandatory reporting laws *(45,105,106)*, by CDC in its state-specific HAI summary report *(107)*, and by the U.S. Department of Health and Human Services in its action plan to prevent HAIs *(108)*.

Device Utilization Ratio

Device utilization (DU) is defined as the number of device days divided by the number of patient days. In the device-associated Module of NHSN, device days consist of the total number of ventilator days, urinary-catheter days, and various types of central-line days. The DU of a critical-care unit or other patient-care location is one measure of the unit's invasive practices that constitute an extrinsic risk factor for certain HAIs. As such, DU may also serve as a marker for the severity of illness of patients in the unit. An IP's attention should not focus solely on infection rates in facilities. Those responsible for delivery of quality medical care must ask whether patients' exposures to interventions (e.g., devices or operative procedures) that increase risks of HAIs have been minimized wherever possible. For critical-care units, for example, the extent of DU may have to be examined. For surgical patients undergoing specific procedures, the distribution of patients by certain risk factors may provide valuable information *(37)*. Examining the appropriateness of an intervention also may aid in determining whether patient exposure was minimized.

Risk Adjustment of HAI Data

The denominator of a rate must reflect the population at risk. To compare a rate among patient groups within a facility, over time, or across facilities, the rate must be adjusted for the variations in *(91)* distribution of the major risk factor(s) that leads to the infection. The importance of risk adjustment was demonstrated when the federal agency then known as the Health Care Financing Administration failed to adjust for the major risk factor predicting mortality (i.e., severity of illness). Because of the absence of risk adjustment, most hospital administrators could not interpret or use these rates *(109,110)*.

A patient's predisposition for becoming infected is strongly influenced by certain risk factors such as personal characteristics and exposures. These risk factors are divided into two categories: intrinsic and extrinsic *(41,91)*. Intrinsic risk factors are those that are inherent in the patient, such as underlying disease conditions and advanced age *(91)*. Knowledge of the intrinsic risk factors is useful because separate risk-specific rates can be calculated, permitting the comparison of rates among patients with similar risks in different facilities or across different time periods. The Acute Physiologic and Chronic Health Evaluation (APACHE II) and diagnosis-related groups are two well-known indices for the severity of illness and are used to predict the risk of death and resource utilization, respectively, among ICU patients *(111)*. They are less useful when applied to HAIs because the factors associated with increased mortality and resource utilization apparently are not the same as the factors that increase the risk of infection. Patients with very high APACHE II scores probably do not survive long enough to acquire an HAI. One review suggests that no current severity of illness scoring system consistently adjusts risk for HAIs. Studies are needed to describe simple objective measures of severity of illness and/or underlying diseases that correlate with site-specific HAIs. These studies should also control for extrinsic risk factors for HAIs, such as exposure to devices.

Extrinsic risk factors may be healthcare worker–based (practices of an individual caregiver) or facility-based (practices in an entire facility). Although many extrinsic factors contribute to HAIs, the factors that have been implicated and studied most frequently are certain high-risk medical interventions, such as the use of invasive devices or surgical operations *(18,112–116)*. There are many reasons to explain the higher HAI rates among patients exposed to certain devices compared with HAI rates of patients not exposed to the devices *(40)*. Patients who require invasive devices may have more severe underlying disease conditions that increase their susceptibility to infections. These devices also provide a pathway for microorganisms from the environment to enter the body; facilitate the transfer of pathogens from one part of the patient's body to another; and act as inanimate foci where pathogens can proliferate, protected from the patient's immune defenses.

The risk of SSI is associated with a number of factors. Among the most important factors are the type and characteristics of the operative procedure performed, the degree of microbial contamination of the operative field, duration of operation, and the intrinsic risk of the patient *(115,117)*. Because infection control practices cannot alter or eliminate all of these risks, SSI rates must be adjusted for these risks before the rates can be used for comparative purposes. Two SSI risk indices—basic and modified—that effectively adjusted SSI rates for most operations were developed by the NNIS system *(117,118)*, and a variant of the basic risk index has been used in the NHSN *(119)*. However, NHSN is replacing this index with procedure-specific multivariable models to achieve even better risk adjustment *(107)*.

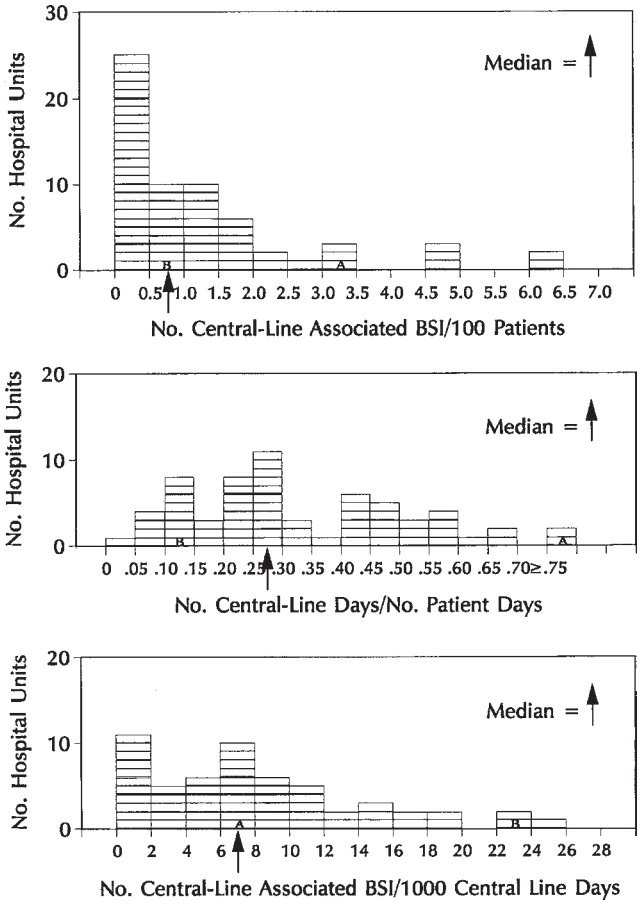

FIGURE 89-1 The effects of units of measure on CLABSI rates. (Adapted from Jarvis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States. National Nosocomial Infection Surveillance System. *Am J Med* 1991;91(suppl 3V):1855s–1915s.)

Figure 89-1 illustrates the effect of risk adjustment when comparing infection rates among various patient groups in hospital ICUs. The rate for hospital unit A, which uses the number of patients in the denominator, was nearly 5 times higher than the median for similar ICUs. However, hospital unit A had the greatest central-line use, that is, more than 80% of patient days were also central-line days. Using central-line days as the denominator of the rate helps to take into account this high use of central lines; thus, hospital unit A's device-associated device-day bloodstream infection rate was slightly lower than the median. Although using hospital unit A's device-associated, device-day bloodstream infection rate kept it from being designated a high outlier, unit A's high frequency of central-line use may need to be reviewed for appropriateness. On the other hand, hospital unit B's central line–associated bloodstream infection patient rate was near the median and its central-line use was low. When hospital unit B's rate was calculated using central-line days in the denominator, it was quite high, suggesting the potential need to review central-line insertion and maintenance practices.

Comparing Risk-Adjusted HAI Data

Facilities use surveillance data to assess their infection control program by comparing infection rates among similar patient populations within the facility (e.g., two separate medical ICUs), their rates with external benchmark rates, or changes in rates over time in their own facility. However, such comparisons can only be made if the rates control for variations in the distribution of the major risk factors associated with the infections. This process of developing comparable rates requires that the rates are site-specific, that uniform definitions and surveillance protocols are used to collect the data, that there is consistent and accurate case finding, and that the risks are similar or controlled for by risk-adjustment methods (such as stratification or standardization) *(120)*. The NHSN system, like the NNIS system before it, uses a population-based surveillance system that provides risk-adjusted rates that can be used for interfacility comparisons *(41,*121).

Testing for significance among infection rates is the subject of Chapter 3. However, the interpretation of those statistical tests should be carefully considered. Many facilities assume that any difference in the rates represents success or failure in the patient-care staff or institutional practices to prevent HAI. Although this may be true, there are other factors that could account for the differences in the rates.

First, surveillance definitions or techniques may not be uniform among the facilities, or they may be used inconsistently over time, causing variations to occur in sensitivity and specificity of infection case finding. Second, inaccurate or insufficient information about clinical and laboratory evidence of infections in the patient's medical record may compromise the validity and utility of the infection rate.

Third, the rates may not be adjusted for patients' intrinsic risks for infection. These risks are usually outside of the control of the facility and vary from facility to facility but are important factors in determining whether patients will develop infections. For example, a facility with a large proportion of immunocompromised patients would be expected to have a population at higher intrinsic risk for infection than a facility without such a population of patients. The unsuccessful attempts to compare unadjusted mortality rates *(109,110)* are reminders to those comparing infection rates that they must be certain to risk-adjust HAI rates. Finally, the size of the population at risk (e.g., number of patients, admissions and discharges, patient days, or operations) may not be large enough to calculate rates that adequately estimate the true rates for the facility. Although it may not be possible to fully correct for these factors, facilities should be aware of how they may affect the infection rate and take them into consideration when interpreting the data.

DATA DISSEMINATION

Surveillance is not complete until the data are disseminated to those who will use it to prevent and control infections. Because of its sensitive nature, information containing identifiers of patients or patient-care staff should be handled carefully. Data should not be used for punitive purposes but rather to augment quality improvement efforts.

It is customary for the IP to regularly provide a narrative summary and tabular and graphic reports of surveillance data to the facility's infection prevention or other oversight committee. The IP should include only those infection rates for which there are sufficient denominator data to

calculate meaningful estimates of risk. Therefore, monthly rate tabulation will not be practical in many small facilities or in larger institutions when small numbers of patients are at risk (e.g., for certain types of operative procedures that are performed infrequently). Infection rates for these instances may have to be calculated quarterly, semiannually, or annually, depending on the size of the denominator, or SIRs can be calculated. In addition, a thorough analysis of numerator data (i.e., the HAI) should be performed to gain insight into their epidemiology, including information on pathogens and risk factors.

Many state health departments are members of HAI prevention collaboratives with healthcare facilities within their borders. Complete data analysis and determination of the effectiveness of prevention efforts in these consortia require such data be shared with health department partners. Often, state health departments are responsible for posting HAI data on public websites, enabling consumer consideration and use in healthcare purchasing decisions.

APPLICATION OF THESE METHODS BEYOND HEALTHCARE-ASSOCIATED INFECTIONS

Nearly all of the best practices of HAI surveillance just described can be applied to monitoring other care processes, such as surgical preparation activities, and noninfectious outcomes of healthcare delivery, such as mortality or patient satisfaction. The characteristics of a successful monitoring and reporting system include the system being nonpunitive, confidential, independent, timely, systems-oriented, responsive, and providing expert analysis (122). IPs experienced in HAI surveillance can share their considerable expertise with colleagues monitoring other adverse events and attempting to improve the quality of care throughout the healthcare facility. Because the systematic collection of reliable data is essential to all successful evaluation efforts, HAI surveillance advances quality improvement and patient safety efforts across the entire healthcare facility.

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CHAPTER 90

Isolation of Patients with Communicable Diseases

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Despite advances in the control of infectious diseases in the last century, there is more interest than ever in the use of isolation precautions to control known and emerging diseases such as multidrug-resistant bacteria, multidrug-resistant tuberculosis (MDR-TB), pandemic influenza, and *Clostridium difficile* infection. These precautions are particularly important in the institutional setting due to the proximity and potential common exposures of patients who have communicable diseases with other patients. The terminology for isolation precautions has changed and developed over the years. Although the universal implementation of Standard Precautions simplified isolation policies to some degree, the terms used for isolation precautions varied among institutions, and some confusion ensued *(1,2)*. In addition, some of the situations outlined above may call for additional measures that are not in "Universal Precautions," as originally defined. The revision of the guidelines for isolation published in 1996 by the Centers for Disease Control and Prevention (CDC) approached isolation as transmission-based and clarified some confusing issues (3). Based on the positive results, this approach was reaffirmed in the most recent revision of the guidelines (4). Still, the infection preventionist (IP) is frequently called regarding the appropriate use of isolation precautions.

HISTORICAL PERSPECTIVE

The concept of isolating persons with communicable diseases was in practice even in ancient times according to biblical accounts of leper colonies, although the leprosy of biblical times may have been other skin diseases *(5)*. In modern times, hospital construction before 1850 featured crowded open wards *(6)*. As a consequence, cross-infection was common, and mortality rates were high in urban hospitals *(7)*. Florence Nightingale's observations from the Crimean War *(8)* led her to advocate small pavilion-type wards joined by open-air corridors. Nightingale emphasized the importance of asepsis and a clean environment. Her teachings were called "fever nursing" and varied from popular concepts of disease at the time, because fever nursing implicated transmission by contact with body substances rather than the environment *(9)*.

The germ theory of infection was accepted in US hospitals in the late 1800s, after the influence of Lister and Pasteur, and conditions began to improve as overcrowding decreased and antisepsis increased *(7)*. Communicable disease hospitals were using individual and group isolation as early as 1889 *(10)*. By the turn of the century, general hospitals were beginning to isolate patients with communicable diseases in an individual room with the use of separate utensils and disinfectants *(9,11)*. Grancher in Paris promoted the theory of communicability by contact rather than airborne spread for most diseases and allowed patients with communicable diseases to be housed in general wards but with separation by wire screens *(9)*. These screens separated the patient from other patients and served as a reminder for staff members to gown and wash their hands. Thus, began the trend in the United States from the isolation hospital to care of communicable diseases in a general hospital setting.

In the early 20th century, Charles V. Chapin of Providence City Hospital used individual isolation cubicles for patients with communicable diseases and documented that fumigation had no effect on secondary cases *(12)*. His work was very important in emphasizing the roles of persons rather than things as spreaders of disease and helped to end the miasmatic theory of transmission *(13)*. Richardson, the physician superintendent of Providence City Hospital, used the barrier method and the cubicle method for isolation of patients, allowing some patients with communicable diseases to be housed in the same room as other patients *(9)*. A card outlining the barrier technique needed was placed on the patient's bed.

The emergence of *Staphylococcus aureus* as a hospital pathogen in the 1950s and 1960s prompted the development of infection-control programs in US hospitals. In 1968, the first edition of the American Hospital Association's manual *(13)* presented a simple barrier precautions scheme for patients with communicable diseases, listing the need for gloves, gowns, masks, and visitor screening.

EARLY RECOMMENDATIONS FROM CENTERS FOR DISEASE CONTROL AND PREVENTION

While conducting healthcare-associated outbreak investigations in the 1960s, the CDC recognized that standardized

policies for isolating hospitalized patients with communicable diseases were lacking *(14)*. A group of experts convened in 1967 to develop the first CDC isolation recommendations, and first published five categories of isolation in 1970 *(15)*. Even in this initial manual, the philosophy behind the more recently developed Universal Precautions was expressed. By 1976, a survey showed that 93% of hospitals in the United States were using the category-specific approach to isolation *(16)*.

Substantial changes were made in the 1983 CDC recommendations (17). The updated category-specific guidelines for isolation published in 1983 (17) included seven categories of isolation: strict isolation, respiratory isolation, enteric precautions, contact isolation, tuberculosis (acid-fast bacillus [AFB]) isolation, drainage/secretion precautions, and blood and body fluid precautions. These isolation categories grouped diseases that require the same isolation precautions. After the more recent transmission-based guidelines from CDC, these categories are now of historical interest, but the terms are still commonly used and confused by some healthcare workers. IPs may be called on to clarify and compare these previous categories with the newer guidelines.

In addition, this 1983 guideline introduced disease-specific isolation as an alternative to category-specific isolation. Disease-specific isolation was offered as an alternative for hospitals wanting a more economic system that directed precautions at preventing transmission of a specific disease while avoiding unnecessary isolation precautions for some diseases. The guidelines stated that hospitals could choose the category-specific or the disease-specific system or design their own systems.

CATEGORY-SPECIFIC ISOLATION

Strict Isolation

Strict isolation was used to prevent transmission of diseases spread by both air and contact. Specifications for strict isolation include a private room with the door closed; masks, gowns, and gloves were indicated for all persons entering the room. This category has now been replaced with the use of Standard Precautions (for all patients) or Contact Precautions combined with Airborne Precautions in the new guidelines.

Contact Isolation

Contact isolation was a category designed to prevent the transmission of epidemiologically important microorganisms causing infection or colonization or highly transmissible microorganisms that do not warrant strict isolation. Conditions in this category are spread by direct or close contact. This category has been replaced by Contact Precautions in the new transmission-based guidelines.

Respiratory Isolation

Respiratory isolation was used to prevent droplet nuclei transmission, that is, transmission of diseases over long distances through the air. In the newer guidelines, this category has been replaced by Airborne Precautions.

Tuberculosis Isolation (Acid-Fast Bacillus Isolation)

Tuberculosis isolation was referred to as AFB isolation on the standard instruction card to protect patient confidentiality (17). Airborne Precautions have replaced this category in the new guideline. However, there are still many issues pertinent to tuberculosis that warrant special consideration regarding isolation, and these are discussed below (see Duration of Isolation in the "Tuberculosis Precautions: Special Considerations" section).

Enteric Precautions

Enteric precautions were used to prevent infections transmitted by feces. Examples would be hepatitis A or bacterial diarrhea. Enteric precautions are now included in Standard Precautions or, in the case of diapered or incontinent patients, Contact Precautions.

Drainage/Secretion Precautions

Drainage/secretion precautions were used to prevent the transmission of infection by direct or indirect contact with drainage from an infected body site or from purulent material. This isolation category was newly created for the 1983 guidelines and used for many infections isolated under wound and skin precautions or discharge and secretion precautions in the previous guideline. Minor skin, wound, or burn infections that can be adequately covered by a dressing previously included in this category are now covered by Standard Precautions. Major infections not covered or not adequately covered by a dressing are now covered under Standard Precautions or Contact Precautions, depending on the clinical setting.

Blood and Body Fluid Precautions

Blood and body fluid precautions were designed to prevent the transmission of blood-borne pathogens. This category is now only for historical reference because Universal Precautions superseded it. Precautions used for blood and body fluids are now recommended in Standard Precautions, which should be used for the care of all patients.

Comments

The advantage of category-specific isolation was that the grouping of diseases with similar routes of transmission was relatively easy to teach to personnel. It consisted of seven categories (six, if blood and body fluid precautions was excluded) that could be adopted, and the diseases grouped accordingly. A disadvantage of the system was that it was diagnosis- or disease recognition–driven and depended on the caregiver to identify the presence or suspected presence of a disease. In addition, drainage/secretion precautions could be confused with contact isolation and vice versa. Universal Precautions recommended barriers to prevent contact with blood and certain body fluids; body substance isolation (BSI) recommends barrier protection for contact with all body fluids or open skin lesions. Because Standard Precautions recommend both, many categories in category-specific isolation are superfluous. Strict isolation, respiratory isolation, and AFB isolation are exceptions but are categorized differently in the new guidelines.

DISEASE-SPECIFIC ISOLATION

Disease-specific isolation was one of two isolation systems recommended by the CDC in 1983 (17). In this system, communicable diseases were considered individually with regard to mode of transmission and infective material, and accordingly, precautions are specified for each disease. The purported advantage of this system is that because precautions are specific for each disease, there are no unnecessary barriers used, and this lowers the cost of isolation. It may also enhance compliance by physicians, who more readily understand the need for specific precautions for each disease. The disadvantage of this system is that because diseases are not grouped by category, it is more difficult to train staff that are not familiar with specific diseases. Another disadvantage is that, like category-specific isolation, this system is diagnosis-driven, and isolation precautions are often important early in the patient's hospital stay, before a diagnosis is made or even suspected.

IMPACT OF THE ACQUIRED IMMUNODEFICIENCY SYNDROME EPIDEMIC

The recognition of the acquired immunodeficiency syndrome (AIDS) epidemic in the mid-1980s affected isolation policies in healthcare institutions unlike any other event in modern medicine. Before 1987, most hospitals placed patients in isolation, based on diagnosis or suspected diagnosis, according to the category-specific or disease-specific precautions as outlined by the aforementioned CDC guideline (17). As it became apparent that transmission of human immunodeficiency virus (HIV) could occur from patient to healthcare worker, new guidelines were established to minimize exposure to blood-borne pathogens from all patients, not just patients with a diagnosis or suspected diagnosis of HIV infection (18). In contrast to the 1983 CDC guideline, the 1987 CDC document (18) recommended blood and body fluid precautions for all patients, regardless of known HIV status. The belief that such precautions were unnecessary in patients not known to have blood-borne pathogens was gone. Specifically, barrier precautions were recommended to prevent contact with blood, certain body fluids, and body fluids containing blood. The application of blood and body fluid precautions to all patients was referred to as "universal blood and body fluid precautions" or "Universal Precautions." In 1988, the CDC published an updated Universal Precautions for the prevention of transmission of HIV, hepatitis B virus (HBV), and other blood-borne pathogens to supplement the 1987 publication *(19)*. This document made it clear that transmission of other blood-borne pathogens, such as HBV, should be prevented as well as that of HIV. In a new precedent for the healthcare industry, the Occupational Safety and Health Administration (OSHA) became involved in regulating and enforcing these guidelines *(20)*. Now healthcare institutions were mandated to apply and enforce what was, in effect, blood and body fluid precautions as a minimum standard for protection of the healthcare worker.

Infection control programs recognized the potential benefit of this universal concept as a means of preventing cross-transmitted pathogens (blood-borne and non–blood-borne) among patients and healthcare workers. It became clear very quickly that an additional isolation system was needed to reduce the risk of transmitting non–blood-borne pathogens, because the CDC-defined Universal Precautions were primarily for preventing transmission of blood-borne pathogens. In the CDC 1988 update *(19)*, category-specific or disease-specific isolation precautions are recommended to fill this need, as described in the 1983 CDC guidelines. IPs at Harborview Medical Center in Seattle, Washington, recognized the problem early. They implemented a BSI system at Harborview in 1984 to control cross-transmission of non–blood-borne pathogens. This system designated all body fluids and tissue as potentially infectious *(21)*. In 1987 and 1990, Lynch et al. *(22,23)* described their system and its advantages in preventing the transmission of both blood-borne and non–blood-borne pathogens. This system provided an alternative to the category-specific or disease-specific systems. Some confusion ensued because the term Universal Precautions was sometimes used to apply to barrier precautions for all body fluids, not just blood and certain body fluids as originally defined *(1,2)*. Although the 1996 CDC guideline for isolation precautions in hospitals includes concepts of both Universal Precautions and BSI, these isolation systems are described briefly below because of their impact on current practices. Universal Precautions (now part of Standard Precautions) are also described in Chapters 73 and 74.

UNIVERSAL PRECAUTIONS

In 1985 and 1986, the CDC published recommendations to prevent the transmission of HIV in the workplace *(24,25)*. In 1987, a more comprehensive document (18) was published in response to increasing concern from healthcare workers about occupational exposure to HIV. These guidelines recommended the application of blood and body fluid precautions to all patients and designated this policy "Universal Precautions" or "universal blood and body fluid precautions."

Universal Precautions as presented by the CDC in 1987 (18) include the following concepts:

1. Healthcare workers should use appropriate barrier precautions to avoid skin and mucous membrane exposure when contact with blood or body fluids from any patient is anticipated. Gloves are to be worn for contact with blood and body fluids, mucous membranes, or nonintact skin; when handling surfaces or items soiled with blood or body fluids; or for venipuncture or other procedures involving vascular access. Gloves should be changed after each patient contact. Masks and protective eyewear or face shields should be worn when procedures are likely to generate aerosols or droplets of blood or other body fluids. Gowns should be worn for procedures that are likely to soil clothing.
2. Hands or skin contaminated with blood or body fluids should be washed immediately. Hands should be washed after removing gloves.

3. Precautions should be taken to prevent sharps or needlestick injuries. Needles should not be recapped, removed from disposable syringes, or manipulated by hand. After use, needles, disposable syringes, scalpels, and other disposable sharp instruments should immediately be placed in a designated puncture-resistant container.
4. Mouthpieces and resuscitation devices should be readily available for use in areas where resuscitation procedures may be anticipated.
5. Healthcare workers with exudative skin lesions should not be involved in direct patient care or handle patient-care equipment until the condition has resolved.

Precautions for Invasive Procedures

These were also outlined in the 1987 document and included routine surgical and obstetric procedures and outpatient physician and dentist office procedures. An invasive procedure was defined as surgical entry into tissues, cavities, or organs or repair of major traumatic injuries in an operating or delivery room, emergency department, or outpatient setting, including both physician and dentist offices; cardiac catheterization and angiographic procedures; vaginal or cesarean delivery or other invasive obstetric procedure during which bleeding may occur; or the manipulation, cutting, or removal of any oral or perioral tissues, including tooth structure, during which bleeding occurs or the potential for bleeding exists. Healthcare workers participating in such procedures should routinely use barrier precautions as needed to prevent skin and mucous membrane exposure to blood and body fluids from all patients. This includes not only gloves and surgical masks for invasive procedures but also protective eyewear or face shields for procedures that are anticipated to generate droplets or splashing of blood or body fluids. Effective barrier gowns should be worn when splashing is anticipated. Healthcare workers in obstetrics should use appropriate barrier precautions during deliveries. If a glove is torn or a sharps injury occurs, the glove should be replaced with a new glove. The needle or sharp instrument involved should also be removed from the sterile field.

Precautions for Dentistry

Blood, saliva, and gingival fluid from all dental patients should be considered potentially infective in both institutional and noninstitutional settings. Dental workers should wear gloves for contact with oral mucous membranes and, in addition, surgical masks and protective eyewear or face shields for procedures in which splashing of blood or body fluids is likely. Hand pieces should be sterilized after each patient use. Hand pieces that cannot be sterilized should at least be flushed, cleaned with a chemical germicide, and rinsed after each patient use. Contaminated dental materials (impressions, bite registration) should be cleaned and disinfected before being handled in the dental laboratory and before being placed in another patient's mouth. Infection control precautions for dentistry are more specifically outlined and updated in later recommendations *(26)* (see also Chapter 54).

Precautions for Autopsies or Mortician Services

Persons participating in postmortem procedures should wear appropriate barrier protective equipment. Equipment and surfaces contaminated during such procedures should be cleaned with an appropriate chemical germicide (see Chapter 80).

Precautions for Dialysis

Blood and body fluid precautions are to be used when dialyzing all hemodialysis patients, not just those identified as hepatitis B surface antigen positive or HIV positive. HIV-infected patients do not need to be isolated from other patients during hemodialysis. The dialyzer may be discarded after use. Institutions that reuse dialyzers may designate a specific single-use dialyzer to a specific patient for reuse after appropriate cleaning and disinfection on the same patient only. HIV-infected patients may be included in the reuse programs; individual dialyzers must never be used on more than one patient (see also Chapter 63).

Precautions for Laboratories

Blood and other body-fluid specimens from all patients are considered infective. Specimens should be placed in a well-constructed container with a secure lid to avoid leakage. Contamination of the outside of the container or the laboratory form should be avoided. Personnel who process specimens should wear gloves. Other barrier protection should be used as needed if splashing or aerosolization is anticipated. Biologic safety cabinets should be used for procedures that are likely to generate droplets or aerosols. After specimen processing, gloves should be changed and hands washed. Mechanical devices should be used for pipetting; mouth pipetting should never be done. Laboratory work surfaces and laboratory equipment should be decontaminated with an appropriate chemical germicide after blood or body fluid spills and when work is completed. Before leaving the laboratory, personnel should remove protective clothing and wash their hands (see also Chapter 77).

ENVIRONMENTAL CONSIDERATIONS FOR HUMAN IMMUNODEFICIENCY VIRUS TRANSMISSION

Disinfection and Sterilization

Environmental transmission of HIV in the clinical setting has not been documented; however, environmental considerations are reviewed, and the same precautions are recommended for all patients. Standard disinfection and sterilization procedures for equipment are recommended for inpatient and outpatient settings, as previously described in the CDC guidelines for environmental control *(27)*. Semicritical items, or items that contact mucous membranes such as endoscopes and bronchoscopes, should be sterilized or undergo high-level disinfection after each patient use. Chemical germicides registered with the U.S. Environmental Protection Agency (EPA) as sterilants may be used for high-level disinfection or sterilization depending on contact time (see Chapter 80). Under such guidelines, instruments used on HIV-positive patients do not require separate processing because high-level disinfection or sterilization should take place after use on any patient.

Housekeeping

Cleaning of environmental surfaces should be done after contamination by any patient; special cleaning is not required for patients with blood-borne pathogen infections. Horizontal surfaces should be cleaned when spills or soilage occurs and when patients are discharged. EPA-registered disinfectant–detergents should be used. Spills of blood or body fluids should be cleaned up immediately. Personnel should wear gloves. Broken glass and any other sharp objects should first be removed using tongs or forceps and placed in a sharps container. Then, visible fluid should be wiped up, the absorbent materials discarded as infectious waste, and the area decontaminated with a chemical germicide that is tuberculocidal and EPA-approved as a hospital disinfectant. For large spills, the contaminated area should be treated first with the chemical germicide and then cleaned and fresh germicide used for decontamination.

Laundry

Soiled linen should be handled in the same way for all patients with a minimum of agitation; linen should be bagged at the location where it was used. Linen with blood or body-fluid soilage should be transported in leak-proof bags. Linen should be laundered with detergent in hot water (71°C, 160°F) for 25 minutes. If a lower temperature is used, suitable chemicals for low-temperature washing must be used.

Infective Waste

Special precautions are recommended for handling certain hospital wastes that may be infective such as microbiology laboratory waste, pathology waste, and blood specimens or blood products. There has been disagreement on whether to classify communicable disease isolation waste as infectious waste. The CDC does not consider such waste as infectious, but before the Medical Waste Tracking Act of 1988, the EPA classified such waste as infectious waste. In the Medical Waste Tracking Act, however, the EPA modified its position and included only certain highly communicable disease waste from patients with infections due to biosafety level 4 etiologic agents (e.g., viral hemorrhagic fevers, such as Marburg, Lassa, and Ebola) as regulated medical waste *(28)*. Bulk blood, body fluids, or excretions may be disposed of through the sanitary sewer system.

Implementation

These recommendations also stated that employers should ensure that workers receive initial orientation and continuing education and training on the transmission and prevention of blood-borne infections and routine application of Universal Precautions in the care of all patients. Personal protective equipment should be provided by the employer, and monitoring of compliance to the recommended protective measures should be followed.

Other Isolation Categories

With regard to other isolation categories as outlined in the 1983 guideline, the implementation of Universal Precautions superseded the need for a separate category of blood and body fluid precautions. Other isolation precautions, however, were recommended as needed for conditions such as infectious diarrhea (enteric precautions) or tuberculosis (AFB precautions).

UPDATE: UNIVERSAL PRECAUTIONS, 1988

After the recommendations for Universal Precautions were published in 1987, hospitals scurried to write their own institutional policies and implement training for their personnel in the prevention of blood-borne diseases in the workplace. In 1988, the CDC published an update to Universal Precautions that indicated these precautions were also for the prevention of other blood-borne pathogens such as HBV and specified that only specific body fluids implicated in the transmission of blood-borne pathogens needed to be included under Universal Precautions. Many hospitals already had policies in place and employees trained by this time, which contributed to confusion in the use of the term Universal Precautions. A variety of different systems carried this term in individual institutions *(29)*. The 1988 update also included further clarification on the use of protective barriers, the use of gloves for phlebotomy, the selection of gloves, and waste management.

Body Fluids to Which Universal Precautions Apply

In terms of occupational exposures, blood is the most important source of HBV, HIV, and other blood-borne pathogens. Infection prevention efforts aimed at preventing occupationally acquired blood-borne infections must emphasize prevention of exposures to blood and promotion of HBV immunization. Universal Precautions apply to semen, vaginal secretions, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, amniotic fluid, and any body fluid containing visible blood.

Body Fluids to Which Universal Precautions Do Not Apply

According to the 1988 update, Universal Precautions do not apply to feces, nasal secretions, sputum, sweat, tears, urine, and vomitus unless they contain visible blood. The risk of blood-borne pathogen transmission from these fluids is very low or nonexistent. The 1983 CDC guidelines (category-specific or disease-specific isolation) are cited for the prevention of non–blood-borne pathogen transmission. Universal Precautions do not routinely apply to saliva; however, special precautions are reiterated for dentistry because contamination of saliva with blood is predictable with dental procedures.

Use of Protective Barriers

The types of barriers needed for different procedures and clinical situations vary, so the healthcare worker must use appropriate judgment. Barrier precautions do not prevent sharps injuries; thus, caution in handling needles and sharps instruments, as previously outlined, is also necessary. Protective barriers should be used when exposure to blood or the above-named body fluids is anticipated. Hands or other surfaces contaminated with blood or the specified body fluids should be washed immediately.

Glove Use for Phlebotomy

Although gloves may reduce the amount of blood contaminating hands during venipuncture, they do not prevent needlestick injuries. The likelihood of exposure during phlebotomy depends on the skill of the personnel, the cumulative risk of the worker, whether the procedure is in a routine or emergency setting, and the prevalence of blood-borne pathogens in the patient population. Even though blood from all patients is considered infectious, the prevalence of HIV or HBV in volunteer blood donor centers is known to be low. Some centers, therefore, have not routinely recommended gloves for phlebotomy in these settings. Gloves should always be available for workers who choose to use them, however. Gloves should always be used for phlebotomy when the healthcare worker has scratches, cuts, or other breaks in the skin; when hand contamination with blood is anticipated, such as when phlebotomy is done on an uncooperative patient; for finger or heel sticks on infants or children; and when personnel are receiving phlebotomy training.

Glove Selection

The Center for Devices and Radiological Health, Food and Drug Administration (FDA), is responsible for the regulation of the medical glove industry. Medical gloves include sterile surgical or nonsterile examination gloves made of vinyl or latex. The gloves selected should be task appropriate, and the following are general guidelines. Sterile gloves should be used for contact with sterile body areas. Nonsterile examination gloves may be used for contact with nonsterile body areas or other procedures that do not require aseptic technique. Gloves should be changed between patient contacts. Gloves should not be washed or disinfected between patients. Exposing the gloves to surfactants used for washing may cause increased penetration of liquids through unseen holes in the glove (wicking). Disinfectants may damage the gloves. General-purpose utility gloves (rubber household gloves) should be used for housekeeping activities and instrument cleaning in which contact with blood or specified body fluids is anticipated. These gloves can be reused after decontamination but should be discarded if torn or visibly damaged. Since the publication of this 1988 update, there have been many studies published evaluating glove integrity (see below, "Are Gloves an Effective Barrier?").

Waste Management

Guidelines on waste management remain unchanged from the 1987 recommendations, but state and local regulations in many areas now supersede these recommendations, and this has been acknowledged.

Comment

Universal Precautions have the advantage of protecting the healthcare worker against unidentified blood-borne pathogen risks. Also, this system is simpler than traditional systems, because the blood and body fluid isolation category applies to all patients. However, the 1988 update, which was intended to clarify which body fluids are infectious, only served to confuse the issue because it is often difficult, at the bedside, to discern whether a body fluid contains blood. Furthermore, it is sometimes difficult to know the origin of a body fluid at the bedside and even more so when the specimen is removed from the bedside. BSI addresses some of these issues. Even so, the issue of cost and compliance in using Universal Precautions may also present a problem (see below, "Impact of Universal Precautions and Body Substance Isolation" section).

BODY SUBSTANCE ISOLATION

Jackson and Lynch *(21)* responded early on to the concern that unrecognized or undiagnosed cases resulted in unsafe exposures for healthcare workers. As early as 1984, these authors pointed out that many infectious agents are transmitted from patients who have only mild symptoms or no symptoms, and they recommended barrier precautions for anticipated contact with blood or any body fluids from all patients and reemphasized the important role of hand washing. Recognizing the limitations of the diagnosis-driven, category-specific, and disease-specific isolation systems, they systematically outlined an alternative system called BSI *(22)*. This approach was similar to the CDC Universal Precautions in that it presumed that all patients were potentially infectious, but it differed in that barrier precautions are used to prevent contact with all body fluids and tissue, not just certain body fluids and blood-tinged body fluids, as recommended in the 1988 CDC update. The term body substance rather than body fluid is used to emphasize that barrier precautions should be used to prevent contact with solids, such as tissue and feces, and body fluids. BSI contains six major components *(22)*:

1. Gloves should be used for anticipated contact with blood, mucous membranes, nonintact skin, secretions, and moist body substances of all patients. The 1987 article stated that hand washing is not necessary unless hands are visibly soiled from breaks in gloves. Gloves should be changed between patients.
2. After other types of patient contact without gloves, hand washing, which is effective in removing transient flora from the hands, should be done (10 seconds of soap and friction followed by a rinse with running water).
3. Other barriers such as gowns, plastic aprons, masks, or goggles should be worn as needed when soiling of clothing and/or skin or mucous membranes is anticipated.
4. Soiled reusable items, linen, and trash should be contained such that no leakage occurs. Double bagging is not needed unless the outside of the bag is soiled.
5. Needles and sharps should be placed in rigid puncture-resistant containers. Needles should not be recapped.
6. Private rooms are indicated for patients with diseases transmissible by the airborne route and for patients who may soil the environment with body substances.

Operational Issues

A single universal reminder sign—"Body substance isolation is for all patient care"—is placed in every patient room or at every bedside. This sign defines body substances and uses graphics and words to indicate when gloves, gowns, masks, or eye protection should be used. A stop sign alert is used on the door of patients with airborne diseases. This sign indicates that persons should check with

the floor nurse before entering the room. The floor nurse will determine if the person is immune and need not wear a mask (e.g., measles, chickenpox) or instruct the person to wear a mask (e.g., tuberculosis). Nonsterile gloves must be accessible near the bedside, and other barriers must be available on the nursing unit. As with Universal Precautions, some judgment by healthcare workers is required in determining when exposures may be anticipated.

Comment

BSI is like Universal Precautions in that it protects workers and patients against the transmission of blood-borne pathogens. BSI is easier to teach to staff and to apply at the bedside than Universal Precautions, as clarified in 1988, because barrier precautions apply to all body fluids not just certain body fluids. BSI has the advantage of protecting against non–blood-borne pathogens as well. Use of gloves has been shown to control cross-transmission of multidrug-resistant enteric gram-negative rods *(30)*. Appropriate use of BSI has indeed been documented to reduce colonization and infection with sentinel microorganisms such as *Pseudomonas aeruginosa*, *Serratia marcescens*, and aminoglycoside-resistant gram-negative bacilli *(23)*. In addition, BSI also has the advantage of lessening the psychological trauma of isolation by emphasizing the isolation of body substances rather than the isolation of people *(31)*. That is, because barrier precautions are used for all patients, additional restrictive isolation practices are not needed for most diseases, except those communicable by the respiratory route.

The system, as it was published in 1987, suggested that hand washing was unnecessary when gloves were used for barrier precautions *(22)*. This prompted criticism of the system by those stating that the wearing of gloves for contact with blood or body fluids did not eliminate the need for hand washing *(14,32)*. Studies have documented that hands can be contaminated with microorganisms even though gloves are worn *(33,34)*. When the system was described in later publications, gloving was not emphasized as a substitute for hand washing. In fact, hand washing is recommended when hands are soiled and between patient contacts *(23)*. Many institutions that have adopted BSI require hand washing after glove removal *(29)*.

ARE GLOVES AN EFFECTIVE BARRIER?

At the time of the publication of the 1988 CDC update, there were no published data on the preference of latex versus vinyl gloves. Since that time, there have been numerous studies addressing the integrity of gloves in general and latex versus vinyl gloves in particular. The standards for testing the integrity of latex gloves were established by the American Society for Testing and Materials (ASTM) of the FDA, and compliance with them is voluntary. In 1977, the standard allowed no more than 15 defects per 1,000 (1.5%) sterile unused latex surgical gloves, as determined by the watertight method of testing *(35)*, and 25 defects per 1,000 (2.5%) latex examination gloves *(35)*. In 1989, the FDA method for testing gloves improved, and the standards changed to an allowable defect rate of 2.5% for surgeon's gloves and 4.0% for examination gloves *(36)*. Due to the continued concern of potential transmission of blood-borne pathogens HIV, HBV, and hepatitis C, the FDA issued a final rule effective December 19, 2008, which further reduced the allowable defect rate for examination gloves to 2.5%. The FDA, using calculated projections based on available CDC data on HIV, HBV, and HCV infections, estimated that this modification in acceptable quality levels could potentially avoid seven cases of HIV infection and seven cases of chronic HBV infection transmitted to healthcare workers over a 10-year period *(37)*.

There are no standards for vinyl gloves. Concern regarding occupational exposure to HIV raised the issue of glove integrity in the clinical setting. In addition, some cases of herpetic whitlow in intensive care unit (ICU) nurses who used gloves focused more attention on this issue *(38)*. Scanning of gloves by electron microscopy has documented inapparent pits from 30 to 50 μm in size, suggesting the possibility that viruses could penetrate this barrier *(39)*.

In addition, several studies have documented leakage rates higher than the ASTM standard of 1.5% to 2.5%. DeGroot-Kosolcharoen and Jones *(40)* showed that although several brands of sterile latex surgical gloves were impermeable to water and blood, some brands showed leakage rates of up to 8%. Nonsterile latex and vinyl gloves showed leakage rates of 0% to 52%. Nonsterile packaging or packaging in suction kits increased leakage rates. Korniewicz et al. *(41)* studied gloves stressed by conditions mimicking those encountered in patient care and found that 63% of vinyl gloves leaked a stock solution of bacteriophage compared with 7% of latex gloves. Korniewicz et al. *(42)* also documented the penetration of 20% of latex gloves and 34% of vinyl gloves by *S marcescens*. These studies indicate that gloves reduce the risk of gross soilage from blood or body fluids but that they are not 100% effective.

Latex hypersensitivity due to repeated exposure and sensitization of the healthcare worker to latex antigens has led to the adoption of nonlatex gloves made out of various synthetic materials such as neoprene, polyurethane, and nitrile. Korniewicz et al. (43) examined both latex and nonlatex surgical gloves for defects after use by surgeons during surgical procedures and found overall glove defect rates of 5.6% and 7.5% for latex and nonlatex surgical gloves, respectively. Based on the data obtained during this review of surgical gloves, the authors recommended that surgeons change gloves within 2 to 3 hours to avoid exceeding defect rates >5%.

Doebbeling et al. *(33)* showed that washing gloved hands was not effective for decontamination, and in fact, 5% to 50% of hands were contaminated after gloves were removed. Washing gloves has also been shown to decrease their integrity *(44)*. Thus, gloves should not be washed and reused between patients. These studies affirm that although gloves can be used as a barrier to reduce gross contamination from blood and body fluids, antisepsis after glove removal remains very important because occult breaks in gloves can and do occur.

The surgical literature has long been concerned with perforations in gloves during surgical procedures. In 1899, Bovie *(45)* stated that careful hand washing was needed, because gloves could be punctured accidentally during an operation.

More recent studies have quantitated the number and location of inapparent perforations that may occur in gloves during surgical or dental procedures. Albin et al. *(46)* showed a 33% leak rate of latex gloves randomly studied after surgical procedures. These authors also documented a leak rate of up to 5.5% in unused gloves. Gloves studied sequentially showed a leak rate of 58.5% at the end of surgical procedures and 32% at the end of dental procedures. Double gloving decreased the leak rate to 25%. In the sequential surgical study, 52% of the leaks occurred in the first 75 minutes; in the sequential dental study, 75% of the leaks occurred in the first 30 minutes. Gloves used in cardiovascular, orthopedic, abdominal, and oral surgical procedures had leak rates of more than 50%. The frequency of occult glove perforation has been noted to be as high as 10% after interventional radiologic procedures *(47)*. In the Albin et al. study evaluating surgical and dental procedures, leak rates for gloves were evaluated for various members of the surgical team and were found to be highest for the surgeon (52%), followed by the first assistant (29%), and then the scrub nurse (25%) *(39)*. Most perforations (60%) occurred in the thumb or index finger of the glove. Other studies have also documented that the largest number of perforations occur in the thumb, index finger, and middle finger *(48,49)*.

IMPACT OF UNIVERSAL PRECAUTIONS AND BODY SUBSTANCE ISOLATION

Universal Precautions are now a minimum standard in US hospitals as a result of OSHA regulations. Many hospitals also have BSI or some modification of BSI in place because of increasing emphasis on the potential infectiousness of body fluids from all patients and the increasing rate of multidrug-resistant pathogens. To review the advantages of these systems over category-specific or disease-specific isolation, the latter systems may be inconsistently or incorrectly applied, whereas precautions that are used for all patients not only are easier to implement but also protect cross-transmission from patients who may lack signs or symptoms of a disease. Furthermore, there is less psychological trauma for individual patients identified as having a microorganism transmissible by blood or body fluids because all patients are treated in a standard manner. Because of healthcare worker concern about HIV in particular, this system at least theoretically eliminates the need for routine screening of all patients and personnel for HIV at periodic intervals—a process that would prove extremely costly *(50)*.

Some disadvantages of the Universal Precautions concept have been proposed. Because gloves were used more extensively for barrier precautions in BSI and in Universal Precautions, some healthcare workers have sometimes neglected to change gloves between patients *(30,32)*, and such practices have been associated with cross-transmission of microorganisms *(51,52)*. Education and reinforcement of appropriate use of gloves and changing gloves between patients can be successful in reducing such practices *(23,51)*.

The CDC has stated that each institution may design its own system of isolation (17). Indeed, as hospitals have tailored Universal Precautions or BSI to their own institutional needs, each system has incorporated elements of the other and the terms have been used interchangeably, even though there are real and philosophical differences between the two systems *(2)*. Consequently, confusion has ensued regarding the term Universal Precautions in particular *(1)*. The primary purpose of Universal Precautions is to reduce healthcare worker exposure to blood-borne pathogens, whereas the primary intent of BSI is to reduce cross-transmission of microorganisms between patients by transient carriage on the hands of personnel. An additional benefit is the protection of the healthcare worker from the patient's microorganisms *(2)*.

The effectiveness of Universal Precautions has been evaluated using the frequency of personnel nonparenteral exposures to blood and body fluids (including sputum, urine, feces) as a monitor. Fahey et al. *(53)* and Wong et al. *(54)* documented a significant decrease in nonparenteral exposures to blood and body substances after the implementation of Universal Precautions. Saghafi et al. *(55)* also documented a reduction in exposure of unprotected skin to blood, but the rate of needlestick exposures remained unchanged. So it appears that although Universal Precautions or BSI may significantly reduce nonparenteral exposures to blood or body fluids, other measures such as engineering controls are needed to reduce parenteral exposures such as needlesticks.

As Universal Precautions or BSI systems were implemented throughout the country, glove use increased substantially and cost became a concern. Doebbeling and Wenzel (56) evaluated the costs of using Universal Precautions, and McPherson et al. *(57)* evaluated the cost of BSI. Universal Precautions increased the total annual costs for isolation materials at a large university teaching hospital by $350,900—an increase, adjusted for inflation, from $13.70 to $22.89 (67%) per admission. Although BSI theoretically could be more costly, it caused an unadjusted increase in cost of 147% for isolation materials compared with an unadjusted increase in cost of 167% for Universal Precautions (56,57). There was an approximately 80% increase in the use of gloves for BSI compared with a 64% increase in glove use for Universal Precautions. Doebbeling and Wenzel (56). estimated that Universal Precautions cost approximately $269 million annually nationwide (using the dollar value from 1989) in hospitals alone and approximately $67 million in the outpatient setting, accounting for $336 million total per year nationwide.

Although these systems are expensive, the alternatives must be considered. The alternative of testing all patients admitted to US hospitals each year is estimated to be $2.6 billion or approximately eight times the cost of Universal Precautions *(58)*. Thus, Universal Precautions are less expensive than universal testing. In addition, a decrease in healthcare-associated infection rates has been documented after the implementation of Universal Precautions and BSI (2,56), providing further evidence for the cost–benefit of these systems in the United States.

Updated CDC Guidelines (1996–2007) and Recent Developments

The CDC's isolation guidelines were revised by the CDC's Healthcare Infection Control Practices Advisory Committee and were published in draft guideline format for public comment in 1994 *(59)* and in final form in 1996 (3).

The guideline contained three important changes from previous recommendations. First, "Standard Precautions" combine the major features of Universal Precautions and BSI. These precautions apply to all patients regardless of diagnosis or known infection status. This first tier of precautions is used to decrease the risk of transmission from recognized or unrecognized infection. Second, the previous categories of isolation (strict isolation, contact isolation, respiratory isolation, enteric precautions, drainage/secretion precautions) and the previous disease-specific precautions are superseded by the three types of transmission-based precautions. These precautions are based on routes of transmission for patients known or suspected to be infected or colonized with highly transmissible or epidemiologically significant pathogens. Third, the new guideline lists specific syndromes in adult and pediatric patients that are suspicious for infection and indicate which precautions to use on an empiric basis pending diagnosis. As with previous guidelines, the CDC recognized that no guideline adequately addresses each hospital's needs. Individual hospitals and healthcare systems are encouraged to review the recommendations and modify them according to their own needs and resources.

The 2007 guidelines expand the guidance from the 1996 guidelines to include settings outside acute care, such as long-term care and home-based care. In addition, the term healthcare-associated infections has taken the place of "nosocomial infections." After the 2003 severe acute respiratory syndrome (SARS) and concern for pandemic influenza, respiratory etiquette has been added to the guidelines. There is an update on protective precautions for severely immunocompromised patients and additional recommendations regarding the personal protective equipment necessary to perform certain procedures and environmental and administrative controls required for a safer healthcare environment (4). The 2007 guidelines reiterate Standard Precautions and transmission-based precautions as keystones of infection prevention in healthcare settings (4). Table 90-1 outlines the categorization of diseases by transmission-based precautions in accordance with these guidelines.

Transmission requires a source of infection, a susceptible host, and a mode of transmission. Transmission-based precautions intend to interrupt this cycle by interfering with the mode of transmission. Sources of infection may include patients, healthcare personnel, and visitors, as well as the environment (*60,61*,62).

The risk of acquiring healthcare-associated infections varies based on the setting where the patients are located. It is particularly high in the ICUs. In other settings, such as long-term care facilities (LTCFs), patients stay for prolonged periods of time. Patients at LTCFs are encouraged to participate in activities involving other residents, and this may result in increasing the risk of microorganism transmission. The isolation precautions used in acute care may not be practical in an LTCF, and prevention of transmission may be challenging.

What Elements May Help to Prevent Transmission in Healthcare Settings?

To improve the chance of success of any isolation-based precautions, some elements are necessary. These include the presence of healthcare system components that have an influence on the effectiveness of the transmission-based precautions, including adequate infection prevention staffing. A ratio of 1 IP per 250 patients was suggested during the study on the efficacy of nosocomial infection control project *(63)* and a ratio of 0.8 to 1 IPs per 100 patients on a more recent survey (64). Because of the increased complexity of patients and programs and the shift to ambulatory services, CDC does not recommend a specific ratio but recommends that there be adequate personnel for the complexity of the program. Designated unit nurses may function as infection prevention liaisons who serve as a contact between bedside nurses and IPs, the clinical microbiology laboratory, environmental services, etc. (4,*65,66*).

General Principles

Hand Hygiene Hand hygiene is the single most important method for preventing healthcare-associated transmission of infection. Despite its importance, compliance with hand hygiene is around 50% to 60% in non-ICU settings and may be even lower in ICUs (around 30%–40%) (67,*68–70*).

Such information must encourage, rather than discourage, IPs to continue to reinforce this basic control measure. Easy access to handwashing sinks or antiseptics may increase compliance and should be available, especially in high-risk areas *(71)*. Hands should be washed even when gloves are used, because small tears in the glove may be present and contamination can occur when the glove is removed (3). In addition, failing to change gloves between patients has been implicated in cross-transmission of hospital pathogens *(51)*. Several studies have shown reduced rates of healthcare-associated infections, including those due to resistant pathogens, with improved hand hygiene *(72)*. However, noncompliance with this simple measure has been documented repeatedly *(73,74)*. Risk factors for noncompliance with hand hygiene include being a physician, a nurse aide, male gender, working during the week, using gowns and gloves, automated sink, and performing activities with a high risk of cross-transmission and a high demand for hand washing (i.e., high workload) (75). High workload is a serious problem, particularly in an ICU, where there may be as many as 40 opportunities for hand hygiene in a 1-hour period *(76,77)*.

Hand washing at the sink is effective but is time-consuming compared to antiseptic hand rub, and frequent hand washing can also result in skin reactions *(78)*. These factors have led to the studies that have documented the efficacy of antiseptic hand rubs as a method for hand hygiene. Pittet et al. *(78)* documented an improvement in hand hygiene compliance from 48% to 66% with use of a hand rub and documented a consistent decrease in healthcare-associated infection rates hospital-wide, including decreased rates of methicillin-resistant *S. aureus* (MRSA) *(78)*. For these reasons, the antiseptic hand rub has been accepted, particularly in high-risk units such as the ICU. Exceptions to use include patients where spore-producing microorganisms are suspected (*C. difficile* infection), after going to the toilet, and when hands are visibly soiled (75) (see also Chapter 91).

Patient Placement and Transport A private room is recommended for patients with some infections that are highly transmissible or when patient hygiene is poor. There is evidence that patients colonized by infectious

TABLE 90-1

Types of Isolation Precautions

Standard Precautions

Use for the care of all patients

Airborne Precautions

In addition to Standard Precautions, use Airborne Precautions for patients known or suspected to have serious illnesses transmitted by airborne droplet nuclei; examples of such illnesses:

- Measles (rubeola)
- Monkeypox (until monkeypox confirmed and smallpox excluded—then Contact Precautions)
- Severe acute respiratory syndrome
- Smallpox (variola)
- Varicella (including disseminated zoster); also use Contact Precautions for patients with primary or disseminated zoster
- Tuberculosis; see specific guidelines *(116)*

Droplet Precautions

In addition to Standard Precautions, use Droplet Precautions for patients known or suspected to have serious illnesses transmitted by large-particle droplets; examples of such illnesses:

- Invasive *Haemophilus influenzae* type B disease, including meningitis, pneumonia, epiglottitis, and sepsis
- Invasive *Neisseria meningitides* disease, including meningitis, pneumonia, and sepsis
- Invasive multidrug-resistant *Streptococcus pneumoniae* disease, including meningitis, pneumonia, sinusitis, and otitis media
- Other serious bacterial respiratory infections spread by droplet transmission, including
- Diphtheria (pharyngeal)
- Mycoplasma pneumonia
- Pertussis
- Pneumonic plague
- Streptococcal disease (group A streptococcus): pharyngitis, pneumonia, scarlet fever in infants and young children, serious invasive disease, or major wound infection without dressing or inadequate containment of drainage by dressing
- Serious viral infections spread by droplet transmission:
- Adenovirus
- Influenza
- Mumps
- Parvovirus B19
- Rhinovirus
- Rubella
- Viral hemorrhagic fevers due to Lassa, Ebola, Marburg, Crimean–Congo fever viruses

Contact Precautions

In addition to Standard Precautions, use Contact Precautions for patients known or suspected to have serious illnesses easily transmitted by direct patient contact or by contact with items in the patient's environment. Examples of such illnesses:

- Gastrointestinal, respiratory, skin, or wound infections or colonization with multidrug-resistant bacteria judged by the infection control program, based on current state, regional, or national recommendations, to be of special clinical and epidemiologic significance
- Enteric infections with a low infectious dose or prolonged environmental survival:
- *Clostridium difficile*
- Rotavirus
- For diapered or incontinent patients: adenovirus, *Campylobacter* spp., cholera (*Vibrio cholerae)*, *Cryptosporidium* spp., enterohemorrhagic *Escherichia coli* O 157:H7, *Giardia lamblia*, Norovirus, *Salmonella* spp., *Shigella, Vibrio parahemolyticus*, *Yersinia enterocolitica*, hepatitis type A and E, or rotavirus
- Respiratory syncytial virus, parainfluenza virus, or enteroviral infections in infants and young children
- *Burkholderia cepacia* in patients with cystic fibrosis, including respiratory tract colonization
- Poliomyelitis
- Human metapneumovirus
- Congenital rubella
- Skin infections that are highly contagious or that may occur on dry skin:
- Diphtheria (cutaneous)
- Herpes simplex virus (neonatal or mucocutaneous)
- Impetigo
- Major (noncontained) abscesses, cellulitis, pressure ulcers, or wounds
- Pediculosis
- Scabies
- Staphylococcal furunculosis in infants and young children
- Staphylococcal scalded skin syndrome
- Zoster (disseminated or in the immunocompromised host)
- Vaccinia (*Eczema vaccinatum*, *Fetal vaccinia*, generalized vaccinia, progressive vaccinia)
- Viral/hemorrhagic conjunctivitis
- Viral hemorrhagic fevers (Lassa fever or Marburg virus)

(Compiled from Siegel JD, Rhinehart E, Jackson M, et al. Guideline for isolation precautions: preventing transmission of infectious agents in health care settings. Available at *www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html,* accessed October 25, 2010; Garner JS, the Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol* 1996;17:53–80.)

microorganisms can cause environmental contamination, which could theoretically lead to cross-transmission, such as MRSA, vancomycin-resistant enterococci (VRE), *C. difficile*, and norovirus *(79–82)*. The private room serves as a physical barrier and helps to reinforce antisepsis before exiting the room. Private rooms used for isolation should also contain bath and toilet facilities. If a private room is not available, patients infected or colonized with the same microorganisms may share a room. Grouping or cohorting with other infected or colonized patients is useful in an outbreak situation or when private rooms are scarce. There may be circumstances when a patient with a transmissible

infection must share a room with a noninfected patient. An appropriate roommate should be selected who is not likely to become infected or in whom consequences of infection would likely not be severe. In these cases, an IP should evaluate the situation to assist in selecting roommates carefully. Ensure that patients have appropriate distance separating them (≥3 ft) and close curtains between patients when available. Personnel caring for these patients should be aware of modes of transmission and take appropriate precautions to prevent spread of the microorganism.

Construction features and ventilation of isolation rooms are outlined in other publications (*83*,84,*85*). A private room with special ventilation (as outlined below) is necessary for those with diseases transmitted by the airborne route. An anteroom between the room and the hallway may be advantageous (although not required) for housing patients on Airborne Precautions by decreasing the possibility of the spread of airborne agents from the room into the hall (see also Chapter 84).

In the acute care setting, limiting the movement of the patient on isolation precautions limits the potential for spread of the transmissible epidemiologically significant pathogen. Thus, it is recommended that these patients leave their room only for medically necessary purposes. When transport is required, the appropriate barriers (dressings, masks, etc.) should be in place, and the personnel in the receiving department should be aware of the patient's isolation precautions and measures needed to reduce transmission. When possible, the patient should be educated about ways they can assist in minimizing spread of the microorganism. In the extended care or rehabilitation setting, residents or patients must leave their rooms for rehabilitation and socialization. There have been modified Contact Precautions recommended in this setting that are discussed below.

Indications and procedures to transport patients on isolation depend on the type of isolation that the patient requires. Patients on contact isolation precautions should have contaminated or colonized areas of the body covered during transport, and HCW should wear clean personal protective equipment (PPE) when handling the patient. Patients on Droplet Precautions should wear a surgical mask during the transport, but the HCW transporting the patient may not require a mask. Patients on Airborne Precautions should wear a surgical mask when they are being transported. Skin lesions should be covered during transport to avoid aerosolization of pathogens (i.e., varicella) (4).

Face Barrier Protection Besides gloves (discussed above) and gowns, barrier protection is also required to protect the face and mucous membranes when splashing of blood or body fluids is anticipated. Various kinds of mask protection, goggles, and face shields may be used as barriers to protect the eyes, nose, and mouth from exposures. This protection is required by the OSHA blood-borne pathogen final rule (3,*20*). A surgical mask can provide protection against large-particle droplets that are transmitted by close contact and travel short distances, as in those diseases covered by Droplet Precautions (see below). Recently, there was controversy over whether N95 respirators or surgical masks should be used to protect against 2009 H1N1 infection *(81)*. However, the current CDC recommendations for influenza recommend adherence to Droplet Precautions with the use of a surgical (or procedure) mask as per the most recent isolation precaution guidelines (4).

Gowns Gowns that are impermeable to liquids should be worn when splashing is anticipated. Leg coverings or shoe covers should be used when splashing is expected to be extensive. The wearing of gowns and protective apparel under such circumstances is mandated by the OSHA blood-borne pathogens final rule (3,*20*). Gowns are used with gloves for Contact Precautions and have been shown to decrease institutional spread of multidrug-resistant microorganisms *(86,87)*. Use of gowns and gloves together has been shown to be more effective to decrease transmission of VRE than using gloves alone (88). It has been shown that MRSA and VRE can contaminate the clothes of the HCW as well as hands *(89)*. In one study, 65% of nurses performing routine care on patients colonized by MRSA contaminated the front of their gowns or uniform with the microorganism *(60)*.

Equipment Whether special handling of equipment or articles is needed depends on the likelihood that the article is contaminated and the ability of the particular microorganism to survive in the environment *(90)*. Articles that are visibly contaminated or likely to be contaminated should be bagged. One bag is sufficient if it is sturdy and does not allow leakage and the outside of the bag is not contaminated when the article is placed in the bag *(91)*. Equipment may be disposable or reusable. Disposable equipment has the advantage of reducing the possibility of equipment becoming a vehicle for transmission of the agent, but use of disposable equipment may increase costs. Equipment that is reused between patients should be appropriately cleaned and disinfected (see also Chapter 80). Waste should be handled according to the institutional policy on waste disposal. Generally, double bagging is not indicated for waste or articles from isolation rooms. Equipment is usually classified using the Spaulding classification method, which defines the degree of disinfection and sterilization required, based on the risk of the equipment to transmit infection when used (92). Equipment is classified as critical items (those that pose a great risk of infection if the item is contaminated with any pathogen, including spores; they require sterilization [i.e., surgical instruments]), semicritical items (those that are in contact with mucous membranes or nonintact skin, and they require high level disinfection [i.e., colonoscopes]), and noncritical instruments (those that are in contact with intact skin [i.e., blood pressure cuffs]) (92).

Linen, Laundry, and Eating Utensils Soiled linen should be handled with a minimum of agitation and placed in a laundry bag in the patient's room or at the location where it was used. It should be transported in bags that prevent leakage. Disposable dishes and eating utensils are not required for patients on isolation. Reusable dishes may be used for patients in isolation, because the combination of dishwasher detergents and high water temperature adequately decontaminates dishes (3,*90*).

Housekeeping Routine daily cleaning procedures should be used in rooms with patients on most isolation precautions. Exceptions are those patients with microorganisms

known to be hardy in the environment (*C. difficile*, VRE). Special measures for these microorganisms include cleaning of the immediate patient environment (bed rails, bedside tables, commodes, doorknobs, horizontal surfaces) daily with an EPA-approved germicide. Terminal cleaning should include items that have been in direct contact with the patient or the patient's infective material. Housekeeping personnel use the same barrier precautions that would be indicated if the patient were still in the room. Horizontal surfaces and floors should be cleaned with a disinfectant–detergent solution. With the possible exception of the tuberculosis (AFB) isolation room, airing of a room or delay in admitting the next patient after an isolated patient's discharge is not needed (17,*90,93*).

Tiers to Prevent Transmission of Infectious Agents

There are two main tiers of the HICPAC/CDC guidelines to prevent transmission of infections in healthcare settings regardless of the presence of an infectious agent. The first tier is the most important strategy to prevent healthcare-associated transmission of infectious agents: Standard Precautions. The second tier is the institution of transmission-based isolation precautions.

Standard Precautions

Standard Precautions combine Universal Precautions and BSI and are based on the premise that "all blood, body fluids, secretions, excretions (except sweat), nonintact skin, and mucous membranes regardless of suspected or confirmed infectious status" may be infectious (4). Standard Precautions involve important interventions including hand hygiene, use of personal protective equipment (based on anticipated exposure), and safe injection practices, as well as appropriate management of environment and equipment.

The 2007 guidelines added to previous recommendations the use of respiratory hygiene/cough etiquette, safe injection guidelines, and use of a mask during certain procedures such as injection of material into spinal or epidural spaces or insertion of catheters into the epidural space (4).

Hand hygiene should be performed with soap and water if hands are visibly soiled. Alcohol-based hand sanitizers should be used after visible soil is removed with soap and water or if hands are not visibly soiled. Hand hygiene should be performed before direct contact with patients; after contact with blood, body fluids, excretions or mucous membranes, nonintact skin or wound dressings; after contact with intact skin if hands move from a contaminated to a noncontaminated body site; or after contact with objects close to the patient or after removing gloves (75).

For Standard Precautions, mask and eye protection or a face shield should be used to protect the eyes, nose, and mouth during activities that may generate splashing of blood or body fluids. A gown should be worn to protect skin and prevent soiling of clothing during such activities as well. Reusable equipment should be cleaned and reprocessed before being used on another patient. Ensure adequate cleaning of environmental surfaces. Handle soiled equipment and laundry in a manner that avoids exposures and transfer of microorganisms to other patients and the environment.

Care should be taken to avoid sharps injuries. Never recap used needles or use a technique that involves directing the point of the needle toward any part of the body. Place used sharps in a puncture-resistant container. Use mouthpieces or resuscitation bags instead of mouth-to-mouth resuscitation in areas where the need for cardiopulmonary resuscitation is predictable.

A patient who contaminates the environment or who cannot assist in using appropriate hygiene should be placed in a private room. If a private room is not available, seek consultation from an IP regarding placement.

Transmission-Based Precautions

The second tier of precautions is for patients with documented or suspected transmissible or epidemiologically significant pathogens that require more than Standard Precautions to prevent cross-transmission. Healthcare-associated pathogens may be transmitted by five major routes: contact, droplet, airborne, vector-borne, and common vehicle. The isolation guidelines are not generally relevant to vector-borne and common vehicle routes. Transmission-based precautions are of three types: Airborne Precautions, Droplet Precautions, and Contact Precautions. Types may be combined for diseases with multiple routes of transmission, and each type is used in addition to Standard Precautions. Another feature of the new guidelines is a list of specific syndromes in adult and pediatric patients that should be considered possibly infectious along with a listing of the type of transmission-based precautions that should be used empirically pending diagnosis.

Airborne Precautions

Airborne transmission usually occurs when a susceptible host inhales airborne droplet nuclei or small particles from an infection source containing microorganisms (i.e., tuberculosis) that may be dispersed over long distances. In addition to respiratory protection with N95 masks, prevention of airborne transmission requires use of special ventilation systems.

Airborne Precautions are used to prevent transmission of microorganisms that persist suspended in the air for long distances (i.e., tuberculosis). These patients should be placed in airborne infection isolation rooms. These rooms are negative pressure rooms with 12 air exchanges per hour in new construction and 6 exchanges per hour on existing buildings, with air exhausted to the exterior or recirculating through high-efficiency particulate air (HEPA) filters.

Healthcare workers should wear an N95 mask when entering the room. The mask should be fit-tested in all healthcare workers.

When airborne isolation rooms are not available, the patient should be placed in a private room with the door closed, and healthcare workers should wear N95 respirators. Patients should remain in their room as much as possible, and they should wear a surgical mask if they need to be transported to essential procedures.

Droplet Precautions

Droplet transmission occurs when an infectious agent is transmitted (usually) from the respiratory tract of a patient to the mucous membranes of another susceptible patient

by respiratory droplets that travel short distances though the air. The distance is usually 3 ft, but there are cases where it may travel up to 6 to 10 ft, especially in the setting of severe infections of SARS *(94)*. Some of these cases were due to lack of appropriate use of personal protective equipment *(94)*.

Droplets may be generated in the course of talking, coughing, or sneezing and during procedures involving the airway, such as intubation or bronchoscopy. Transmission via large droplets differs from airborne transmission in that the former requires close contact (within 3 ft) between the source and the recipient person and because large droplets do not remain suspended in the air and usually travel only short distances. Examples of diseases for which Droplet Precautions are recommended are meningococcal meningitis, multidrug-resistant pneumococcal meningitis or pneumonia, pertussis, streptococcal pharyngitis or pneumonia, influenza, and parvovirus B19 (for patients with aplastic crisis or chronic infection). Occasionally, pathogens not usually transmitted by way of droplets (such as *S. aureus* in the setting of pneumonia) can be transmitted through this route. The patient should be placed in a private room. If a private room is not available, patients with infection due to the same microorganism may be cared for in the same room (cohorted). If both private rooms and cohorting are unavailable, an IP should be consulted. There should be spatial separation of at least 3 ft between the infected patient and other patients and visitors. A mask should be worn when one is within 3 ft of the patient. It is most practical to wear a mask upon entering the room. The patient should leave the room only when necessary and should wear a surgical mask when doing so.

There are pathogens that are usually transmitted through droplets or contact but under special circumstances have been suspected to be transmitted through the airborne route such as SARS-associated coronavirus, influenza, and norovirus *(95,96,97)*. Droplet Precautions with a surgical mask is recommended for routine care of influenza patients. For procedures that will cause aerosolization of respiratory droplets, an N95 respirator should be used.

Contact Precautions

Contact transmission occurs when a microorganism is transmitted from one individual to another by a person or an object. Direct transmission occurs when the transmission happens without an intermediary object or person. Indirect contact transmission occurs when the bacteria is transmitted by healthcare workers or by instruments or devices.

Contact Precautions are designed to prevent direct or indirect transmission of microorganisms spread by contact. They are also indicated when there is fecal incontinence, abundant wound drainage, or other secretions or excretions of the body that lead to excessive environmental contamination. Ideally, patients on Contact Precautions should be placed in individual rooms. When individual rooms are not available, consultation with an IP should be obtained to decide whether cohorting or spatial separation of 3 ft or more (in multi-patient rooms) is indicated.

Healthcare workers entering the room or evaluating patients on Contact Precautions must wear a gown and gloves and perform hand hygiene before putting on PPE and after removing it. PPE should be donned before entering and leaving the room.

Gloves should be used as a barrier, as with Standard Precautions, for contact with blood and body substances. Also, under Contact Precautions, gloves should be changed after contacting infective material with high concentrations of microorganisms (e.g., feces and wound drainage). Gloves should be removed before one leaves the patient's room, and hands should immediately be cleansed with an antiseptic agent. A clean nonsterile gown should be worn if substantial contact with the patient is anticipated, the patient is incontinent of stool, or the patient has wound drainage that is not well contained by a dressing. The gown should be removed before one leaves the patient's environment. In the acute care setting, movement of the patient from the room should be for essential purposes only, and precautions should be maintained by the receiving department. When feasible, the use of noncritical equipment should be dedicated to a single patient or a cohort of patients. If equipment must be shared, it should be disinfected before use by another patient.

Examples of diseases for which Contact Precautions are recommended include infection or colonization with multidrug-resistant bacteria; *C. difficile* infection; respiratory syncytial virus (RSV) infection in children; and skin infections due to scabies, impetigo, and varicella zoster. Some diseases that are communicable by contact and by the respiratory route require Contact Precautions in combination with Droplet or Airborne Precautions; examples include viral hemorrhagic fevers such as Lassa fever or Marburg virus (Contact and Droplet Precautions), disseminated varicella (Contact and Airborne Precautions), and smallpox (Contact and Airborne Precautions).

Duration of Contact Precautions

The optimal duration of Contact Precautions for colonized or infected individuals remains controversial. In general, during outbreaks or clusters of infection, patients must remain in Contact Precautions during the duration of their hospital stay or the outbreak. In selected settings, especially among those patients that are detected during active surveillance outside the epidemic setting and are colonized or infected with microorganisms like MRSA or VRE, three negative cultures taken 1 week apart can reasonably be used to discontinue Contact Precautions (62). In other patients, resolution of symptoms that lead to the isolation (such as diarrhea in the case of *C. difficile* infection) may be a reasonable time to stop isolation (62).

Vancomycin-Resistant Enterococci

VRE have emerged and are quite prevalent in some areas of the United States and much less common in others. Patients colonized or infected with these microorganisms may be handled under Contact Precautions. Guidelines from the CDC for preventing transmission of VRE have also been published *(98)* and emphasize the principles of Contact Precautions. Environmental cleaning is also quite important for control of this microorganism because of its hardiness on environmental surfaces. For this reason, a daily cleaning of the patient's immediate environment (bed rails, bedside table, commode, doorknobs, horizontal surfaces) with an EPA-approved germicide is indicated.

A multifactorial approach in controlling this microorganism is recommended, such as antibiotic utilization efforts including appropriate vancomycin use by both the oral and the parenteral routes *(98)*. In some institutions, restriction of broad-spectrum cephalosporins has been helpful for control of VRE as well as other multidrug-resistant pathogens such as extended-spectrum β-lactamase-producing *Klebsiella pneumoniae (99)* (see also Chapter 33).

Vancomycin-Intermediate and Vancomycin-Resistant *Staphylococcus aureus*

Vancomycin-intermediate (or glycopeptide-intermediate) *S. aureus* (VISA; minimum inhibitory concentration [MIC], 8 μg/mL) was initially reported from Japan in 1996 and was subsequently reported from the United States *(100)*. Later, the Clinical Laboratory Standards Institute changed the vancomycin breakpoints for *S. aureus*. Isolates with a vancomycin MIC of >2 μg/mL are considered VISA *(101)*. Although these isolates showed reduced susceptibility to vancomycin rather than complete resistance, VISA was a concern because most reported patients required alternative therapy other than vancomycin *(100)*. VISA has been associated with a high mortality rate in ICU outbreaks in France *(102)*.

The CDC published guidelines for the prevention and control of staphylococcal infection associated with reduced susceptibility to vancomycin in 1997 *(100)*. These guidelines reiterate conservative use of vancomycin as a preventive measure. In addition, laboratory methods for susceptibility testing of these strains have been revised for more accurate detection. For preventing the spread of these microorganisms, the laboratory should immediately notify infection control personnel and the patient's attending physician. Infection control personnel, in conjunction with the state health department and the CDC, should initiate an epidemiologic investigation. Contact Precautions should be strictly enforced in the care of the patient. The number of personnel caring for the patient should be minimized, and specific healthcare workers should be assigned to the care of the colonized/infected patient or patients. Infection control personnel should inform healthcare workers regarding the epidemiologic significance of VISA and assist in monitoring compliance with Contact Precautions and other control measures. In coordination with public health officials as above, baseline surveillance cultures of the anterior nares and hands of those exposed to the patient, including healthcare workers and roommates, may be indicated to determine whether transmission has already occurred. Transfer of the patient within the facility or between facilities should be avoided. If transfer is necessary, the receiving unit or institution should be fully informed. Additional recommendations have been published by Wenzel and Edmond *(103)* that include excluding healthcare workers at risk for staphylococcal colonization from caring for patients with VISA and the use of mupirocin for eradication of nasal *S. aureus* colonization (see also Chapter 28).

In addition to VISA, the existence of hetero VISA (hVISA) makes isolation compliance even more compelling. This resistance, hVISA, is defined as the presence of small subpopulations of MRSA with intermediate resistance to vancomycin, which are difficult to detect and are present in only about 1 in 10^5 to 10^6 microorganisms *(104)*. They have been associated with increased rates of congestive heart failure and persistent bacteremia in patients with MRSA infective endocarditis *(104)*.

As of December 2007, there have been nine cases of fully vancomycin-resistant *S. aureus* (VRSA) in the United States: seven from Michigan, one from Pennsylvania, and one from New York (105). The concern with these isolates is not only the complete resistance to vancomycin but also genetic analysis suggests conjugative transfer of the *vanA* resistance gene from *Enterococcus* species to *S. aureus* and *in vitro* studies suggest that *vanA* can also be transferred from VRSA to MRSA (105). Thus, this may become a more significant problem than VISA. The CDC recommends the same guidelines for control of VRSA as for VISA, emphasizing strict Contact Precautions.

Multidrug-Resistant *Acinetobacter* spp.

Multidrug-resistant *Acinetobacter baumannii* has emerged as an important cause of healthcare-associated outbreaks, especially in the ICU setting *(106)*. This microorganism can be transmitted by contact with the hands of healthcare workers or by contamination of the environment (including linen and beds) or equipment (respiratory therapy, mechanical ventilation equipment, intravenous fluids, water humidifiers, other reusable medical equipment, wound care equipment, etc.) *(106–108)*. During a recently reported outbreak in an ICU, the recovery rate of *Acinetobacter* spp. from HCW hands was over 28% *(109)*. *A. baumannii* is one of the most difficult gram-negatives to control and eradicate in outbreak settings and has become a severe problem among injured soldiers returning from Afghanistan and Iraq (110).

Hand hygiene, strict Contact Precautions, aggressive environmental cleaning and disinfection, active surveillance and cohorting have been used to control outbreaks. However, interventions may fail, and closure of the units may be required for control *(107)* (see also Chapter 35).

Respiratory Hygiene/Cough Etiquette The SARS pandemic led to the development and implementation of certain precautions to prevent transmission of infections from patients with respiratory symptoms at the initial point of care. The elements of respiratory hygiene/cough etiquette are (a) education of HCWs, families, and visitors; (b) posted signs with easily understood instructions for patients and accompanying persons; (c) source control interventions (covering the mouth/nose with a tissue when coughing or sneezing, proper disposal of used tissues/appropriate use of masks by persons who are coughing); (d) hand hygiene when contact with respiratory secretions has occurred; and (e) maintaining a distance of ≥3 ft from persons who are coughing.

Protective Environment

This environment is used for the protection of allogeneic hematopoietic stem cell transplant patients. It minimizes the spore count in the air and is composed of environmental controls including HEPA filtration of incoming air, directed room air, positive pressure in the rooms when compared with the corridor, well-sealed rooms with no air entrance from the exterior, ventilation with 12 air exchanges per

hour or more, prevention of dust accumulation, and banning dried and fresh flowers and plants in the rooms.

Patients should remain in this protective environment and should wear N95 masks any time they leave the protected environment. Hand hygiene should be strictly enforced, but gowns and gloves are not routinely required. Rooms should be sealed and provided with HEPA filters, maintaining a positive pressure when compared with the corridor and at least 12 air exchanges per hour. In this setting, avoid carpets and perform regular cleaning with EPA-registered disinfectants, preventing dust dispersion. Furniture and furnishings with cloth upholstery that is difficult to clean should be avoided (see also Chapters 59, 83, and 84).

TUBERCULOSIS PRECAUTIONS: SPECIAL CONSIDERATIONS

There was a substantial increase in tuberculosis cases in the mid-1980s, primarily in association with the HIV epidemic. In 1990 and 1991, several healthcare-associated outbreaks of MDR-TB were documented *(111,112)*. In each outbreak, a delay or lapse in airborne infection isolation was a major factor in transmission. This resurgence of tuberculosis, emergence of strains of *Mycobacterium tuberculosis* resistant to isoniazid and rifampin, and documentation of healthcare-associated outbreaks of *M. tuberculosis* prompted the expansion and revision of CDC airborne infection isolation guidelines in 1990 *(113)*. In 1993, expanded updated guidelines were published in draft form in the Federal Register *(114)*, and more extensive guidelines were published in 1994 *(94)*. Due to enhanced containment and directly observed therapy, tuberculosis cases declined from 1993 to 2003, and the incidence of tuberculosis in the United States decreased by 44% to reach a historic low level in 2004 (115).

Major changes in airborne infection isolation included requirements for a high-efficiency filtration mask and duration of isolation based on clinical improvement and an emphasis on ventilation controls. Although special ventilation requirements were mentioned in the 1983 CDC guidelines for tuberculosis and certain diseases under strict isolation, the 1990 and subsequent guidelines emphasize these as particularly important control measures. Hospitals with older ventilation systems, which include many public hospitals with patients at risk for tuberculosis, have looked at ways to retrofit isolation rooms to meet the ventilation criteria outlined. In addition, the 1990 guidelines recommended special ventilation in bronchoscopy suites and areas where cough-inducing procedures, such as aerosolized pentamidine treatments, are performed. Infection control programs have also experienced OSHA involvement in this area because healthcare workers were involved in healthcare-associated outbreaks. Although the 1994 guidelines mentioned above focused on traditional hospital-based facilities, the 2005 guidelines expanded the range to include laboratories, outpatient areas, and other nontraditional healthcare settings *(116)* (see also Chapter 84).

Respiratory Protection

The 1983 guidelines for airborne isolation stated that a (surgical) mask should be worn if the patient is coughing and does not reliably cover his or her mouth (17). One report suggests that poorly fitting standard surgical masks are not protective *(117)*, but data on the efficacy of well-fitted masks (high-efficiency filtration or otherwise) in the clinical setting are lacking. The standard surgical masks used before the 1990 guidelines are adequate for barrier precautions but are not designed to seal tightly on the face and filter small particles. Disposable particulate respirators were originally designed for industrial use and filter particles that are 1 to 5 μm in size. They provide a better fit and filtration capability.

The 1990 guidelines stated that persons entering the room should wear a mask and specify that it should be a disposable, valveless, particulate respirator *(113)*. The 1993 draft guidelines called for a HEPA filtration mask *(114)*. The guidelines stated that the HEPA respirator mask is currently the only National Institute for Occupational Safety and Health (NIOSH)-certified mask meeting all suggested performance criteria regarding fit and filtration. NIOSH-certified dust–mist or dust, fume, and mist respirators had not been evaluated for these criteria. There was much controversy, discussion, and public comment regarding the need for these much more costly and uncomfortable masks in the clinical setting, particularly because the role of respiratory protection devices in preventing transmission of tuberculosis is not known. After a public comment period, guidelines were published in 1994 *(93)* with respirator criteria unchanged; however, in 1995, NIOSH subsequently revised the respirator certification to allow a broader range of respirator alternatives *(91)*. NIOSH indicated that the N95 (N category at 95% efficiency) meets CDC performance criteria for a tuberculosis respirator, and this respiratory protection is now widely used. This CDC/NIOSH-certified respirator continues to meet the minimum standards for respiratory protection in the usual areas where TB infection is encountered in the 2005 guidelines. These most recent guidelines suggest that further respiratory protection should be considered in situations where aerosol-producing or cough-inducing procedures are performed *(116)* (see also Chapter 38).

Duration of Isolation

Before 1990, the duration of isolation for tuberculosis patients was 2 to 3 weeks after beginning antituberculous therapy (17,*118,119*). However, even the 1983 guidelines state that isolation should be continued until there is a clinical response and a decrease in the number of microorganisms on smear (17). This qualification is further emphasized in recent guidelines because of failures of empiric therapy in MDR-TB cases in healthcare-associated outbreaks in the late 1980s *(113)*. The 2005 guidelines recommend that a hospitalized patient remain under airborne isolation precautions until certain criteria are met: three consecutive sputum samples obtained 8 to 24 hours apart (including one morning specimen) are AFB-smear negative, 2 weeks of an appropriate antituberculous medication regimen has been completed, and overall clinical improvement has been noted *(116)*. MDR-TB raises additional concerns due to the grave consequences of continued transmission and additional difficulty in treatment regimens. For patients with suspected or confirmed MDR-TB, many providers would continue Airborne Precautions throughout

hospitalization or until sputum cultures have converted to negative, regardless of sputum AFB smear status *(116)*.

Barrier Protection

Gowns are needed only if soiling of clothing is anticipated. Gloves are not indicated except, as dictated under Standard Precautions, for contact with blood or certain body fluids. As with other types of isolation, hands should be washed after touching the patient or potentially contaminated articles and before contact with another patient.

Decontamination

It is rare for inanimate articles to be involved in tuberculosis transmission. Procedures for cleaning, disinfecting, or sterilizing an item should be determined by its intended use. As for items used on any patient, critical items should be sterilized, semicritical items should undergo high-level disinfection or sterilization, and noncritical items should be cleaned (see also Chapter 80). Recent guidelines from the Association for Professionals in Infection Control and Epidemiology have recommended a 20-minute disinfection time for semicritical instruments such as bronchoscopes, to ensure tuberculocidal activity. Exceptional terminal cleaning to disinfect environmental surfaces is rarely needed. Routine cleaning with a hospital-grade EPA-approved germicide/disinfectant is recommended *(27)*. Routine daily cleaning procedures should be used to clean the rooms of patients on Airborne Precautions.

Ventilation

The American Society of Heating, Refrigerating, and Air Conditioning Engineers and the Federal Health Resources and Services Administration have published standard recommendations for indoor air quality in healthcare facilities (*83*,84,*85,120*). Special ventilation requirements for a patient on Airborne Precautions include negative pressure in relation to the hallway or anteroom; a minimum of 12 air changes per hour in new construction and renovation and six air changes per hour in existing facilities, including two outside air exchanges per hour; and direct exhaust to the outside. If direct exhaust to the outside is not feasible, then recirculation of air is permitted only through HEPA filtration to the air handler exclusively serving the isolation room *(116,120)*. The negative pressure room maintains airflow into the room from the hallway to minimize potential spread of tuberculosis bacilli into surrounding areas. The door must be kept closed to maintain negative pressure, and the direction of airflow should be monitored while the room is used for airborne infection isolation. A separate anteroom is not required but, if used, may serve as an airlock to minimize spread of droplet nuclei into the hallway. The anteroom should also have directional airflow. Direct exhaust to the outside must be away from intake vents, people, and animals in accordance with federal, state, and local regulations for environmental discharges.

The 2006 guidelines from the American Institute of Architects/Facility Guidelines Institute also address ventilation in patient waiting areas. Emergency room waiting areas should have at least 12 air changes per hour *(120)*. The guidelines also suggest that air from clinics with patients at high risk for tuberculosis should not be recirculated except through a HEPA filter. Because this may be very difficult to achieve in many clinic areas, early identification of patients with suspected tuberculosis followed by placement of the patient in a designated isolation room in the clinic or emergency room will assist prevention (see also Chapter 84).

Patient Management

Patient management issues arise for all types of isolation but may be particularly difficult for patients on Airborne Precautions. Patient and family education is particularly important when Airborne Precautions are implemented so that the patient understands the rationale for isolation and the psychological aspects and stigma of isolation can be minimized. The patient should be educated about coughing into a tissue and wearing a mask when it is necessary to leave the room. In general, the patient should not leave the room except for medically necessary procedures.

SPECIAL CONSIDERATIONS IN PEDIATRIC PATIENTS

Because pediatric hospitalizations are often due to communicable diseases, isolation guidelines are particularly relevant for this group of patients. Previous guidelines have stated that infants and very young children with pulmonary tuberculosis do not require isolation precautions because cough is rare and AFB in bronchial secretions is minimal. Exceptions could include pediatric patients with cavitary disease and patients with positive AFB smears. Concerns have also been raised recently about HIV-infected pediatric patients with tuberculosis. The 2005 guidelines for the prevention of tuberculosis transmission state that although children with tuberculosis are less likely to be infectious, transmission can still occur. It is recommended that children be screened for potential transmission risk using similar criteria as used for adult patients (i.e., cough >3 weeks, cavitation on chest radiograph, and/or respiratory tract or upper airway disease). Although gastric lavage is helpful in determining the presence of tuberculosis infection in the pediatric patient, the degree of AFB positivity cannot be correlated with tuberculosis transmission risk *(116)* (see also Chapter 38 for additional information on control of tuberculosis in healthcare facilities).

The psychosocial effects of isolation on hospitalized children have not been extensively studied, but a Swedish study suggests that isolation does not have a negative effect on a child as long as that child can observe the staff *(121)*. Another blinded, prospective study performed in Toronto evaluated isolated and nonisolated pediatric patients and found no significant difference in duration of interaction time between providers and patients or in parental satisfaction with quality of care *(122)*. As in adult patients, Standard Precautions are used, and thus, the category of blood and body fluid precautions is no longer necessary. Transmission-based precautions are currently recommended in addition, but disease-specific or category-specific isolation may be used, depending on the institution's choice. The Report of the Committee on Infectious Diseases (the Red Book) recommends transmission-based precautions, according to current CDC recommendations *(123)*. Some

institutions may choose BSI instead of transmission-based precautions. In the category-specific system, several pediatric diseases, which are grouped under Contact Precautions, include acute respiratory infections in infants and young children due to croup, bronchitis, adenovirus, and parainfluenza viruses. Under the new transmission-based guidelines, Droplet Precautions and Airborne Precautions are used more frequently on the pediatric ward because of the more common occurrence of airborne illnesses such as varicella, pertussis, measles, and erythema infectiosum.

Isolation Precautions for Newborns and Infants

The 1983 CDC guidelines outline modifications for the newborn or infant requiring isolation (17). Such modifications are needed because generally only a small number of private rooms are available for this group of patients, and because it is frequently necessary to cohort newborns and infants when outbreaks occur. Private rooms for isolation of newborns and infants are seldom indicated (or available), provided the following conditions are met: an adequate number of nursing and medical personnel are on duty and have sufficient time for appropriate hand washing, sufficient space is available for a 4- to 6-ft aisle or area between newborn stations, an adequate number of sinks for handwashing are available in each nursery room or area, and continuing instruction is given to personnel about the mode of transmission of infections. When these criteria are not met, a separate room with hand washing facilities may be indicated (17).

Forced-air incubators do not substitute for private rooms because they filter incoming air but not air being discharged into the nursery. In addition, the surfaces of incubators can become contaminated with healthcare-associated microorganisms and can colonize the hands and forearms of personnel caring for infants through portholes. Thus, forced-air incubators provide some protective isolation for the infants but do not prevent cross-transmission.

Cohorts of well newborns are also useful in minimizing cross-transmission of infection in a large nursery setting:

- A cohort usually consists of all well newborns from the same 24- or 48-hour birth period; these newborns are admitted to and kept in a single nursery room and ideally are taken care of by a single group of personnel who do not take care of any other cohort during the same shift. After the newborns in a cohort have been discharged, the room is thoroughly cleaned and prepared to accept the next cohort.
- Cohorting is not practical as a routine for small nurseries or in neonatal ICUs or graded in care nurseries. It is useful in these nurseries, however, as a control measure during outbreaks or for managing a group of infants or newborns colonized or infected with a multidrug-resistant or epidemiologically significant pathogen. Under these circumstances, having a separate room for each cohort is ideal but not mandatory for many kinds of infections if cohorts can be kept separate within a single large room and if personnel are assigned to take care of only those in the cohort.
- During outbreaks, newborns or infants with overt infection or colonization and personnel who are carriers, if indicated, should be identified rapidly and placed in cohorts; if rapid identification is not possible, exposed newborns or infants should be placed in a cohort separate from those with disease and separate from unexposed infants and newborns and new admissions. The success of cohorting depends largely on the willingness and ability of nursing and ancillary personnel to adhere strictly to the cohort system and to meticulously follow patient care practices (17).

Specific recommendations regarding the design of newborn nurseries are available *(124,125)* and specify the amount of floor space that should be allowed per bassinet for adequate separation of infants. Barrier precautions should be followed according to Standard Precautions for all patients and according to BSI in institutions that have this policy. The routine use of an overgown in the nursery has not been shown to decrease healthcare-associated infection rates or intravascular catheter colonization rates or to change hand washing practices *(126)*. Policies regarding gown use in nurseries vary between institutions, and nurseries should establish their own guidelines based on what is most appropriate for their personnel and problems. Gowns may be useful in decreasing the spread of microorganisms transmitted by droplets (see below, Respiratory Syncytial Virus) and should be used in those situations. A barrier such as a blanket or gown should be used when the infant comes into contact with staff, such as during a feeding *(126)*. Personnel do not need to wear masks, caps, and hairnets routinely.

Equipment shared by infants in a unit should be disinfected between uses with alcohol or a bleach solution. Nebulizers should be sterilized by autoclaving or gas sterilization at every shift. Soiled linens are handled as in other areas and removed from the nursery at every shift *(126)*.

Respiratory Syncytial Virus

Another special consideration in pediatric patients is RSV, a major lower respiratory tract pathogen causing community-acquired or healthcare-associated infection in infants and children. Large community epidemics occur characteristically from midwinter to early spring. Bronchiolitis due to RSV is included in Contact Precautions under the category-specific system, which recommends a gown when soiling of clothes is likely. The current CDC transmission-based guidelines recommend Contact Precautions for pediatric and adult RSV disease (4). Viruses such as RSV and rhinovirus can be transmitted by close person-to-person contact by large droplet spread, which occurs during coughing and sneezing *(127,128)*. In addition, respiratory secretions are also spread by hand-to-hand contact or by contaminated fomites *(127,129)*. Persistent shedding of RSV is common after infection, and RSV persists for a long period of time on environmental surfaces as well *(128)*. Thus, it is easy to see why RSV is transmitted easily in both the community and hospital settings and has been documented to cause symptomatic infections in 40% to 60% of infant contacts and 50% of hospital staff *(130)*. Control measures are particularly important in newborn nurseries that house premature infants and infants with pulmonary disease. In these high-risk hosts, mortality from RSV may be 35% to 50% *(131)*.

The CDC published surveillance data of RSV activity in the United States from 2005 to 2006, which revealed that 91% of the RSV infections detected occurred from November

2005 through April 2006. Given the risk of transmission and the potential severity of disease, RSV should be considered in the differential diagnosis of respiratory infections during its annual peak so that appropriate precautions can be taken *(132)*. A study performed in New York suggested that screening for the presence of RSV infection and cohorting patients with RSV effectively reduced the healthcare-associated transmission of RSV infection *(133)*.

Disposable eye–nose goggles decreased healthcare-associated RSV transmission in patients and staff during a 3-week period in one study *(129)*. When goggles were used, 5% of staff and 6% of infants acquired RSV disease compared with 34% of staff and 43% of infants when goggles were not used. Another study observed a 5% rate of disease in staff members using goggles versus 61% in those not using goggles *(134)*. Long-term efficacy, compliance, and cost-effectiveness of these goggles have not been evaluated.

The use of gowns and masks has not been effective in reducing cross-transmission *(135,136)*. The use of gowns and gloves has been effective as evaluated in a long-term interventional study in which compliance was also followed (137). The infection rate before intervention, when compliance with gown and glove isolation precautions was only 40%, was three times the rate of infection after intervention when compliance had increased to 80%. Glove and gown precautions have also been effective in other studies *(138)*.

Parvovirus

Human parvovirus B19 is the etiologic agent of erythema infectiosum (fifth disease), a common childhood exanthem resulting in a slapped-cheek appearance. It occurs in the community sporadically and in outbreaks. In addition to causing asymptomatic or mildly symptomatic disease in healthy adults, human parvovirus B19 may cause chronic anemia in immunodeficient patients and aplastic crisis in patients who have hematologic conditions with accelerated red blood cell turnover such as sickle cell anemia, hereditary spherocytosis, β-thalassemia, pyruvate kinase deficiency, and autoimmune hemolytic anemia *(139)*. This agent is transmitted by contact with respiratory secretions. Persons with erythema infectiosum—the most common form of infection due to this agent—do not require Droplet Precautions when admitted to the hospital because they are unlikely to transmit infection after the onset of the characteristic rash *(119,123)*. However, patients acutely infected with parvovirus B19 during aplastic crises can transmit the virus to patients and staff in the healthcare setting through contact with respiratory secretions, although this is uncommon *(138,139)*. Patients with chronic parvovirus B19 infection are probably less likely to transmit the virus in the healthcare-associated setting, perhaps because of lower levels of viremia *(140–142)*.

The following recommendations are suggested for the control of healthcare-associated transmission of parvovirus B19. Patients who have hereditary or acquired chronic hemolytic anemias presenting with aplastic crisis and immunosuppressed persons with aplastic crisis should be evaluated for parvovirus B19 infection *(143,144)*. Persons with suspected or proven acute or chronic infection (other than erythema infectiosum) should be on Droplet Precautions (3,*139,142,143*) (see also Chapter 51).

Burkholderia cepacia in Cystic Fibrosis Patients

Burkholderia cepacia is a multidrug-resistant gram-negative bacillus that chronically colonizes and may infect the respiratory tract of some cystic fibrosis patients. Colonization or infection with *B. cepacia* in cystic fibrosis patients is significant because colonization is difficult to eradicate and infection often results in rapid decline in pulmonary function and earlier death *(145)*. Several studies have suggested that person-to-person transmission is important *(146–148)* both inside and outside the hospital. In the hospital, *B. cepacia*–positive cystic fibrosis patients should not be housed in the same room as *B. cepacia*–negative cystic fibrosis patients. Contact Precautions or BSI should be used in the care of *B. cepacia*–positive cystic fibrosis patients.

PROTECTIVE ISOLATION

Although the technique for protective isolation was outlined in previous editions of the CDC isolation techniques for use in hospitals, the 1983 CDC guidelines eliminated this isolation category. Protective isolation requiring the use of gown, gloves, and mask for all persons entering the room of a patient immunocompromised by hematologic malignancy, chemotherapy-induced granulocytopenia, or solid organ transplant has not been shown to reduce infection risk (17,*149,150*). Nauseef and Maki *(143)* studied acute nonlymphocytic leukemia patients with chemotherapy-induced granulocytopenia and found that protective isolation did not decrease rates of infection, time of onset to first infection, or days with fever. In fact, there was a higher rate of bacteremia in isolated patients, perhaps because of neglected intravenous catheter care in this group. Walsh et al. *(150)* studied the value of protective isolation in cardiac transplant patients. There was no difference in isolated versus nonisolated patients in infection rate, infection-related deaths, types of infection, or overall outcome.

The lack of a demonstrable beneficial effect from protective isolation may result from the fact that infections in these patients are often due to their own endogenous flora; to transmission of microorganisms by unwashed hands of personnel; to the use of nonsterile items in routine protective isolation such as patient-care equipment, food, or water; and to the presence of nonsterile air (17). CDC guidelines state that, in general, compromised patients should be taken care of by using precautions that are no different from routine good patient care techniques, but for these patients, routine techniques must be emphasized and enforced. Healthcare workers involved in the care of these patients should be meticulous about hand hygiene before and after each patient contact. Such immunocompromised patients should be in a private room, when possible, and should be housed separately from infected patients or those likely to have an infection (17).

The total protected environment (TPE) has shown efficacy, however, in preventing infections in patients with prolonged granulocytopenia *(151)*. TPE includes a private room; HEPA air filtration; disinfection or sterilization of all objects coming in contact with the patient; the use of sterile gowns, masks, gloves, caps, and boots by hospital

personnel and visitors entering the room; the use of sterile water and semisterile or low microbial count food; and decontamination of the gastrointestinal tract *(151)*. This approach is expensive and may have poor patient acceptance *(151–155)*. Although TPE has been shown to lower the incidence of infection, the rate of survival may not differ in patients in TPE as compared with a standard hospital room *(155)*. This is largely due to improved management of infections and makes TPE a cost–benefit issue. Invasive aspergillosis is an infection that is often refractory to therapy and has a high mortality in these patients *(156)*. For this reason, the use of HEPA filtration and a private room is recommended for patients with prolonged granulocytopenia, such as bone-marrow transplant patients *(157)* (see also Chapter 59).

SPECIAL CONSIDERATIONS FOR PATIENTS IN EXTENDED CARE OR REHABILITATION

Long-Term Care and Home-Based Care

LTCFs are becoming more important as the population ages. Patients managed in LTCFs are being admitted with more acute diseases and are at increased risk of developing healthcare-associated infections *(158)*.

Consideration for transmission-based isolation precautions in long-term care is different than that of acute care hospitals. Isolation precautions should be individualized based on the likelihood of transmission and the mobility of the patients (4). Given prolonged stays and the need to maintain a "home-like environment," strict Contact Precautions cannot always be recommended, and adverse consequences of isolation should be considered *(158)*. Some institutions have adopted the use of gloves alone when in contact with patients on Contact Precautions, in addition to Standard Precautions and a hand hygiene program. This has been shown to contribute to increased compliance with isolation (among HCW using gloves alone vs. gloves and gowns during interactions) without increased transmission of microorganisms *(159)*. In patients with adequate mobility and multi-drug resistant organism (MDRO) infection, Standard Precautions may be adequate, but in those that require complete support and have uncontrolled secretions/excretions, Contact Precautions similar to those in the acute care setting may be needed. Airborne Precautions and Droplet Precautions may still need to be similar to those employed in acute care settings; however, the 2007 guidelines emphasize the need to individualize isolation decisions in this patient population.

Noncritical equipment should be assigned to each patient, but if this is not feasible, equipment should be appropriately disinfected between patients. Transportation and mobility of patients in isolation should be handled in a manner similar to that of acute-care settings.

The risk of infection during home-based care is reduced due to the limited contact with personnel and other patients. However, there is still a risk of transmitting infections from healthcare workers or family members to patients, such as influenza and scabies, or to transmit infections from patients to family members (e.g., tuberculosis). Noncritical items should remain at the home of the infected or colonized patient when possible and should be cleaned with a low to moderate level disinfectant before removing them from the patient environment (home) (see also Chapter 99).

In ambulatory settings, patients requiring isolation precautions should be moved to an individual room as soon as possible. When the patient requires Contact Precautions, they should be placed in an individual room and the HCW should wear appropriate PPE. If the patient requires Droplet Precautions, then he/she should be instructed on respiratory hygiene/cough etiquette as well.

In the ambulatory setting, patients requiring Airborne Precautions should be immediately identified and placed in a room with negative pressure and 6 to 12 air exchanges per hour with exhaust of the air to the exterior or through a HEPA filter. The patient should wear a surgical mask until he/she can be moved to a negative pressure room with the door closed. If a negative pressure room is not available, the patient should keep the mask on, and after the patient leaves, the room should remain empty for an adequate period of time (usually 1 hour).

As the number of elderly patients in extended care increases and as rehabilitation programs continue to proliferate, there will likely be an increasing number of patients with multidrug-resistant microorganisms in these settings. These patients have often been in the acute-care setting for extended periods of time or for frequent readmissions and have had multiple opportunities to acquire microorganisms such as MRSA, VRE, and multidrug-resistant *K. pneumoniae*. Rehabilitation and socialization in these settings are critical to maintaining or increasing functional status, and keeping patients restricted to their rooms on Contact Precautions, as outlined for acute care, may not be practical. Studies have documented that MRSA colonization is common in the nursing home, but infections are not frequent. This may also be the case with VRE as the data are accumulating *(160)*. The Long-Term-Care Committee of the Society for Healthcare Epidemiology of America has published guidelines recommending minor modifications of Contact Precautions in the long-term care setting *(160)*. This approach recommends education of personnel in these units regarding basic infection control measures. Surveillance cultures may be used in an outbreak of infection but are not cost-effective in the nonoutbreak setting. When a resident is transferred to another unit or facility, the receiving party should be made aware of that resident's colonization with a multidrug-resistant microorganism.

A private room is recommended when possible or if necessary. If this is not feasible, the patient who is colonized with VRE and is continent without diarrhea or has an open wound that is infected or colonized with VRE may be placed with another patient. The roommate should be selected with care and should not be severely immunocompromised, have open wounds, and preferably should not be receiving antibiotics or have an indwelling urinary catheter or drainage device. Gloves should be used for contact with the patients and their environment. Because soap may not adequately remove VRE from hands, chlorhexidine or an alcohol-containing antiseptic should be used after caring for VRE-infected or colonized patients. Gowns are recommended if contact is anticipated with the patient, the

patient's secretions, or the environment. VRE-infected or colonized residents may leave their room provided that they can understand and are compliant with basic personal hygiene, are continent of stool (or diapered to contain stool), and wear clean clothing. Resident education is particularly important, as much as is feasible, regarding good hygiene and hand washing. Patient-care equipment should be dedicated when possible, and the use of individual thermometers is recommended. In the rehabilitation unit, where equipment may be central, the patient may be scheduled at the end of the day and equipment disinfected after use. As with recommendations for VRE in acute care, daily environmental cleaning with a germicide is recommended. Vancomycin and cephalosporin use should be prudent.

Such modified Contact Precautions may be used as a model for other problematic multidrug-resistant microorganisms in the extended care setting. A similar protocol has been used in a unit with VRE and multidrug-resistant *K. pneumoniae*. Stool surveillance prevalence studies from 1 year compared with the next showed no significant increase in colonization with these microorganisms using these principles of modified precautions *(161)*.

CATEGORY A BIOTERRORISM AGENTS AND ISOLATION

Since potential bioterrorist diseases are not routinely seen, the healthcare epidemiologist and infection control department must be aware of whether and what type of isolation precautions are needed, particularly for category A agents—deemed the most likely bioterrorist agents.

Anthrax

Person-to-person transmission of anthrax is not a concern *(162)*. The natural life cycle is that hoofed animals inhale or ingest infective spore forms of *Bacillus anthracis* from soil or dust. The spore forms then germinate to become vegetative forms as they multiply, causing massive infection and toxin release associated with edema, hemorrhagic necrosis, and death. The carcass then decomposes; vegetative spores are exposed to oxygen; and the spore forms are regenerated. Humans can be an incidental host by skin contact with the spore forms; 95% of natural anthrax cases are cutaneous. Humans can also become an incidental host by inhalation of spores, occurring primarily by wool-sorting in endemic areas. Since the vegetative forms cause the disease in the body, anthrax is not transmissible person-to-person. The intentional anthrax attacks in October 2001 caused cutaneous cases from mail handling and inhalation cases from aerosolization of spores from mail-sorting equipment. There was no person-to-person transmission from these cases *(163)*. Standard Precautions is the only isolation category recommended for anthrax (see also Chapter 103).

Smallpox

Transmission of smallpox (variola) has generally occurred only in close contacts, but healthcare-associated spread has been reported. Droplet spread is the major mode of transmission, but airborne transmission through fine-particle aerosol can occur, particularly in severely ill patients *(164)*. The skin lesions of smallpox are also contagious and, unlike varicella, are contagious until the scabs separate. Contact Precautions and Airborne Precautions should be instituted immediately when there is high suspicion for smallpox, and public health officials should be notified. Masks of N95 quality or higher, disposable gloves, gowns, and shoe covers should be used for all contact with patients. Personnel should remove and dispose of protective garb before contact with others. Reusable bedding and clothing should be autoclaved or laundered in hot water with bleach to inactivate the virus. If smallpox is confirmed, these isolation precautions should continue until the scabs are separated. Clinical specimens should not be sent through the pneumatic tube system and should be carefully packaged for referral to a public health laboratory (see also Chapter 104).

Botulism

Botulism is a toxin-mediated disease due to botulinum toxin produced by *Clostridium botulinum*, and thus, is not transmitted person-to-person. Botulinum toxin can be detected in stool and serum and, if accidentally ingested or inhaled, could cause disease. Standard Precautions should be used in the handling of blood and body fluids *(164,165)* (see also Chapters 47 and 103).

Plague

Natural cases of plague, due to infection by *Yersinia pestis*, are usually bubonic, associated with the characteristic buboes as a result of transmission from the bites of infected fleas. Primary plague pneumonia is uncommon in natural disease but would be the expected form of intentional, or bioterrorist, plague. Person-to-person spread of pneumonic plague may occur by respiratory droplets. Therefore, Droplet Precautions are recommended for cases of pneumonic plague until at least 48 hours of appropriate antibiotic therapy is administered and the patient shows clinical improvement *(166)*. Patients with natural cases of bubonic plague without secondary pneumonic plague require only Standard Precautions (see also Chapters 47 and 103).

Viral Hemorrhagic Fevers

This diverse group of viruses, including Ebola, Marburg, and Lassa, are spread in a variety of ways but may be transmitted by the respiratory route or as a blood-borne pathogen. Droplet and Contact Precautions should be used *(59)* for these patients. Equipment should not be shared between patients, and materials contaminated with body fluids should be disinfected with a bleach solution or phenolics. Special laboratory handling is required, including a biosafety cabinet and barrier precautions. Laboratory personnel should be notified when this disease is suspected (see also Chapters 47 and 103).

Tularemia

The most common form of natural disease due to *Francisella tularensis* is ulceroglandular disease with associated lymphadenopathy; natural tularemic pneumonia is less common. Bioterrorist disease would be expected to be tularemic pneumonia, however, because of intentional aerosolization. Person-to-person transmission does not occur,

so only Standard Precautions are required. However, this disease is transmitted quite easily in the laboratory, and should be handled under a biosafety cabinet; therefore, the laboratory should be notified if tularemia is suspected *(167)* (see also Chapter 103).

CONCLUSION

Isolation guidelines have changed tremendously over the past couple of decades, largely because of the AIDS epidemic and the recognized risk of transmission of infection within the healthcare setting. The positive aspect of this change is that guidelines designed to protect against blood-borne pathogen transmission are standard for all patients. Precautions to prevent non–blood-borne pathogen transmission, including multidrug-resistant pathogens, are now more widely used and are standard in many institutions. The revision of CDC isolation guidelines has addressed some of the confusion in terminology that occurred with the implementation of Universal Precautions. Two tiers of precautions are used: Standard Precautions for the care of all patients, and a second tier of transmission-based precautions (Airborne Precautions, Droplet Precautions, and Contact Precautions) for patients with known or suspected diseases spread by these routes.

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CHAPTER 91

Hand Washing and Hand Disinfection

Manfred L. Rotter

Although the importance of hands for the transmission of infectious diseases was not demonstrable before the 19th century when medicine began to adopt scientific ways of thinking, an idea of their role must have existed long before the Hungarian obstetrician Ignaz Philipp Semmelweis made his epidemiologic observations on the horrible spread of puerperal fever, which caused maternal mortality rates of up to 18% in some months at a Vienna, Austria, lying-in hospital during the years 1841 to 1847. At least from examples of the historical tradition, it may be concluded that hand washing is an old cultural heritage of human civilization. The idea has been handed down to us that this procedure not only served for the removal of dirt but also to deliver people symbolically from physical and moral evils, such as illness and sin. It is characteristic of the efficacy of modern scientific methodology that hands were identified as transmitters of disease even at a time when microorganisms were not yet recognized as a cause of infection. Semmelweis applied epidemiologic rather than microbiologic methods to test his hypothesis that preventing hands from introducing a fatal something into the maternal birth canal during vaginal examination would also end the hyperendemic situation of puerperal fever at his hospital. His attention was especially drawn to the markedly lower maternal mortality at the second obstetric department of the same hospital where, in contrast to his working place, where usually midwives conducted deliveries (Fig. 91-1) *(1)*. He identified the distinguishing moment in the incidence of puerperal fever by the fact that midwives had no contact with the autopsy room where, he postulated, hands were contaminated with the fatal etiologic agent.

Although the role of hands in the transmission of puerperal fever had been recognized as early as 1795 by Alexander Gordon and in 1843 by Oliver Wendell Holmes *(2)*, Semmelweis was the first to take appropriate action by introducing hand disinfection into clinical practice in May 1847. A little later and probably without knowledge of Semmelweis' findings, the Scottish surgeon Joseph Lister tested and proved Louis Pasteur's hypothesis that microorganisms not only cause fermentation and putrefaction but may also initiate suppuration in living tissues. By inactivating and keeping the causative microorganisms away from the surgical site, he prevented surgical site infection. Among other vehicles and sources, he also recognized the importance of the hands of the surgical team and consequently tried to eliminate their microbial flora before surgery.

MICROBIAL FLORA OF HANDS

Although it is not always feasible *(3,4)*, three groups of microorganisms may be distinguished on the skin: (a) microorganisms that reside on the skin, which the American surgeon Price (5) termed "resident" flora; (b) those that happen to be there as contaminants, which Price termed "transient" flora; and (c) pathogens that cause infections on the hands, such as panaritium digiti or paronychia, which can be called "infectious" flora.

Resident Flora

Except for the anaerobic propionibacteria that are located mainly at the ducts of sebaceous glands, most of these microorganisms reside on the uppermost part of the stratum corneum *(6,7)*, on corneocytes, and are embedded in a mass of lipids and cell detritus of the pars disjuncta *(8,9)*. They multiply in the upper regions of the hair follicle *(10)*. The deeper regions of the skin are, the ducts of eccrine and apocrine glands, not colonized *(11)*. The composition of skin flora has been described in several reviews *(12–19)*. Recently, molecular biologic diagnostic tools such as a novel pyrosequencing-based method, allowed characterizing a hitherto unknown diversity of skin bacteria on the palmar surfaces of the hands of young adults *(20)*. According to the findings of Fierer et al. *(20)* hands harbored, on average, 158 (in the range 46–401) unique species-level bacterial phylotypes, and among the 51 healthy volunteers, they identified a total of 4,742 unique phylotypes across the 102 hands examined. The bacterial diversity was more expressed in females than in males. The bacterial skin flora varies qualitatively and quantitatively by body site, gender, age, health condition, hospitalization, season *(6,11,21–23)*, handedness, and the time interval between last hand washing and skin sampling *(20)*. Except for areas with large numbers of sebaceous glands where propionibacteria prevail, the main portion of the skin flora is made up of *Micrococcaceae* such as staphylococcal species (*Staphylococcus epidermidis, Staphylococcus*

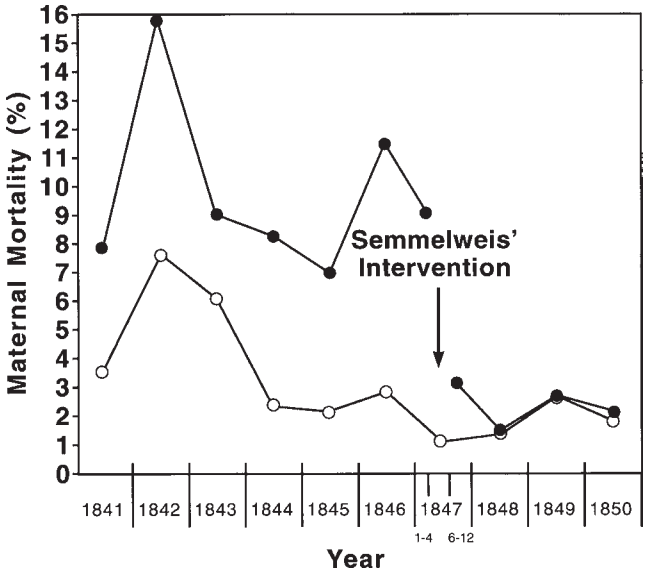

FIGURE 91-1 Maternal mortality at the First and Second Imperial-Royal Obstetric Department of the General Hospital in Vienna, Austria, 1841–1850. •, First Department; ○, Second Department. (From Rotter ML. Semmelweis' sesquicentennial: a little noted anniversary of hand washing. *Curr Opin Infect Dis* 1998;11:457–460, with permission.)

hominis, Staphylococcus capitis, etc.) and micrococci. Also, *Staphylococcus aureus* may temporarily colonize the skin, especially the perineal region, nose, hands, face, and neck. This occurs more often with children than with adults *(3)*, but healthcare personnel are especially prone to this colonization; the prevalence of colonization with *S. aureus* in healthcare personnel was reported by Larson et al. *(24)* to reach 18%. In the intensive care unit (ICU) of a German teaching hospital, Hofmann et al. *(25)* found *S. aureus* on 18.4% of nurses' hands and on 36% of doctors' hands. These data more likely reflect, however, a state of repeated contamination rather than true long-term carriage. Lipophilic and nonlipophilic corynebacteria are common inhabitants of the skin—the former usually in hairy regions, the latter more in bald regions *(6)*. The antibiotic-resistant *Corynebacterium jeikeium* may cause therapeutically difficult nosocomial infections in high-risk patients. Although the most common site of isolation is the perineum *(23)*, it may also occur on the hands. *Propionibacterium acnes* and *Propionibacterium granulosum*—the latter of which is less often isolated—multiply at sebaceous body sites *(11,26)*, but they can also be found in small numbers on the hands, although most likely as transients *(9)*. Fierer et al. *(20)*, however, identified them as the most abundant bacterial group on the palmar hand surfaces of their undergraduate student-volunteers who had, just prior to sampling, taken an examination. This may be because the students had often and intensely touched their sebum-rich forehead while thinking and, by this, contaminated their hands.

Gram-negative bacteria such as *Acinetobacter* and *Enterobacter* species may be isolated mainly from moist skin areas *(26–29)* but also regularly from the hands, where they may be regarded as residents *(30)*. Larson *(31)* found that 80% of persons outside the hospital and 21% of hospital personnel persistently carried *Acinetobacter* species and members of the *Klebsiella–Enterobacter* group. Males were significantly more likely to be carriers than females, and persons who washed their hands less than eight times per day were more likely to persistently carry the same gram-negative species than those who washed more than eight times. Well known is the report by Casewell and Phillips *(32)* of a hospital outbreak with *Klebsiella* colonizing the hands of hospital personnel. Attendants with close patient contact, as in ICUs, were especially likely to carry gram-negative bacteria on their hands *(33)*. A list on the contamination frequency with nosocomial pathogenic species on healthcare workers' hands and their persistence on hands and inanimate surfaces has been presented in a recent review by Kampf and Kramer *(34)*.

The population density of resident skin bacteria ranges somewhere between 10^6 colony-forming units (CFU)/cm^2 on the sebum-rich scalp and 10^2 to 10^4/cm^2 on the forearm *(35)*. Fingertip counts assessed by agar contact methods ranged from 0 to 300 *(36)*. The density remains remarkably stable for any given individual over long periods of time (5,*20,36–38*). Only diseases of the skin and agents interfering with the biocenosis, such as antibiotics or disinfectants, may cause long-term alterations *(6,14,26,39)*. The greatest short-term fluctuations (1–2 hours) are seen after intense contact with water *(40)*.

The normal microbial skin flora fulfills the important function of colonization resistance, thereby preventing colonization with other and potentially more pathogenic microorganisms. The influencing factors are the presence of free fatty acids liberated from skin lipids by bacterial metabolism, the presence of bacteriocins and other antibiotic-like bacterial secretions, and the low water content of the stratum corneum *(3,17,41,42)*. The pH value and osmotic conditions are less important *(21)*. Unless introduced into body tissue by trauma or in the presence of foreign bodies such as catheters or implants, the pathogenic potential of the resident flora is usually regarded as low *(43,44)*. Resident flora is difficult to remove by mechanical means. Washing hands with soap and water reduces the release of skin bacteria every 5 minutes by only 50% (5,*45,46,*47).

Transient Flora

Members of this group are characterized by their inability to multiply on the skin. They occur as skin contaminants. Among them, microorganisms with high pathogenic potential may also be found. Usually transient flora does not survive for very long, but sporadically multiply on the skin surface *(34)*. Besides the above-mentioned factor of colonization resistance, the inhospitable physicochemical environment may be another reason for the failure of transient flora to survive. Medical personnel, however, should never rely on this. In contrast to natural microbial skin flora, transient flora is easily removed by mechanical means such as hand washing. If hands are washed for 1 minute with soap and water, the reduction of bacterial release was measured to be two to three orders of magnitude (*48–53,*54). Even rubbing hands with water alone is effective *(52)*.

Infectious Flora

This group includes the etiologic agents of actual infections such as abscesses, panaritium, paronychia, and infected eczema on the hands. They are of proven pathogenicity.

S. aureus and β-hemolytic streptococci are the species most often encountered.

STRATEGIES OF HAND HYGIENE

Strategies for the prevention of hand-associated microbial transfer must take into consideration the fact that it is much easier to reduce the release of transient flora from the hands than that of resident flora and that, more than ever, infectious lesions must be healed before the hands may be regarded as safe. Therefore, the choice of preventive measures depends on which group of microbial flora is to be attacked. The precautions proposed in Table 91-1 are discussed below.

If microbial contamination is to be expected, the strategy is to *keep* hands clean, because this is much easier to do than to *make* them clean. If used intelligently, both the no-touch technique (use instruments rather than fingers) and protective gloves are suitable remedies against microbial transfer. This implies, of course, that instruments and gloves are changed after every patient. Although it was reported that transient bacteria were washed from gloves more easily than from hands *(49)* and that used gloves can be successfully cleaned of adhering microorganisms *(55,56)* and even of hepatitis B virus (HBV) antigen *(55)* by washing or disinfecting gloved hands for 30 to 120 seconds, this could not be confirmed by Doebbeling et al. *(57)* under conditions more appropriate to clinical practice with various treatments of only 10 seconds. The authors recultured the microorganisms used for artificial contamination not only from 4% to 100% of the gloves in counts between 0 and 4.7 log but also from the hands after the removal of the gloves *(57)*. They concluded that it may not be prudent to wash and reuse gloves between patients and that hand washing or disinfection should be strongly encouraged after removal of protective gloves *(57)*.

If hands are known to be or are suspected of being contaminated, the undesired transient microbial flora must be eliminated to render the hands safe for the next patient contact. This may be achieved by washing or disinfecting the hands. If, in contrast to an ordinary hand wash, a postcontamination treatment of hands involves the application of an antimicrobial preparation—either an antiseptic detergent (with water) or an antiseptic rub (without water)—it is termed "hygienic" ("hygienic hand wash" and "hygienic hand rub," respectively) in Europe to indicate that these measures aim only at the contaminating transient flora without consideration of the number and fate of the resident skin flora.

Recently, two excellent guidelines were published that delineate indications and details for hand hygiene (58,59). The WHO publication, in particular, offers an enormous amount of information with more than 1,100 references. Below, some additional perspectives are considered.

The decision of which of the above-mentioned measures to use in a particular situation depends on the probability that hands may have become contaminated with pathogens during a potential or known exposure. The higher the risk is, the more important it is to use a microbicidal postcontamination treatment that is effective and safe. In this context, "effective" means efficiently reducing the release of transients, and "safe" means that the treatment should not disseminate pathogens to be eliminated into the vicinity. It has been demonstrated that vigorous hand washing can disperse pathogenic microorganisms such as *Salmonella typhi* into the environment and onto the washing person *(60,61)*. Because hygienic hand rubs kill most transients still on the hands, rub-on techniques can avoid microbial dispersal and should therefore be used after every contagious contact, be it in the dissecting room, the microbiology laboratory, or in patient care, especially if the contact is to be ranked as "very dirty" on the Fulkerson scale *(62,63)* (Table 91-2) involving infected sites (ranks 13–15). Often, however, hygienic hand rubs are used not because of a specific indication but for purely practical reasons, such as availability and the simplicity of their application *(40)*. All other dirty contacts (ranks 8–12) may be followed by hand washing with unmedicated soap, but it should be realized that the complete procedure, including the journey to and from the washplace, makes an uneconomic use of time because it takes three to four times as long as a hygienic hand rub with an alcoholic solution delivered from a dispenser next to the patient's bed *(64)*. An additional advantage of the latter measure is that this method is less sensitive against poor performance

TABLE 91-1

Strategies for the Prevention of Microbial Transfer by Hands

Objective Situation	*Strategy*
To reduce the release of transient flora	*Keep hands clean (noncontamination)*
Hands are still clean	No-touch technique Gloves (protective)
Hands are contaminated	*Render hands clean (elimination of transients)*
After contacts without known or suspected "dangerous" contamination (Fulkerson scale 5–7)	Hand wash or Hygienic hand wash or Hygienic hand rub
After known or suspected contacts with patient secretions, excretions, blood, and infected sites (Fulkerson scale 8–15)	Hygienic hand rub
After working in a microbiology laboratory	Hygienic hand rub
To reduce or prevent the release of transient and resident flora	*Prevent microbial release*
Before surgical activity	Surgical hand disinfection and gloves (surgical)
Before patient care in protective isolation	Hygienic hand wash and gloves (sterile)
Colonization of hands with pathogens	*Treat the diseased skin* Chemotherapy (?) Antiseptic washings (?)
To avoid transmission of pathogens from infected lesions on the hands	*Refrain from activities involving infectious hazard* (e.g., surgery, handling foodstuffs and pharmaceuticals)

TABLE 91-2

Fulkerson Scale Ranking Contacts of Nursing Personnel from Clean to Dirty

Rank[a]	*Contact With*
1	Sterile or autoclaved materials
2	Thoroughly cleaned or washed materials
3	Materials not necessarily cleaned but free from patient contact (e.g., papers)
4	Objects contacted by patients either infrequently or not expected to be contaminated (e.g., patient furniture)
5	Objects intimately associated with patients but not known to be contaminated (e.g., patient gowns, linens, dishes, bedside rails)
6	Patient, but minimal and limited (e.g., shaking hands, taking pulse)
7	Objects in contact with patient secretions
8	Patient secretions or mouth, nose, genitoanal area, etc.
9	Materials contaminated by patient urine
10	Patient urine
11	Materials contaminated with feces
12	Feces
13	Materials contaminated with secretions or excretions from infected sites
14	Secretions or excretions from infected sites
15	Infected patient sites (e.g., wounds, tracheotomy)

[a]"Clean" activities, 1–7; "Dirty" activities, 8–15.
(Data from Fox MK, Langner SB, Wells RW. How good are hand washing practices? *Am J Nurs* 1974;74:1676–1678, and Larson E, Lusk E. Evaluating hand washing technique. *J Adv Nurs* 1985;10:547–552, with permission.)

of hand hygiene *(65)*. The necessary time expenditure may also be one of the reasons for poor compliance of healthcare workers with hand washing.

Hygienic hand washes with an antiseptic detergent are designed to rapidly wash off most of the transient flora by their mechanical detergent effect and to exert an additional microbicidal activity, with some agents accompanied by a sustained effect on the remaining hand flora. This latter effect may be useful in areas where microbiologically clean hands are desired during extended periods of time such as in protective isolation and in surgery, as well as in the food and pharmaceutical industries.

For these indications, hands play not only the role of a microbial vector, but they may also be an important source of undesired microorganisms multiplying in and being shed from the skin. The strategy to prevent this microflora from reaching sensitive areas such as surgical wounds, foodstuff, or pharmaceuticals is to reduce their release from the hands. This is best attained by using (sterile) gloves. Surgical hand disinfection can greatly reduce the release of transient and resident skin flora and is usually meant as an adjunct to surgical gloves in case they become punctured or torn. Scrubbing hands with unmedicated soap alone removes transient flora efficiently but has only a negligible effect on the resident skin bacteria (see below). For presurgical preparation of the surgeon's hands, prolonged scrubbing with unmedicated soap is, therefore, worth neither the effort nor the strain on the skin. Helpful recommendations for surgical hand scrubs have been provided by the Association of Operating Room Nurses (66), the new WHO guidelines (59), and most recently, by Widmer et al. (67).

Antiseptic hand washing may also be used therapeutically to clear carriers from pathogenic resident flora *(68)*.

Hands with infected purulent lesions are very dangerous sources of microbial flora with proven pathogenicity. Therefore, the only effective strategy is to prohibit any activity involving infectious risks such as engaging in surgery and other types of patient care or handling foodstuff and pharmaceuticals.

METHODS OF ELIMINATING MICROORGANISMS FROM THE HANDS

Mechanical and chemical methods for the reduction of microbial release from the hands are summarized in the following subsections.

Hand Washing

Although in German-speaking countries the term "hand washing" is exclusively reserved for the use of unmedicated soap and water (with or without a brush), in other parts of the world, it also implies the application of antiseptic soaps (disinfectant–detergents). In this chapter, the term is applied *sensu strictu* to washing hands with unmedicated detergent and water.

The objective of hand washing is to remove dirt (consisting of extraneous substances, sweat, skin lipids, epithelial debris, etc.) and loosely adhering microbial skin flora, which will include most of the transient but only a small part of the resident flora. In fields of application where the microbiologic aspect dominates, the aim is, of course, to reduce microbial release from hands to an extent that may be considered safe for the intended purpose. In the medical field, this purpose is usually to prevent hand-borne infection.

The efficacy of a hand wash depends on the time taken and the technique. Unfortunately, this period is usually rather (too?) short in normal hospital work. The average duration was reported by several authors to be between 8 and 20 seconds *(24,69,70)*. This period of time, however, does not include the additional time needed to approach and return from the washplace. Therefore, the complete process takes considerably longer. In fact, it has been measured to take 40 to 80 seconds *(64)*. Table 91-3 indicates how effectively the release of transient bacteria from artificially contaminated hands can be reduced by hand washing. The greatest reduction is achieved within the first 30 seconds; it ranges between 0.6 and 1.1 log after 15 seconds and between 1.8 and 2.8 log at the end of 30 seconds. Extending the washing time to 1 minute results in reductions of 2.7 to 3.0 log. A further prolongation of the procedure is not worth the effort, because after 2 minutes the reduction increases negligibly to only 3.3 log and after 4 minutes to only 3.7 log.

TABLE 91-3

Reduction of the Release of Test Bacteria from Artificially Contaminated Hands by Washing with Soap and Water

Duration	*Mean $\log_{10}$ Reduction*	*References*
15 s	0.6–1.1	*(71)*
30 s	1.8	*(50,75)*
	2.3–2.5	*(53)*
	2.5–2.8	*(48,49)*
1 min	2.7	*(49)*
	3.0	*(52,73)*
2 min	3.3	*(52)*
4 min	3.7	*(52)*

Although in most instances these reductions are probably sufficient to prevent infection-generating transmission of pathogens *(51,53,72,74–76)*, this is not always the case. Semmelweis, for instance, observed that normal hand washing did not always prevent the spread of fatal infection. Eleven parturient women died of puerperal fever after having been examined immediately after contact with a patient suffering from a foully discharging medullary carcinoma *(77)* by attendants who, in between, had washed their hands with only soap and water. After this experience, Semmelweis extended his order to disinfect hands in a solution of chlorinated lime from before entering the delivery or patient room to using it before each vaginal examination *(77–80)*. It is important to understand that some procedures of hand disinfection are significantly more efficient in reducing the bacterial release from hands than hand washing with soap and water.

Although highly sophisticated washrooms with fully automated functions have been shown to be even counterproductive rather than motivating healthcare personnel to adhere to hand washing rules *(81)*, certain requirements for washrooms must be fulfilled for minimal compliance. Wash basins should be conveniently located; no overflow or plug is necessary because hands should be washed only under running water. A mixer tap helps to provide water of comfortable temperature that, under the best conditions, is controlled thermostatically. Operating the water flow without using hands (elbow, knee, foot, sensor) may be desirable in certain critical areas. Suitable dispensers for soap, disinfectant (rub is better than detergent), hand lotion, and one-way towels are accepted requirements. There must also be a container furnished with a liner for used towels. If liquid soap is used, dispensers must either be easily removable and heat resistant for thermal reprocessing or they should be equipped with disposable bags. Liquid soap dispensed from refillable containers should be bacteriostatic to prevent microbial growth; topping of these containers is to be strictly prohibited.

An appropriate hand washing technique includes adjusting the water flow and the temperature (both activities can be accelerated by suitable technical devices), wetting hands, taking soap, rubbing hands to produce a lather without splashing, and performing wash movements that include rubbing palm to palm, rotational rubbing with clasped fingers of right hand in palm of left hand and vice versa, moving right palm over left dorsum and vice versa, palm to palm with fingers interlaced, backs of fingers to opposing palm with fingers interlocked, and rotational rubbing of right thumb clasped in left palm and vice versa. Each movement is to be repeated four times. This technique was proposed by Ayliffe et al. *(71)* as a standard technique when testing antiseptic hand washes. It could also represent a routine hand wash technique. Some authors demonstrated, however, that, after appropriate instruction, allowing each individual his or her own "responsible application" resulted in a better coverage of all hand surfaces *(82)*; and this is a prerequisite for a correct technique. Finally, hands are rinsed with fingertips up, and the water is cautiously shaken off. As concluded from the results of laboratory-based *in vivo* tests, the whole procedure should take not less than 30 seconds, a goal nearly impossible to attain during patient care. The subungual spaces harbor, by far, the main part of the bacterial hand flora *(83)*. The importance of this observation for the transmission of nosocomial infections by medical personnel is unknown, but Tanner et al. *(84)* found that, at least in presurgical hand preparation, nailbrushes and nail picks do not decrease bacterial numbers and are, therefore, unnecessary. After washing, the hands are dried with a disposable towel (paper or textile). Unless the water flow is discontinued by an automatic device, the water should be turned off by using the same towel rather than by the freshly washed hands *(73)*. The towel is then discarded into the appropriate container, and a hand lotion should be applied onto the hands. This latter step is extremely important to prevent chapping. Electric hand dryers are useless in hospitals because, with them, hand drying takes too long and because they lack the friction of towels to remove the remaining soap from the skin.

No matter how well and detailed hand washing techniques may be described, Larson and Kretzer *(85)* are probably right in suggesting that a subject of much greater concern is how to motivate personnel to wash their hands in the first place, because hand washing practices still remain suboptimal.

Hygienic Hand Rub

The objective of a hygienic hand rub is to reduce the release of transient pathogens with maximum efficacy and speed, so that hands can be rendered safe after known or suspected contamination. This should be done in a way that avoids microbial dispersal into the environment. A sustained effect is not required. The fate of the resident skin flora is disregarded in this procedure.

The technique of hygienic hand rubs includes rubbing small portions of 3 to 5 mL of a fast-acting antiseptic preparation onto both hands. This can be a very convenient way of treating hands after known or suspected contamination, because dispensers for hand rubs can easily be made available wherever necessary; for instance, they may be placed in the vicinity of every patient bed in high-risk areas. All areas of the hands must be covered by the disinfectant, but this is often not done *(70)*.

The antimicrobial spectrum necessary for hygienic hand rubs depends on the intended use. Commonly, the antimicrobial spectrum required includes only bacterial and fungal pathogens. Sporicidal activity is, if at all, only

needed in certain situations such as in *Clostridium difficile* outbreaks. But there are hardly any chemicals that are sufficiently strong and fast acting as well as skin-tolerable at the same time, so the mechanical action of a hand wash is usually used for spore reduction. "Hand washing with soap and water showed the greatest efficacy in removing *C. difficile* and should be performed preferentially over the use of alcohol-based hand rubs when contact with this pathogen is suspected or likely," concluded Oughton et al. *(86)* from the results of their laboratory-based experiments with artificially contaminated hands of volunteers. However, as the usually encountered nosocomial pathogens can still be around, it is recommended to first use an alcohol-based hand rub before washing hands. Activity against mycobacteria is required only at certain places such as in tuberculosis hospitals, wards for acquired immunodeficiency syndrome patients, and in pathology and microbiology laboratories. The antituberculous effect must be proven and stated on the label. Virucidal activity is not a general requirement and is only justified in special situations. Furthermore, it should only be claimed if the (proven) antiviral spectrum of a product also includes enteroviruses such as polio or hepatitis A virus together with an acceptable exposure time.

There is only a small range of possible agents for hand rubs, such as alcohols in high concentration, used alone or mixed with other antiseptics; aqueous solutions containing halogens such as chlorine or iodine; chlorhexidine; quaternary ammonium compounds; phenolics; triclosan; aldehydes; metallo-organic compounds; and oxidizing agents such as peracetic acid. Except for the alcohols, aqueous solutions of chlorine, povidone–iodine, and chlorhexidine, the other agents are usually used solely as adjuncts to alcohols (quaternary ammonium and ampholytic compounds, phenolics); are contained in antiseptic detergents (phenol derivatives, povidone–iodine, chlorhexidine, triclosan); or are not used at all because of poor efficacy, allergenicity, irritant or toxic potential, or ecologic considerations (aldehydes, metallo-organic, and peracetic acid). There is no doubt that alcohols are much more comfortable to rub onto the skin than aqueous solutions because of specific features such as excellent spreading and quick evaporation.

Table 91-4 summarizes examples of results from evaluations of commonly used active agents for their antibacterial efficacy, which was assessed in standardized tests simulating practical conditions on artificially contaminated hands of volunteers (*9,45,52,*54*,71,72,87,98,102–109*). As demonstrated, the alcohols *n*-propanol, isopropanol, and ethanol, and the halogen releasers sodium tosylchloramide and povidone–iodine appear superior to aqueous solutions of chlorhexidine diacetate, chlorocresol, and hydrogen peroxide. Among the results with the alcohols, there is a clear positive association between the extent of bacterial reduction and the concentration used. If mean log reductions obtained with the three alcohols are compared with each other at equal concentrations, *n*-propanol is the most effective and ethanol is the least effective alcohol. The efficacy of aqueous solutions of sodium tosylchloramide and povidone–iodine compares well with that of isopropanol at a concentration of 60% v/v.

Tuberculocidal activity has been demonstrated for the alcohols mentioned *(88–90,92,93,99)*, although with prolonged exposure *(89)*. Several recommendations suggest disinfection times of 1 to 5 minutes with 70% ethanol, 60% to 70% isopropanol, or 50% to 70% *n*-propanol *(87, 91,94)*. The halogen-based preparations are also regarded as active *(60,94)*.

The virucidal activity of alcohols is generally good with enveloped viruses *(54,95,96)*, including the human immunodeficiency virus (HIV). An exception is the rabies virus, which is reported to be ethanol-resistant *(97)*. Naked viruses, such as enteroviruses, are inactivated only by high concentrations of alcohols *(100)*, the most effective of which is reported to be ethanol *(96,101)*. Laboratory *in vivo* tests have shown that the effectiveness of alcohols against some difficult viruses such as entero- and rotavirus is significantly better than that of hand washing with unmedicated soap (*101,110–118*). Absolute ethanol reduced, for instance, the viral release from the hands by 3.2 log, 80% ethanol (v/v) by 2.2 log, and absolute *n*-propanol by 2.4 log (*110*). In contrast, individual hand washing for 10 to 55 seconds caused a reduction of only 1 log. Testing a commercial preparation containing a high-alcohol concentration, Schürmann and Eggers *(100)* concluded that this rub was effective against enteroviruses only under favorable environmental conditions such as high temperature, large disinfectant-to-virus volume ratio, and low protein load. In another study, the reduction in the release of human rotavirus strains from the hands by 70% (v/v) ethanol or isopropanol was approximately 100 times that of the reduction attainable with tap water or liquid soap *(111)*. A reduction of >3 log by a 60% ethanol preparation was demonstrated *in vivo* with the nonenveloped rota-, adeno-, and rhinoviruses *(112)*. Over the last several years, another nonenveloped virus, the norovirus (the former Norwalk-like virus), belonging to the family of caliciviruses, has been recognized as an important cause for epidemic and sporadic food-, water-, and airborne diarrheal disease. As, at present, the human norovirus cannot be grown in cell culture systems, related animal noroviruses have been and are used as surrogate viruses to evaluate the virucidal efficacy of antiseptic agents, especially alcohols. In fingertip experiments according to ASTM International E-1838-96 *(113)*, Gehrke et al. *(114)* found that a 70% (v/v) concentration of each of three tested alcohol species was more effective than their 90% counterpart. Ethanol turned out to be the most efficacious, followed by 1-propanol and 2-propanol, with the respective viral reductions being 3.78, 3.58, and 2.15 log.

In other fingerpad experiments, a combination of ethanol with 10% 1-propanol, 5.9% 1,2-propandiol, 5.7% 1,3-butandiol, and 0.7% phosphoric acid proved active at a much lower concentration of 55% against polio type 1 with a log reduction of 3.04 within 30 seconds, whereas with 2-propanol only 1.32 log were achieved. Within the same exposure time, feline calicivirus was reduced by 2.8 log *(115)*. (In quantitative suspension tests, with and without protein load, this formula reduced infectivity titers of seven enveloped and four nonenveloped viruses by $>10^3$ log within 30 seconds. Only ethanol at a concentration as high as 95% exerted a comparable activity.) Similarly, in another *in vivo* study using the then-amended fingerpad test method E 1838-02 of ASTM International *(119)*, it was also a combination of ethanol 70% (v/v), in this case, with polyquaternium-37 and citric acid that succeeded in

TABLE 91-4

Hygienic Hand Rub: Efficacy of Various Agents in Reducing the Release of Test Bacteria from Artificially Contaminated Hands

			Mean Log Reduction Exposure Time (min)			
Agent	***Concentration[a] (%)***	***Test Bacterium***	***0.5***	***1.0***	***2.0***	***References***
n-Propanol	100	*Escherichia coli*	—	5.8	—	*(103)*
	60	—	—	5.5	—	*(104)*
	50	—	—	5.0	—	*(104,105)*
	—	—	3.7	4.7	4.9	*(104)*
	40			4.3		*(104)*
Isopropanol	70	*E. coli*		4.9		*(104)*
				4.8		*(107)*
		—	3.5	—	—	*(71)*
	60	—	—	4.4	—	*(105)*
	—	—	—	4.3	—	*(72,107)*
		—	—	4.2	—	*(106)*
		—	—	4.0	—	*(54)*
	—	*Serratia marcescens*	—	4.1	—	*(108)*
	50	*E. coli*	3.4	3.9	4.4	*(104)*
Ethanol	80	*E. coli*	—	4.5	—	*(104)*
	70	—	—	4.3	5.1	*(109)*
	—	—	—	4.3	4.9	*(52)*
	—	—	—	4.0	—	*(105)*
	—	—	3.6	3.8	4.5	*(104)*
	—	—	3.4	4.1	—	*(53)*
	—	*Staphylococcus aureus*	3.7	—	—	*(53)*
	—	—	2.6	—	—	*(75)*
	—	*Staphylococcus saprophyticus*	3.5	—	—	*(53)*
	60	*E. coli*	—	3.8	—	*(104)*
Tosylchloramide (aq. sol.)	2.0[b]	*E. coli*		4.2		*(102)*
Povidone–iodine (aq. sol.)	1.0[b]	*E. coli*	—	4.0–4.3	—	*(45)*
Chlorhexidine diacetate (aq. sol.)	0.5[b]	*E. coli*	—	3.1	—	*(49)*
Chlorocresol (aq. sol.)	1.0[b]	*E. coli*	—	3.6	—	*(9,98)*
Hydrogen peroxide	7.5	*E. coli*	—	3.6	—	*(87)*

[a]If not stated otherwise, v/v.
[b]w/v.
(From Rotter ML, Kramer A. Hygienische Händeantiseptik. In: Kramer A, Gröschel D, Heeg P, et al., eds. *Klinische Antiseptik*. Berlin, Heidelberg, New York: Springer-Verlag, 1993:67–82, see ref. 102, with permission.)

reducing the release of murine norovirus, which is nowadays regarded as a more relevant surrogate virus *(116)*, by 2.84 log within 30 seconds as compared to only 0.91 log achieved with pure ethanol 75% v/v *(117)*. (When tested in suspension, this test product reduced the infectivity of the nonenveloped viruses: human rotavirus, polio type 1, feline calicivirus, and murine norovirus by >3 log after a 30-second exposure.)

For years, HBV was thought to be extremely resistant to the action of chemical disinfectants. Dried or liquid human plasma containing high-titer HBV, however, did not cause hepatitis if the sera were treated before inoculation into susceptible chimpanzees with 70% isopropanol for 10 minutes, 80% ethanol for 2 minutes, 0.1% glutaraldehyde for 5 minutes, povidone–iodine with 0.8% available iodine for 10 minutes, or hypochlorite solution with 500 mg/L free chlorine for 10 minutes, whereas the control animals receiving untreated plasma developed the disease *(120,121)*. In another test system—the so-called morphology alteration and disintegration test—the HBV appeared significantly altered and disintegrated after exposure to 82% ethanol *(122)*. Ethanol was reported active against HBV at a concentration as low as 70% when in combination with agents such as hexachlorophene, quaternary ammonium compounds, octenidine, biphenylol, or hydrogen peroxide *(121–125)*.

Hepatitis C virus is likely to be inactivated by concentrations of 60% to 70% ethanol *(126)*.

As is evident from the above, alcoholic rubs are very well suited for hygienic hand disinfection, because their antimicrobial performance is excellent and fast, thus saving time; no wash basin is necessary for their use, and they can be positioned next to any patient bed; furthermore, their application does not cause microbial contamination of nurses' uniforms. However, one must bear in mind that the antimicrobial efficacy of alcohols is very sensitive to dilution with water and is, therefore, vulnerable to inactivation, especially with the small volumes of 3 to 6 mL, which, for hygienic hand rubs, are distributed all over both hands. If, for instance, 60% (v/v) isopropanol is rubbed onto wet hands in two portions, each of 3 mL, for 30 seconds, the mean log bacterial reduction achieved was measured to be 3.7, as opposed to 4.3 with dry hands *(107,127)*. Although being not as comfortable, an aqueous solution of povidone–iodine may be used as an alternative hand rub, if necessary, for any reason.

Mainly in North America, there is now a trend toward gel formulations. Comparative tests between liquid and gel formulations of alcohol-based hand rubs revealed, however, that the bactericidal efficacy of gels is significantly lower than that of rinses. Kramer et al. *(128)* compared the efficacy of 10 commercial gels and four rinses using the test method of the European standard EN 1500. No single gel met the requirements within 30 seconds of application, whereas all rinses did. From a report by Kampf et al. (129), it appears, however, that gels with a very high alcohol content can meet the requirement of EN 1500. A new gel containing 85% (by weight) ethanol proved to be bactericidal in suspension (when tested according to prEN 12054) and on volunteers' hands (EN 1500). Furthermore, in suspension tests, the gel was shown to be fungicidal (EN 1275), tuberculocidal (test according to the German Society of Hygiene and Microbiology with *Mycobacterium terrae* as a surrogate test bacterium for *Mycobacterium tuberculosis*), and virucidal (defined as a ≥4 log reduction, within different exposure times) for orthopox and herpes simplex 1 and 2 viruses (15 seconds); rotavirus and HIV (30 seconds); and adeno- (2 minutes), polio- (3 minutes), and papovavirus (15 minutes).

Also, in a prospective clinical trial, where immediately before and after direct contact with a patient pre- and postcontaminations were assessed, it was demonstrated that, on the hands of healthcare workers, equally good respective bacterial reductions of 1.28 and 1.29 log were achieved with both a rinse and a gel—the former containing a mixture of a high concentration of *n*-propanol (30% w/w) and isopropanol (45% w/w), the latter containing 85% (w/w) ethanol—whereas with another gel containing a mixture of 53% (w/w) ethanol plus 17% (w/w) isopropanol, a significantly inferior reduction of 0.51 log was seen *(130)*.

Despite the high alcohol concentration, the user acceptability was described as excellent, although it was even better with the gels. Owing to the ease of its performance, the hygienic hand rub not only offers the advantage of being fast and efficacious but also has the potential to improve the compliance of healthcare givers with hand hygiene.

For hygienic hand rubs, only a few clinical correlates with results from disinfectant testing exist. In one controlled study trying to relate the use of alcoholic rubs to infection rates *(131)*, isopropanol was used in a way that cannot be regarded as a real hygienic hand rub, namely, with average volumes of 0.9 mL per application, which is much too small to cover the surface of both hands and to remain there long enough to exert bactericidal effects. The study demonstrates, however, that a hygienic hand wash with chlorhexidine detergent, which was also tested, is clinically more effective than an individual hand wash with soap and water, which was followed by rubbing a bit of alcohol onto the hands; the study also demonstrated that, despite a preceding intensive education program, it seems very difficult to persuade and motivate medical personnel to observe the simplest rules for the most efficient procedure in the prevention of healthcare-associated infections.

Because hand rubs have a high antimicrobial potential, they can also be used in situations where direct contact with dangerous pathogens has occurred, such as after spillage in the microbiology laboratory or after touching infectious lesions. A high-level requirement for efficacy is, therefore, justified. With this perspective, a requirement for the performance of a reference hand rub was formulated by the Austrian and German Microbiological Societies *(132,133)* and, finally, by the European Committee for Standardization (134), choosing among the best-acting rubs available. From these, 60% (v/v) isopropanol was taken arbitrarily as an active agent to be used in two portions, each of 3 mL, during a total disinfection period of 60 seconds. The requirement of EN 1500 is that the reduction of transient flora assessed with a product for hand rubs shall not be significantly inferior to that with the reference rub, when tested in parallel, with the same volunteers, on the same day, in a crossover fashion.

Hygienic Hand Wash

The objective of the hygienic hand wash with antiseptic soaps is to reduce the release of transient flora by a washing procedure of significantly stronger efficacy than that of an ordinary hand wash with unmedicated soap. Even if the effect on the resident flora is usually disregarded in most indications, a residual effect may be desirable in some areas, such as in protective isolation, during hospital outbreaks *(69,71)*, and for handling foodstuffs as well as pharmaceutical preparations. The technique is similar to that of a normal hand wash but is performed according to the instructions of the manufacturer. As with the hygienic hand rub, the antimicrobial spectrum required depends on the area of intended use. But, in general, an antituberculous or antiviral activity is not necessarily expected from these antiseptics.

Active agents most often used in detergent preparations are iodophors, chlorhexidine gluconate, triclosan, biphenylol, and chloroxylenol. Hexachlorophene is not used anymore because of its neurotoxic activity *(135–137)* after transdermal absorption *(135,137)* and its poor activity against gram-negative bacteria *(49,52,138,139)*. Amphotensides and quaternary ammonium compounds are better suited to act as adjuncts to alcohols than to being used as active agents alone, because they are easily neutralized by anionic detergents and—at least quaternary ammonium compounds—by protein and hard water.

Table 91-5 summarizes examples of results on general antibacterial efficacy as assessed by the test method of the

TABLE 91-5

Hygienic Handwash: Efficacy of Various Antiseptic Detergents in Reducing the Release of Test Bacteria from Artificially Contaminated Hands

Detergent	*Concentration (%)*	*Mean Log Reduction*
Povidone–iodine	0.75[a]	3.5[b]
Chlorhexidine gluconate	4.0[a]	3.1
Triclosan	0.1[c]	2.8
2-Biphenylol	2.0[c]	2.6
Octenidine	0.5[c]	2.5
Soft soap	20.0[a]	2.7

Duration of treatment: 1 min.
[a]w/v.
[b]Significantly superior to soft soap.
[c]w/w.
(From Rotter ML, Koller W. A European test for the evaluation of the efficacy of procedures of the antiseptic hand wash. *Hyg Med* 1991;16: 4–12, with permission.)

European standard EN 1499 (54,140). It can be seen that among five antiseptic detergents tested concomitantly, only povidone–iodine liquid soap would have met the pass criterion to be significantly more efficacious than unmedicated soap. The activity of chlorhexidine gluconate detergent was stronger than that of soft soap, although not quite significantly, at least in this test (54). It is important to note that the hygienic hand rub with 60% isopropanol, tested concomitantly as a control in the same experiment, caused a significantly stronger bacterial reduction (4.0 log) than any of the tested hand washes (54). These results compare well with those of Ayliffe et al. *(71)*, who found that alcohol-based preparations, particularly *n*-propanol and isopropanol, were the most effective, followed by chlorhexidine and povidone–iodine detergent preparations, all of which were significantly more effective than nonmedicated soap. However, triclosan-containing soaps were no more effective than nonmedicated soap. In these experiments, the chlorhexidine detergent was found to be significantly more effective than the povidone–iodine preparation.

These results demonstrate clearly that compared with other methods of postcontamination hand treatment, alcoholic hand *rubs* are, at present, the most effective measure to quickly reduce the release of transient microbial flora from the hands. Consequently, it may be inferred that alcohol-treated hands are less likely to transfer bacteria than washed hands. Indeed, this has been shown by Ehrenkranz and Alfonso *(141)*, who demonstrated that after contact with heavily colonized patient groins, hand washing failed to prevent the transfer of aerobic gram-negative bacilli by healthcare workers' hands to urinary catheters in 11 of 12 experiments; after hand treatment with 70% (v/v) isopropanol, however, bacteria were transferred in only 2 of 12 experiments. Furthermore, soap failed to stop subsequent colonization in each of the 12 experiments, whereas alcohol failed in only five. The authors concluded that soap was generally ineffective in preventing hand transfer of gram-negative bacilli to catheters after contact with a heavy contamination source, whereas alcohol was generally effective.

In another clinical trial, it was shown that measures of hand hygiene prior to the insertion of peripheral venous catheters significantly influenced the relative risk of infectious complications, in that local reddening, swelling, pain, purulence, or fever of unknown origin occurred in only 51% or 61% of cases when gloves were worn or hands were rubbed with an alcoholic rinse, respectively, as compared to washing hands with plain soap or no hand hygiene at all *(142)*.

Unfortunately, definitions for the requirements of the efficacy of procedures for both hand rub and hand wash can hardly be based on sound epidemiologic data. Besides Semmelweis' experience that soap and water was not sufficient for some situations *(77,79)*, only a few more or less well-controlled field trials relate the use of certain hand washing procedures to the infection ratio *(143–145)*. Even if one or another detail in these studies may be criticized, they all indicate that the use of disinfectants results in a reduced infection frequency as compared with the use of unmedicated soap or with no hand washing. If this is translated into terms of disinfectant testing, which is easier to do *(71,127)*, one might be tempted to speculate that disinfectant–detergents, exerting an antimicrobial effect similar to that of chlorhexidine detergent or better, may have the potential to reduce the frequency of healthcare infections more efficiently than ordinary soap. With this in mind, the European Committee for Standardization has decided that, as a pass criterion for the hygienic hand wash, the bacterial reduction assessed in a test simulating practical conditions shall be significantly greater than that obtained with unmedicated soap. This shall be tested in parallel with the same volunteers, on the same day, and in a crossover design (140).

Surgical Hand Disinfection

The objective of surgical hand disinfection is to reduce the release of skin bacteria from the hands of the surgical team for the duration of an operation in case the surgical glove is punctured or torn. The intention is, thus, to bring down the amount of bioburden in the glove juice as much as possible to keep the inoculum at and in the surgical wound below the threshold for induction of infection. The infectious dose varies, however, and is unknown in the individual case, because it depends not only on the kind and virulence of bacteria entering the surgical site but also on the effectiveness of the host's defense mechanisms. These mechanisms, however, can be impaired by circumstances determined by the type of surgery (such as implantation of foreign bodies), by the need to operate on patients with an impaired immune system, or by the failure to completely remove necrotic tissue.

Although at least one outbreak of surgical site infections was reported when an antiseptic scrub was replaced by unmedicated soap (146), in contrast to hygienic hand disinfection, rub, or wash, surgical hand disinfection has never been proven in a controlled study to be necessary or clinically effective. Nevertheless, it is justified, because it is an integral part of the concept of aseptic surgery, the value of which can be regarded as having been proved by Lister's findings. Indeed, indirect evidence for the necessity

of a further precaution in addition to the surgical glove can be drawn from results compiled by Cruse and Foord *(147)*, who reported for clean surgical sites an infection ratio of 1.7% if gloves remained intact but of 5.7% for operations where gloves were punctured. To keep the bacterial load low on the skin of gloved hands is therefore an important goal. Because latex gloves are vulnerable, they cannot be relied on. Hoborn *(148)* reported in a study on glove perforation that 38% of all gloves used by the surgical team in orthopedic surgery were perforated. The following details are of interest: left-hand gloves were more often perforated (47%) than right-hand gloves (29%). The surgeons' gloves were most often damaged (53%), followed by those of the operating nurse (41%) and the assistant (19%). The index finger of the left hand was the most endangered site (29%), followed by the palm (24%). The left index finger was involved in 43% of all specifically surgeon-associated perforations. In soft tissue surgery, glove punctures were found at a significantly lower frequency. The overall ratio was 16%; left-hand gloves were involved in 22% and right-hand ones in 11%. The sequence of persons was the same as above: surgeon, 28%; operating nurse, 16%; assistant, 4%.

These data confirm those reported earlier by Furuhashi and Miyamae *(149)*. A later study by Palmer and Rickett *(150)* arrived at similar conclusions.

Recently, the incidence of microperforations in surgical gloves has been investigated *(151)* by employing the "watertight test" described in the European norm EN 455, part 1 *(151)*. Wearing gloves for 90 minutes or less resulted in microperforations in 15.4%, whereas wearing them for 91 to 150 minutes showed results in 18.1% and again in 23.7% if gloves were worn for longer. There were no significant differences in the frequency of microperforations between the surgeons', the first assistants', or the surgical nurses' gloves (23%, 19%, and 20.5%, respectively). Sixty-seven percent were found on the left (nondominant) hand glove, predominantly on the left index finger (32.3%). Concluding from these results, the authors recommended that the above-mentioned members of the surgical team change gloves regularly after 90 minutes of surgery *(151)*.

In another study *(152)*, this problem was investigated in a clinical setting where double-gloving was used during septic laparatomies. To measure bacterial passage through punctures to the outside of the inner glove, a modified Gaschen-bag method was used for sampling. For distinguishing bacteria coming from the surgical site as opposed to those coming through perforations of the outer glove, intraoperative swabs were taken. Depending on the duration of glove wear, the maximum proportion of perforated outer gloves was 15%. Approximately 82% of these perforations remained unnoticed by the surgical team. A proportion of 86% occurred in the nondominant hand glove, with the index finger punctured in 36%. Bacterial passage from the surgical site onto the outside of the inner glove was detected in 4.7% of the gloves. Here, too, the authors recommended changing gloves every 90 minutes *(152)*.

The bacterial leakage through pinholes in gloves has been experimentally found to range between 10^3 and 10^4 CFU *(147,148)*. In contrast, when hands were disinfected before donning gloves, the bacterial counts from leaking gloves did not exceed 100 CFU *(149)*. In fact, clinical indications show a causal link between hand preparation of the surgical team and the incidence of surgical site infections (146).

Although the aim of surgical hand disinfection is to render hands microbiologically clean with as little microbial release as possible, the antimicrobial spectrum need not include tuberculocidal, fungicidal, or virucidal activity, because pathogens belonging to these groups of microorganisms do not usually cause surgical site infections. Bacterial spores can only be mechanically removed by scrubbing hands—a procedure that should be carried out regularly before the first operation on a day. Surgical antiseptics must be active against the resident flora and against bacteria that are associated with surgical site infection.

With regard to antimicrobial effects, an *immediate* effect must be distinguished from *sustained, cumulative*, and *persistent* effects *(153)*, the occurrence of which depends also on the frequency and regularity of contacts with the antiseptic, as follows:

- The *immediate* effect immediately follows the antiseptic procedure.
- After a single contact, the *sustained* effect is defined as short-term antimicrobial activity retarding bacterial regrowth, maintaining the viable count, or even further reducing the bioburden under the glove.
- After multiple contacts, the *cumulative* effect is a microbial reduction that increases with every application of the antiseptic.
- With regular contacts, the *persistent* effect is a progressive reduction of skin flora during a longer period. This is, for instance, demonstrable after several days of regular application *(154)*.

As at the time of the first operation after the weekend or after a vacation, the surgeon's hands should be as safe as after several days' use of an antiseptic, neither cumulative nor persistent effects are really advantageous. Furthermore, in the interest of colonization resistance, it is not desirable to completely eliminate the resident skin flora by multiple or regular use of a highly active antiseptic. Admittedly, to attain this would be very difficult, anyway. In contrast, a sustained effect may be desirable to keep the bacterial numbers low under the glove during an operation, especially if preparations with only moderate immediate effect are used for surgical hand antisepsis. Because most operations are completed within 3 hours and because during long-lasting operations gloves should be changed anyway, 3 hours may be a reasonable time span to check on this feature when testing the efficacy of products.

Because the technique of surgical hand disinfection is of considerable influence on the release of skin flora, it is described here in detail. Useful guidelines for the surgical hand scrub have been published by the Association of Operating Room Nurses (66) and, most recently, in the WHO guidelines (59) and by Widmer et al. (67). On entering the operating suite, hands should first be treated as if they were contaminated, and transients should be removed with a social hand wash or, preferably, with an alcoholic hand rub. Then, the subungual spaces should be cleaned with soft wooden sticks, because most bacterial flora resides under the nails *(83)*. Long-lasting wash procedures with unmedicated soap and scrubbing are counterproductive, because they cause skin damage without significantly

reducing the release of resident skin bacteria (5,*45,46,*47). In fact, a preceding treatment with soap may even hamper the effect of an alcohol treatment *(155–157)*. For this reason, clean hands should not be washed before applying an alcohol-based rub excepting the first presurgical hand preparation of the day. A soft brush should be used only to brush nails and subungual spaces but not the skin as this may cause damage. Sterile disposable sponges may also be used. Fingertips should always point upward, with elbows down, to avoid recontamination of clean fingers and hands by water running down from contaminated proximal areas. If hands were (pre)washed, drying them is of great importance if an alcohol rub is to be used subsequently to avoid its dilution. In this case, the towels—paper or textile—need not be sterile but clean.

There are two principal techniques of surgical hand disinfection, both of which have advantages and drawbacks. If performed with a suitable antiseptic such as one containing an alcohol at high concentration, the *surgical hand rub* is very efficient in reducing the skin flora and, after antisepsis, hands need only be air-dried. It lacks, however, the cleaning function of a *surgical hand scrub*. This, in turn, requires hand drying and is much less efficient (see below).

The *surgical hand rub* is performed by pouring a small volume (~3 mL) of a suitable antiseptic, usually an alcohol preparation, into the cupped dry hands, rubbing it onto the entire surface of hands and forearms, keeping them wet for the scheduled time by adding further portions as necessary, and carrying out wash movements. Usually, total volumes of 9 to 12 mL are needed for a 3-minute period. However, the applied volume is not important as long as hands are kept wet during the scheduled duration of application *(158)*. All other techniques, such as bathing hands in a bowl with an antiseptic solution, are either wasteful and create an increased risk of skin damage and fire hazard or their antimicrobial effect is poor as with alcohol wipes and sprays. In contrast, smoothly brushing an alcoholic preparation into the subungual spaces increases the effect considerably *(156)*. Alcohol-wet hands should not be gloved but air-dried before donning gloves to avoid skin damage. During and between operations, surgical rubs can easily be performed after removal of gloves.

The *surgical scrub* is performed with antiseptic detergents according to the instructions of the manufacturer. Drying hands with fresh one-way towels or sterile drapes is usually necessary before donning surgical gloves.

A combined two-phase technique that includes a surgical hand wash followed by a surgical hand rub may also be used. If the antimicrobial agents are properly chosen, hands may be cleaned with an antiseptic detergent without reducing the antimicrobial efficacy of the subsequent hand rub, as is the case when an alcohol-based rub immediately follows a hand wash with unmedicated soap *(157,159)*. In contrast, a hand rub should never be followed by a hand wash, because this has been shown to considerably lessen the effect of the rub (*160,*161,162,*163–174*).

The duration of any preoperative treatment of the surgical team's hands should be kept as short as possible but as long as necessary to attain the goal of keeping the bioburden in the glove low. From the literature and from results of our own laboratory-based experiments with volunteers according to EN 12791, which has been found to be workable and the results of which are reproducible (161), it can be shown that the antimicrobial effectiveness of both surgical hand rub and scrub is significantly associated with the duration of the procedure (Tables 91-6 and 91-7). In a recent *in vivo* study, the immediate effects of 1-, 3-, or 5-minute hand rubs with *n*-propanol 60% (v/v) were found to result in respective bacterial reductions of 1.0, 2.0, and 2.3 log. With isopropanol 70% (v/v), they amounted to 0.7, 1.5, and 2.1 log, respectively. This trend was highly significant ($p < .001$). The same was true for the 3-hour effects when gloves had been worn for 3 hours (162).

A duration of 3 minutes for presurgical hand antisepsis is common nowadays, but with highly effective alcohol-based products, 1.5 minutes are effective, as demonstrated in laboratory-based *in vivo* experiments *(163–166)*.

Also, in a clinical setting, it could be shown that application of a highly efficacious alcohol-based product during 1.5 minutes was sufficiently active, which confirms the above-mentioned experimental data *(167)*.

As a rule, when choosing surgical hand antiseptics, one should never rely on results from suspension tests as they differ greatly from those obtained from *in vivo* trials *(168)*.

There is only a limited list of possible agents that can be used for the surgical hand rub. An indication of their antimicrobial efficacy is shown in Table 91-6, in which results obtained by comparable test methods are compiled from the literature. A clear association of the bacterial reduction with the nature and concentration of the antiseptic and with the duration of application can be seen (*45*,46,47,*51,* 91,*106,156,159–160*, 161,162,*165,166,169–174,176,179*). Similar data have been produced also by more recent studies *(177,178)*. As with the hygienic hand rub, *n*-propanol is the most active of the agents listed, followed by isopropanol, ethanol, povidone–iodine solution, and peracetic acid. An aqueous solution of chlorhexidine gluconate alone exerts only a mediocre immediate effect but is the only agent listed with a definite sustained activity *(154)*. In combination with alcohol (in this case), ethanol 61% w/w, however, the results are considerably more favorable *(177,178)*; although in one study *(177)*, the magnitude of an immediate reduction of 2.5 log within approximately 2.0 to 2.5 minutes raises the suspicion of incomplete neutralization of the chlorhexidine gluconate adjunct (Table 91-6). (It is important to realize that insufficient neutralization can result in false-positive efficacy assessment (181)). The immediate effect of an aqueous povidone–iodine solution compares well with that of 60% (v/v) isopropanol. Among the list of hand antiseptics, peracetic acid must be disregarded for toxicological reasons.

As with products for hygienic hand disinfection, the preparation of hand antiseptics in the form of gels is a new trend. And indeed, one gel containing 85% (w/w) ethanol was found to pass the strict requirement of EN 12791 (129).

The efficacy of frequently used antiseptic detergents is shown in Table 91-7 and compared with that of unmedicated soap (*45,46,*47,*106,149,153,170,176,182–186*). Here again, the association between bacterial reduction and duration of hand wash can be seen, although it is not as strong as that seen with the rubs. Unmedicated soap, used for 5 minutes, has only a poor immediate effect and no sustained effect, whereas povidone–iodine liquid soap causes a significantly stronger immediate reduction but also remains

TABLE 91-6

Surgical Hand Rub: Efficacy of Various Rubs in Reducing the Release of Resident Skin Flora from Clean Hands

			Mean Log Reduction		
Rub	*Concentration[a] (%)*	*Time (min)*	*Immediate*	*Sustained (3 h)*	*References*
n-Propanol	60	5	2.9[b]	1.6[b]	*(45)*
	—	5	2.7[b]	NA	*(156)*
	—	5	2.5[b]	1.8[b]	*(159)*
	—	5	2.3[b]	1.6[b]	*(157)*
	—	3	2.9[c]	NA	*(170)*
	—	3	2.4	NA	*(170)*
	—	3	2.3	1.5	*(175)*
	—	3	2.0[b]	1.0[b]	*(157)*
	—	1	1.1[b]	0.5[b]	*(157)*
Isopropanol	90	3	2.4[c]	1.4[c]	*(169)*
	80	3	2.3[c]	1.2[c]	*(169)*
	70	5	2.4[b]	2.1[b]	*(171)*
	—	5	2.1[b]	1.0[b]	*(157)*
	—	3	2.0[c]	0.7[c]	*(169)*
	—	3	1.7[c]	NA	*(170)*
	—	3	1.5[b]	0.8[b]	*(157)*
	—	2	1.2	0.8	*(172)*
	—	1	0.7[b]	0.2	*(157)*
	—	1	0.8	NA	*(173)*
	60	5	1.7	1.0	*(107,171)*
Isopropanol + chlorhexidine gluconate (w/v)	70 + 0.5	5	2.5[b]	2.7[b]	*(171)*
		2	1.0	1.5	*(172)*
Ethanol	95	2	2.1	NA	*(153)*
	85	3	2.4[c]	NA	*(170)*
	80	2	1.5	NA	*(138)*
	70	2	1.0	0.6	*(172)*
	61 (w/w)	2–2.5	1.1	1.4	*(177)*
Ethanol + chlorhexidine gluconate (w/v)	95 + 0.5	2	1.7	NA	*(51)*
	77 + 0.5	5	2.0	1.5[d]	*(47)*
	70 + 0.5	2	0.7	1.4	*(172)*
	1.0	09	NA		*(178)*
	61 (w/w)	2–2.5	2.5	2.9	*(177)*
Chlorhexidine gluconate (aq. sol., w/v)	0.5	2	0.4	1.2	*(172)*
Povidone–iodine (aq. sol., w/v)	1.0	5	1.9[b]	0.8[b]	*(106)*
Peracetic acid (w/v)	0.5	5	1.9	NA	*(179)*

[a]v/v unless otherwise stated.
[b]Tested according to the method of *Deutsche Gesellschaft für Hygiene und Mikrobiologie (DGHM)*; German Society of Hygiene and Microbiology *(133)*.
[c]Tested according to European Standard EN 12791 *(180)*.
[d]After 4 h.
NA, not available.
(From Rotter M. Chirurgische Händedesinfektion. In: Kramer A, Gröschel D, Heeg P, et al., eds. *Klinische Antiseptik*. Berlin, Springer-Verlag, 1993:67–82, with permission.)

without noticeable sustained action. The immediate effect of a chlorhexidine gluconate (4%) detergent was found to be comparable to that of the former, but the tested product demonstrated prolonged activity.

In another study mentioned above *(177)*, an initial (first day) preoperative scrub resulted in an unusually high immediate bacterial reduction of 1.6 log and a first-day 3-hour effect of 1.8 log, raising the suspicion of an incomplete neutralization (Table 91-7).

For toxicological reasons, hexachlorophene should no longer be used for surgical hand wash. In contrast to the immediate effect, which is similar to that of unmedicated soap, it possesses strong sustained activity. Quaternary ammonium compounds such as benzethonium chloride,

TABLE 91-7

Surgical Hand wash: Efficacy of Various (Antiseptic) Detergents in Reducing the Release of Resident Skin Flora from Clean Hands

			Mean Log Reduction		
Detergent	*Concentration[a] (%)*	*Time (min)*	*Immediate*	*Sustained (3 h)*	*References*
Unmedicated	—	5	0.4[b]	–0.1[b]	*(45)*
	—	5	0.4[b]	NA	*(156)*
	—	5	0.4	0.0[c]	*(47)*
Povidone–iodine	0.8	5	1.1	0.3[c]	*(47)*
	—	5	1.0	NA	*(156)*
	—	5	1.0[b]	0.2[b]	*(106)*
	—	5	0.9[b]	0.2[b]	*(107)*
	—	2	0.5	NA	*(182)*
Chlorhexidine gluconate	4.0	6	1.2	NA	*(149)*
	—	5	0.9[b]	0.9[b]	*(45)*
	—	5	0.9	0.6	*(47)*
	—	3	1.2[d]	1.4	*(183)*
	—	3	0.9[d]	NA	*(149)*
	—	3	0.8[b]	1.0[b]	*(45)*
	—	3	0.8[b]	0.8[b]	*(107)*
		3	0.8	NA	*(178)*
	—	3	1.6	1.8	*(177)*
	—	2	0.9	1.6	*(184)*
	—	5	1.6	2.0	*(185)*
Hexachlorophene	3.0	4	0.3	1.0	*(153)*
Benzethonium chloride	10.0	6	1.3	NA	*(149)*
	—	3	0.9	NA	*(149)*
Zephirol	0.1	2	0.4	NA	*(176)*
	—	2	0.3	NA	*(182)*
Cetrimide	1.0	2	0.4	NA	*(182)*
Chlorocresol	0.3	2	0.4	NA	*(182)*
Triclosan	1.0	5	0.6	0.5[c]	*(47)*
	2.0	5	0.8	1.1	*(185)*

[a]w/v.
[b]Tested according to DGHM method (133).
[c]After 4 h.
[d]Tested according to European Standard EN 12791 *(180)*.
NA, not available.
(From Rotter M. Chirurgische Händedesinfektion. In: Kramer A, Gröschel D, Heeg P, et al., eds. *Klinische Antiseptik*. Berlin, Springer-Verlag, 1993:67–82, with permission.)

benzalkonium chloride, and cetrimide share comparable activity among each other. They are usually not used alone but, like chlorhexidine gluconate, are frequently added as supplements to alcohol rubs for synergistic and sustained effects that are, for instance, clearly demonstrable for chlorhexidine-alcohol preparations (Table 91-6). Triclosan shows some sustained activity, but even with five consecutive scrubs, each of 3 minutes, the bacterial reductions reported are rather disappointing *(185)*.

From the above results, it is evident that the antimicrobial efficacy of all antiseptic detergents currently available on the European market is significantly inferior to that of alcohol rubs or povidone–iodine aqueous solution. This is also depicted in Figure 91-2, which contains results that, except for hexachlorophene, were obtained by the same test method (*187*; updated 1993). From there, it can be seen that highly concentrated short-chain aliphatic alcohols, such as iso- and *n*-propanol, are up to 100 times more effective in reducing the release of skin bacteria. With this strong immediate effect, the question arises whether a sustained action, which is not demonstrable for alcohols, is needed and desired, as after such an extensive reduction, regrowth of the resident skin flora takes several hours for complete restoration (Fig. 91-2) *(188)*.

The consecutive use of a detergent and isopropanol, both containing chlorhexidine, results in a significant increase in effectiveness compared with unmedicated soap and alcohol (Table 91-8) *(149,159)*.

To develop a standard for the efficacy of surgical hand disinfection is difficult because epidemiologic information on the effectiveness of various procedures on the ratio of surgical site infections is not available. Therefore, it has been decided arbitrarily by the expert authorities in some European countries *(133,189)* to choose a reference

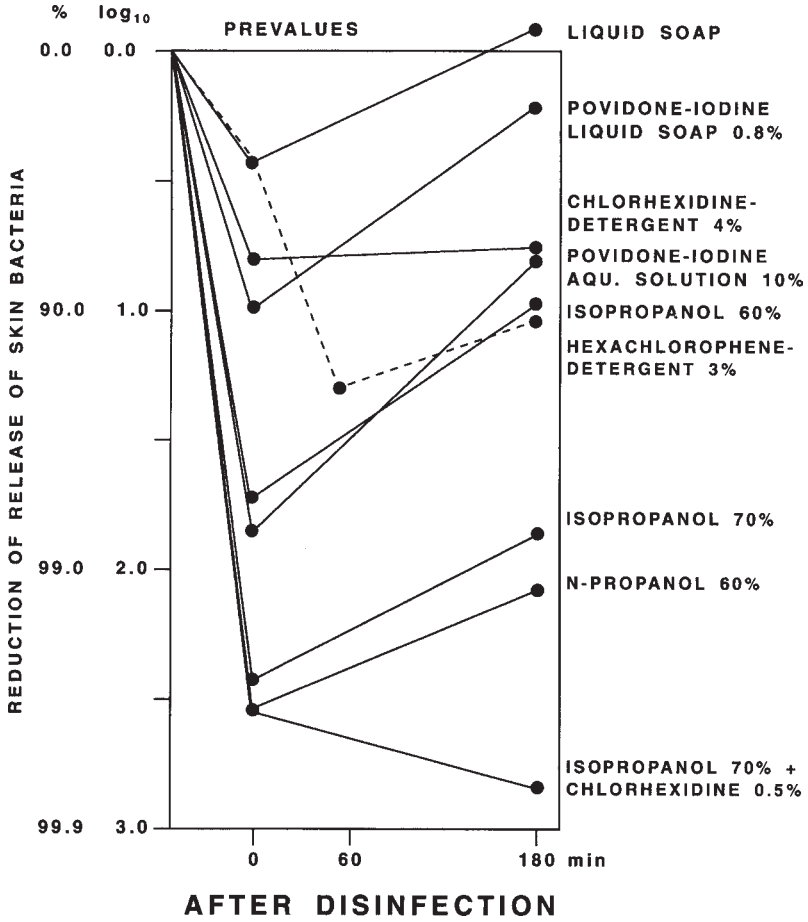

FIGURE 91-2 Killing curves showing the efficacy of various antiseptics for surgical hand disinfection (187; updated 1993) as assessed by the test model of the Austrian *(132)* and German *(133)* Societies for Hygiene and Microbiology and (for hexachlorophene, 4 minutes) according to the results of Michaud et al. *(153)*.

procedure for efficacy that ensures maximum reduction of skin flora at tolerable levels of skin strain and time expenditure. Efficacy, thus, is defined not by a numerically fixed measure of microbial reduction but by the mean reduction achieved by a reference disinfection procedure that is tested in parallel with a product to be evaluated with the same volunteers in two experiments that are carried out in a crossover design. Each volunteer acts as his or her own control. The requirement is then that the mean bacterial reduction assessed with the procedure under evaluation shall not be significantly inferior to that of the reference. This procedure involves rubbing and keeping hands wet with 60% (v/v) *n*-propanol (for details, see ref. *190*). For the European standard EN 12791 on surgical hand disinfection (180), a disinfection period of 3 minutes was chosen. With a well-trained team, the mean reduction in bacterial release will reach a magnitude of up to 2.9 log (Table 91-6). It is, however, unknown whether *in vivo* laboratory test results correlate with the ratio of surgical site infections. The results of one study comparing the clinical effect of a 75% alcoholic rub with that of surgical scrubs with either povidone–iodine or chlorhexidine (4%) gluconate detergents throw some doubts on this assumption: Although the bacterial reduction of skin flora achievable with the alcoholic rub was significantly superior to that assessed with the two scrubs, the clinical outcome of clean and clean–contaminated operations was virtually the same *(191)*. However, more data will have to be generated before a final conclusion will be possible.

COMPLIANCE WITH HAND HYGIENE

Compliance and Clinical Effectiveness of Hand Hygiene

As Elaine Larson *(192)* stressed more than a decade ago, even the most effective antiseptic procedure for removal of transient microbial flora from the hands is futile if it is ignored. Thus, compliance with the rules of hand hygiene is equally important for preventing the transmission of pathogens via hands and, by this, reducing the risk for the emergence of healthcare-associated infection.

By changing behavioral patterns of the staff and by creating an organizational climate in which hand hygiene was a definite goal, Larson et al. *(192)* succeeded, as a positive example, to reduce the incidence of infections due to methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant enterococci by considerably improving compliance to hand hygiene in two critical-care units of the intervention hospital as compared with the situation in comparable units of a control hospital.

In a similar attempt to promote hand hygiene by implementing a program with emphasis on alcohol-based hand rubs, Pittet et al. (193) improved the compliance of the

TABLE 91-8

Surgical Hand Disinfection: Efficacy of Consecutive Use of Chlorhexidine (4%)–Detergent and Chlorhexidine (0.5%)–Isopropanol (60%) as Compared with Unmedicated Soap and Alcohol

		Mean Log Reduction	
Washing (3 min)	*Rubbing in (4 min)*	*Immediate*	*Sustained (3 h)*
Unmedicated soap	Isopropanol	1.7	1.1
CHG-detergent	Isopropanol + CHG	2.5[a]	1.7[a]

[a]$p < .1$.
CHG, chlorhexidine gluconate.
(From Rotter ML, Koller W. Surgical hand disinfection: effect of sequential use of two chlorhexidine preparations. *J Hosp Infect* 1990;16:161–166, with permission.)

staff from 48% to 66% within 3 years. As a consequence, the overall ratio of healthcare-associated infections decreased from 16.9% to 9.9%. Also, the transmission frequency of MRSA decreased from 2.16 to 0.93 episodes per 10,000 patient days.

Likewise, in five wards of a rehabilitation hospital, Girou et al. observed a strong negative association of the degree of hand hygiene compliance and MRSA prevalence *(194)*.

In another study, it was found that the carrier rate of rifampicin-resistant MRSA, being as high as 38.4 patients per 1,000 occupied beds—thought to result from bad hand hygiene practices—dropped to an average monthly rate of MRSA acquisition of 3.2 patients per 1,000 occupied beds during the period from October 2004 to October 2005. This was thought to be the consequence of implementing several hygiene measure interventions including the empowerment of the nurse at the bedside to be the patient's advocate *(195)*.

To cite another example of the beneficial effects of hand hygiene, in a neonatal unit, a three-phase intervention–observation study was conducted, comprising a multifaceted education program with hand hygiene compliance assessed during successive observational surveys and prospective monitoring of healthcare-associated infections. Across three study phases, the overall compliance improved from 42% to 55%, accompanied by an increase in hand rub consumption from 66.6 to 89.2 L per 1,000 patient days. This improved adherence to hand hygiene was independently associated with a reduction of the infection ratio among very low weight neonates from 15.5% over 10.7% to 8.8% per 1,000 patient days *(196)*.

Although the association of compliance with hand hygiene and infection ratio seems logical, the correlation is not that simple for various reasons: interventions to reduce the frequency of healthcare-associated infections are usually multimodal; hence, it is often difficult to ascribe a desired clinical effect to one measure alone, as, for instance, in the case of improving compliance *(197)*. Besides the degree of adherence to hand hygiene, other factors are equally important, such as the infection susceptibility of the patients, the number of potentially "dangerous" contacts (with respect to the transmission of pathogens), the effectiveness of a hand hygiene measure (with respect to its microbicidal efficacy and the quality of performance), the degree of nurse cohorting (number of patients one nurse has to care for), and the number of potential transmission pathways. The interaction of these factors has intelligently been laid down in a mathematical model by Austin et al. and by Beggs et al. *(198,199)*.

Considering these factors, it is not surprising that some authors have had the experience that compliance with hand hygiene is not necessarily associated with detectable changes in the incidence of healthcare-associated infection for whatever reasons *(69,200)*.

Monitoring the frequency of transmission episodes of nosocomial pathogens and the frequency of healthcare-associated infections in five ICUs, Eckmanns et al. *(201)* also found no correlation between the incidence of transmission episodes and hand hygiene compliance (as well as hand rub consumption). However, they noted that, in their study, the infection ratio was a relatively good indicator for the identification of pathogen transmission.

In a concise review, Allegranzi and Pittet *(202)* have recently summarized the most relevant studies assessing the impact of hand hygiene promotion on healthcare-associated infections and came to the conclusion that multimodal intervention strategies lead to improved hand hygiene and to a reduction in nosocomial infection; however, this could not be demonstrated in some studies.

Motives and Attitudes for Compliance

To understand motives and attitudes and to identify reasons for poor compliance, many studies have been carried out since the early 1980s. They were summarized by Pittet and Boyce *(203)*. An analysis of their own data by Pittet et al. (204) revealed that the average compliance was found to range below 50%, although it varied greatly. Doctors were less compliant than nurses, and the following risk factors for poor compliance were found: being a doctor (odds ratio [OR] 2.8 vs. nurse) or a nursing assistant (OR 1.3 vs. nurse), working during the week (OR 1.7 vs. weekend), activities with high-risk of cross-contamination (OR 1.8 vs. low risk), working in ICU (OR 2.0 vs. internal medicine units), and high intensity of patient care (OR up to 2.1 vs. low intensity).

In a study to elucidate behavioral determinants of hand washing among nurses, Whitby and McLaws *(205)* undertook an investigation, employing in focus-group

discussions supported by professional market researchers a semistructured interview technique and a questionnaire to explore attitudes, beliefs, and practices on hand washing. Responses from 754 nurses were analyzed by backward linear regression for hand washing intention. The authors reasoned that hand washing results in two behavioral practices, which they called "inherent" and "elective" hand washing. The former is an emotional driver and occurs when healthcare workers perceive themselves as "at risk" and cleanse their hands for self-protection, usually with water. The latter is acquired by education and is significantly predicted by nurses' belief in the benefits of hand hygiene, by peer pressure of seniors, and by role modeling but only to a minimal extent by the reduction in effort in changing from hand washing to a hand rub routine without having to use water. Therefore, the authors believe that the introduction of hand rubs alone without an accompanying behavioral modification program is unlikely to induce a sustained increase in hand hygiene compliance.

Another study, also based on structured interviews with nurses, physicians, medical residents, and medical students in five hospitals, led to the conclusion that beliefs about self-protection are the main reasons for performing hand hygiene and that a lack of positive role models and social norms may hinder compliance with hand hygiene *(206)*.

The importance of role models with respect to hand hygiene has also been found by others to be a significant factor for compliance, whereas increasing the number of hand-washing sinks, as a sole measure, had no positive effect in a newly built hospital *(207)*.

To quantify the behavioral determinants of healthcare workers' motivation to comply with hand hygiene, a cross-sectional study in a university hospital with a long history of hand hygiene campaigning revealed that perceptions that nosocomial infections are severe for the patients, that hand hygiene is effective at infection prevention, that pressure from superiors and from colleagues is important, and that hand hygiene is easy to perform was rated higher for motivation than reasoning about the impact of hand hygiene on patient safety *(208)*.

Other means of improving adherence with hand hygiene have been proposed, such as patient information and empowerment *(209)* or utilizing social marketing methods *(210)*. Also, certain logistic methods for planning hand hygiene campaigns have been proposed *(211)*.

ACCEPTABILITY OF HAND WASHING AND HAND DISINFECTION

To ensure compliance with hand washing rules, detergents and antiseptic preparations must be acceptable to the user *(212)*. Healthcare personnel often complain about dry skin, skin irritation, or even frank symptoms of acute irritant contact dermatitis, which increase the risk of colonization with potential pathogens from the hospital environment *(23,213)*. Therefore, suitable preparations should have minimal toxicity of any kind, including allergenic and irritant properties. However, only a few chemicals meet this requirement to an acceptable degree.

Frequent application of alcohol preparations may cause skin drying and, in some persons, irritant dermatitis *(175)*. Defatting of the skin is sometimes suspected as one of the possible reasons (47), but this seems more likely to occur with detergents that remove skin lipids, whereas evaporating alcohols leave dissolved fats behind. On the whole, skin dryness from frequent alcohol application is usually mild and may be easily prevented by the addition of suitable emollients to alcohol-based hand antiseptics. In a study evaluating the effect of emollients in alcohol-based hand rubs, even after extensive usage, a blinded dermatologist had difficulty identifying differences in the condition of hands treated with *n*-propanol with or without emollients *(175)*. Contrary to a general opinion in countries where alcohols are not much used for hand disinfection, they have been found well acceptable to healthcare personnel with less drying than, for instance, chlorhexidine-containing detergents *(177,178,191,203,214–217)*. Common mistakes in the use of alcohol-based hand rubs have been identified in applying them onto preirritated skin and washing hands before hand antisepsis *(218)*. Short-chain aliphatic alcohols are very rarely allergenic.

In contrast, it seems that many detergent antiseptics possess a certain allergenic potential. But reports on the acceptability of the various agents are contradictory, depending probably on the composition of the product with regard to emollients *(23,71)*. This may signify that variables other than the antiseptic agents may be involved in reported adverse reactions.

For chlorhexidine gluconate, the allergenic potential seems proven *(219)*. Reports on adverse reactions after application of chlorhexidine-containing preparations, however, do not always permit conclusions to be drawn as to whether they were the consequence of true allergies or other reactions *(220)*. In an ethanol-based preparation, it proved significantly more acceptable than in a detergent-based product *(215)*.

Povidone–iodine- and triclosan-containing products were judged differently, depending on the individual preparation *(23,71,221)*; therefore, a general judgment does not seem possible. In one report, the acceptability of triclosan detergents was comparable with that of soap and of a chlorhexidine detergent and better than that of ethanol and povidone–iodine liquid soap; the latter was considered especially harsh (47). In another report among 14 products, a triclosan preparation was noticed to be especially harsh, whereas two other triclosan detergents did not cause noticeable skin damage *(71)*.

Chloroxylenol is a proven allergen. The incidence of allergic reactions has been reported by the North American Contact Dermatitis group to be around 1% *(23)*.

A list of potentially allergenic agents used as hand antiseptics was published by Lautier et al. *(222)* in 1978. It contains relevant agents and indices for primary inflammation and surface irritancy according to dermatologic criteria.

Absorption of alcohols during frequent hand antisepsis with alcohol-based formulations also needs to be dealt with. With a view to the conditions in practice, there are two routes by which absorption can occur: dermal and pulmonary. A study by Turner et al. assessing blood alcohol levels in 10 healthy volunteers before and after applying an isopropanol-containing hand rub onto their hands every 10 minutes over a 4-hour period revealed that, after the final application, concentrations within a range of 0.5 to 1.8 mg/L

(corresponding to 0.0005–0.0018%) were measurable. From these results, the authors concluded that they had proved transdermal absorption (although they had not reported any preventive measures against pulmonary absorption, which, without protecting the breathable air, must inevitably have occurred!). These blood levels seem rather low, although it was reasoned that a 4-hour test is much shorter than a nurse's shift, so in real life under similar conditions, higher concentrations could accumulate *(223)*.

In a more recent study, the total dermal and pulmonary absorption of ethanol after excessive hand disinfection was studied by Kramer et al. (224). Twelve volunteers applied three hand rubs containing 95%, 85%, or 55% ethanol onto their hands. For hygienic hand disinfection, 4 mL were used 20 times for 30 seconds each time with a pause of 1 minute between applications. The highest median blood levels amounted to 20.95 mg/L, 11.45 mg/L, and 6.90 mg/L (equaling 0.02%, 0.011%, and 0.007%), respectively. The highest median acetaldehyde concentration was 0.57 mg/L after 30 minutes. For surgical hand antisepsis, 20 mL of each hand rub was applied to hands and forearms 10 times for 3 minutes each time with a break of 5 minutes between applications. The highest median of ethanol blood levels for the three products were 17.50 mg/L, 30.10 mg/L, and 8.80 mg/L, respectively (equaling 0.017%, 0.029%, and 0.008%). The highest median acetaldehyde level was assessed to be 3.99 mg/L. The dermal and pulmonary absorption of ethanol was rated to be below toxic levels in humans, and it was concluded that the use of the evaluated ethanol-based hand rubs is safe (224).

AGENTS USED FOR DISINFECTION OF HANDS

This section summarizes the agents most often used for hand disinfection. Hexachlorophene is not included, because it is no longer an accepted ingredient of hand and skin antiseptics.

Alcohols

Only short-chain aliphatic alcohols that are completely miscible with water are used as the main carriers of antimicrobial activity in hand rubs. These are ethanol and iso- and *n*-propanol. Although it is also a member of this group, methanol is seldom used. Low concentrations of higher alcohols such as butanol and aromatic alcohols such as benzylalcohol are sometimes contained in alcoholic preparations as synergistic supplements.

The antimicrobial effect of alcohols is based on protein denaturation. Alcohols have excellent, and the most rapid, bactericidal and fungicidal activity of all agents used in hand disinfection. They also possess good mycobactericidal activity. Enveloped viruses, including HIV, are readily inactivated, with rabies virus being the only exception. Inactivation of naked viruses such as picornavirus takes longer and requires higher concentrations (from 80% v/v upward), as does HBV. Dry bacterial spores may survive in alcohols for long periods of time *(225)*. Alcohols evaporate quickly from the skin and do not have a sustained activity. Because of their extraordinarily high bactericidal activity, including good activity against the resident skin flora, the latter property may, in fact, be needed only in surgical antisepsis or in special situations such as in protective isolation. After a 3- to 5-minute exposure to high concentrations of iso- or *n*-propanol, it takes the resident flora several hours to regrow to the original level (Fig. 91-2).

As shown in Tables 91-4 and 91-5, the bactericidal activity decreases in the order *n*-propanol > isopropanol > ethanol. From the available data *(226,227)*, it appears that identical bactericidal activity can be expected on the skin at the following concentrations (v/v): 42% *n*-propanol = 60% isopropanol = 77% ethanol. Methanol is infrequently used because of its toxicity and because of its relatively poor activity *(227)*.

The addition of some chemicals may increase the immediate effect of alcohols significantly and/or provide a sustained effect. With a supplement of 1% (v/v) hydrogen peroxide, the activity of ethanol was, for instance, increased by 0.26 log *(228)*, and with lower concentrations, the alcohol may even become sporicidal during storage *(229)*. This feature is used in the two WHO formulations, which contain final concentrations of 0.125% hydrogen peroxide (59). A combination with 1% to 2% iodine is classic and known as "iodine tincture." It must, however, be removed from the skin after drying because of possible skin irritation *(154)*. With low concentrations of iodophors as a supplement, no noticeable improvement was seen *(45)*. Additions of chlorhexidine, quaternary ammonium compounds, ampholytic and phenolic compounds, triclosan, and octenidine serve mainly to furnish the alcohol with sustained activity *(102)*. Organic matter slightly diminishes the antimicrobial activity of alcohols *(87)*. With blood, a bacterial reduction of 3.6 log resulting from a short-time rub (30 seconds) was diminished by 0.1 to 0.4 log, and after a longer rub (60 seconds), one of 3.8 to 4.4 log was diminished by 0.2 to 0.7 log *(228)*.

Short-chain alcohols are flammable. Because there exist strict fire regulations in most countries, which require special storage conditions for liquids with a flash point <21°C (easily flammable), it may be wise to shift the flash point of alcohol-based formulas above this critical temperature. Products such as these are categorized as "flammable," can be stored in larger volumes and at less stringent conditions, and meet these safety requirements at the following (or lower) concentrations (v/v), which have been assessed according to EN 22719: ethanol ≤68%, isopropanol ≤70%, and *n*-propanol ≤82%. Mixtures of ethanol or isopropanol with the latter alcohol increase both the flash point and the antimicrobial efficacy.

In the fields of application discussed above, alcohols are nontoxic; they also lack allergenic potential. Skin drying and irritant skin reactions may be avoided by adding suitable emollients such as glycerol, volatile silicone oils, refatting agents, and probably most importantly, rehydrating agents.

Iodophors

The use of elemental iodine as (alcoholic) tincture of iodine or as an aqueous solution of potassium iodine (Lugol's solution) has, nowadays, been replaced by preparations containing complexed iodine, usually with polyvinylpyrrolidone, polyether glycols, or polyoxyethanol derivatives, for better acceptability. The main mechanism of

microbicidal activity is based on the oxidizing potential of iodine. It is important to note that the strongest antimicrobial effect occurs with dilute rather than concentrated iodophor solutions *(230,231)*, the latter of which have sometimes been found to harbor live bacteria *(232)*. As can be noted from Tables 91-4, 91-5, and 91-6, an aqueous solution of povidone–iodine, the most commonly used iodophor, is approximately as effective in reducing skin flora as 60% (v/v) isopropanol, but preparations in liquid soap are much less active.

The antimicrobial spectrum of iodine preparations is wide, even including bacterial spores *(233)*. But in hand disinfection, this latter activity is too slow to be useful *(49,234)*. There are, however, important gaps in the spectrum, especially with enteroviruses *(235)*. If at all present, a claimed sustained effect is small and only short-lived (91,*236*). Organic matter reduces antimicrobial activity slightly *(231)*, but blood may abolish the antimicrobial effect altogether *(228,237)*. One gram of hemoglobin can inactivate 58 mg of iodine *(238)*. Unless special precautions are taken, the antimicrobial efficacy of povidone–iodine preparations wanes during storage *(231)*.

Because iodine is absorbed through the intact skin of neonates and across mucous membranes, the use of iodine-containing preparations may be associated with undesired side effects such as hypothyroidism and allergic reactions. But this is seldom a problem with iodophors in the field of application discussed here. In contrast, skin irritation and damage occur rather often, and may thus, adversely influence compliance with hand disinfection (47,*239*). However, acceptability may vary with the type of preparation and brand.

Chlorhexidine

Chemically, chlorhexidine is a cationic bisbiguanide compound. Its most commonly used water-soluble form is the digluconate salt, but the acetate and hydrochloride have also been used *(240,241)*, and hydrochloride is used in a powder preparation. There are aqueous and alcoholic solutions and detergent preparations. Chlorhexidine is incompatible with some nonionogenic chemicals, such as Tween 80, and with some anions, such as soap, phosphates, and nitrates. Some protein-containing solutions such as pus, blood, serum, or milk interfere slightly with the antimicrobial effect, which is best at pH 8 *(240,241)*. Chlorhexidine exerts its antimicrobial activity by increasing the permeability of the microbial cell, causing disruption of the cytoplasmic membrane and precipitation of the cellular contents. The antimicrobial spectrum is broad. There are, however, gaps that should be known. The activity against gram-positive is better than the activity against gram-negative bacteria and against fungi; activity against mycobacteria is poor. Chlorhexidine has no sporicidal activity. It is effective against lipophilic viruses *(242)* but hardly active against nonenveloped viruses such as entero-, rota-, and adenoviruses (58).

The immediate antibacterial activity is definitely slower than that of alcohols (91), but the residual effect of chlorhexidine, which is based on the strong affinity for surfaces, is regarded as being probably the best of any antiseptic available *(242,243)*. This feature has been and is still being used in surgical hand antisepsis to extend the antimicrobial activity of alcohols on the gloved hand (Table 91-6 and Fig. 91-2) and is thought to build up an antimicrobial layer when used permanently *(159)*. However, the question was raised whether this sustained effect is real or originates only from methodical difficulties in neutralizing its bacteriostatic activity in the various test models *(244)*. In a clinical study, the rate of central catheter–associated infections was significantly reduced by preparation and regular care of the site at the catheter entrance with chlorhexidine as compared with alcohol alone or povidone–iodine treatment *(245)*. When chlorhexidine was used for routine hygienic hand washes in ICUs as opposed to hand washing with unmedicated soap, a reduction of hospital infections was observed *(131,143–145,246)*.

Except for ototoxicity when instilled into the middle ear *(247)*, chlorhexidine is regarded as a safe antiseptic, even when used regularly on the skin of newborn infants *(248,249)*. There is no indication of absorption through the adult skin *(249,250)*, but low levels (up to 460 mg/L) were found in venous blood specimens of babies bathed with a chlorhexidine-containing detergent at the age of a few days *(251)*. Potential toxicity, however, was rated low *(252)*. Skin irritation is usually regarded as low *(233)* but not always *(220)*.

Triclosan

This trichlorinated dioxydiphenylether (Irgasan DP-300) is poorly soluble in water but dissolves well in alcohols and various detergents, such as anionic soaps. It is incompatible with lecithin and some nonionogenic detergents such as Tween 80 *(253)*. It probably acts on the cytoplasmic membrane of the microbial cell. Except for *Pseudomonas aeruginosa,* the antibacterial spectrum is broad, mainly bacteriostatic, with minimal inhibitory concentrations between 0.1 and 10 mg/L but with minimal bactericidal concentrations of 25 to 500 mg/L at 10 minutes of exposure *(253)*. Acceptable mycobactericidal activity has been reported *(219)*. Fungistatic (10 mg/L) and fungicidal (25 mg/L per 10 minutes) activities toward *Candida* species are good *(254)* but poor against molds such as *Aspergillus* species (minimal inhibitory concentration 100 mg/L). Triclosan is contained in detergents (0.4–2%); in alcohols (0.2–0.5%) used for hygienic and surgical hand or preoperative skin disinfection; and in many cosmetic products such as soaps, toothpaste, and deodorants. Compared with alcohols and even iodophors and chlorhexidine, its immediate effect is slow but more rapid than that of hexachlorophene. Although not as strong as that of chlorhexidine gluconate *(255)*, there is a definite sustained effect (Table 91-7) that is minimally affected by organic matter or blood *(256)*. There is no indication in the literature that triclosan has a toxic, allergenic, mutagenic, or carcinogenic potential for humans, although it is very toxic for aquatic organisms. Acceptability of use on the hands was rated differently.

Phenol Derivatives

Only a short synopsis is given here inasmuch as phenol derivatives are less used today than in past decades because of ecologic concerns.

2-Phenylphenol (2-Biphenylol, 2-Hydroxybiphenyl, 2-Phenyol) This agent is similar to chlorocresol and is incompatible with nonionogenic detergents, quaternary ammonium compounds, and proteins. It has a broad

antimicrobial spectrum, including mycobacteria, fungi, and viruses such as adenovirus, herpes, and influenza but not enteroviruses; in combination with propanols and detergents, 2-phenylphenol is active against HBV. Fields of application include hygienic hand wash (2%), skin antisepsis (0.2%), and preservation of cosmetics *(253)*. Rotter and Koller (54) did not observe activity significantly different from that of unmedicated soap when used for 1-minute hand washes. A sustained antimicrobial effect has been reported *(253)*. In appropriate concentration, it is well tolerated and nontoxic for humans.

Chlorocresol (4-Chloro-3-Methylphenol) This agent is poorly soluble (0.4%) in water but dissolves well in alcohols. It is incompatible with nonionogenic detergents and quaternary ammonium compounds. Chlorocresol is usually used in combination with other phenol derivatives in alcohols or soap for hygienic hand disinfection. It is a weak allergen, has low toxicity in appropriate concentrations, and is well tolerated *(253)*.

Chloroxylenol (Para-Chloro-Meta-Xylenol) This agent is similar to chlorocresol but has slightly better antimicrobial activity due to enzyme inactivation and cell wall alteration. It has a broad antimicrobial spectrum, including mycobacteria and some viruses (e.g., vaccinia). The bactericidal effect is less than that noted for chlorhexidine and iodophors *(257,258)*. It exerts some sustained effect. Organic matter has little impact on its effectiveness. It is used for hygienic hand washes in concentrations of 0.5% to 1%. The highest allowable concentration as a preservative in cosmetics in European countries of the Common Market is 0.5%, but in toilet and deodorant soaps, it may be used at a concentration of 2% *(238)*. It is less toxic than chlorocresol and has been documented to be a mild allergen.

Quaternary Ammonium Compounds

Common properties of this group of agents, which include benzalkonium chloride, benzethonium chloride, cetrimide, and cetylpyridinium chloride *(253)*, are as follows: They are mainly bacteriostatic and fungistatic, as well as microbicidal, but only at high concentrations, especially against gram-negative bacteria (*P. aeruginosa*); they have no activity against mycobacteria but are active against some viruses, especially in combination with alcohols (lipophilic viruses, rabies); they are incompatible with anionic detergents and have reduced effectiveness in the presence of organic matter and ion-rich water. Nowadays, these compounds are seldom used alone for skin and hand disinfection but are rather used in combination with other antiseptics, such as alcohols, to confer on them a sustained effect. Quaternary ammonium compounds have low allergenic and toxicity potentials, but these undesired effects are usually 3 to 10 times more frequent than observed with the substituted phenol derivatives discussed above *(253)*.

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CHAPTER 92

Education of Healthcare Workers in the Prevention of Healthcare-Associated Infections

Karen K. Hoffmann and Eva P. Clontz

In the healthcare setting, ongoing education is required for several reasons. First, all healthcare providers need to participate in ongoing education to remain abreast of the scientific innovations in the field of infection control. Second, technological innovation demands learning new skills. Examples include the increasing use of computers in managing and analyzing healthcare-associated infection surveillance data and the increasing use of molecular epidemiology to evaluate healthcare-associated outbreaks. Third, regulatory bodies (e.g., Occupational Safety and Health Administration [OSHA] and The Joint Commission) require that workers receive ongoing training in a variety of areas depending on their job duties. Such training includes instruction on isolation techniques, aseptic practices, prevention of blood and body fluid exposure, and proper handling of hazardous chemicals.

The results of the national certification examination job analysis survey, administered to infection preventionists (IPs) between 1982 and 2010 by the Certification Board of Infection Control and Epidemiology (CBIC), consistently identified the task of education as one of the major areas of responsibility for IPs *(1)*. The 2010 analysis includes tasks in education and research (Table 92-1) *(2)*.

This chapter discusses education of healthcare personnel and patients/patient caregivers for the prevention of healthcare-associated infections and reviews educational requirements mandated by government and licensing agencies and research findings regarding education about specific areas in infection control. The chapter also includes a brief introduction to human factors engineering (HFE), learning theory, and the educational program planning process.

Practice competencies for infection prevention and control education were identified by a Delphi panel of experts in 2008. The final matrix of competencies may be a first step toward the development of a framework for standardized infection prevention education and training materials for hospital-based healthcare workers. The next step will be using the matrix to determine the validity of training materials (Table 92-2) *(3)*.

INFECTION CONTROL EDUCATION FOR HEALTHCARE WORKERS

Regulatory Educational Standards

The Joint Commission expects that new employees will receive orientation that covers the organization's infection control program and the individual's role in the prevention of infection. Another suggested activity is that continuing education be part of a problem-oriented or outbreak response. When infection rates are not reduced by the feedback of surveillance rates alone, The Joint Commission suggests using innovative educational approaches beyond the routine or standard in-services. Another expectation is for at least yearly education and training of all personnel to maintain or improve knowledge and skills based on findings from infection control activities such as healthcare-associated infection rates or outbreak investigations *(4)*.

The OSHA Occupational Exposure to Bloodborne Pathogens: Final Rule requires appropriate training for employees who are reasonably anticipated to come into contact with blood or other potentially infectious materials in the performance of their job duties. The standard mandates training initially upon an employee's assignment and annually thereafter *(5)*. The OSHA Compliance Directive CPL 2.106 Enforcement Procedures and Scheduling for Occupational Exposure to Tuberculosis (TB) requires worker training and information to ensure appropriate recognition and isolation of TB-infected patients *(6)*. Specific training elements must be included for each of these standards. Training records for blood-borne pathogens must be maintained for 3 years and must include dates, contents of the training program or a summary, the trainer's name and qualification, and names and job titles of all persons attending the sessions *(5)*.

Educational Offerings Designed for Infection Preventionists

Formal education specifically designed for the training of healthcare professionals in infection control began with a

TABLE 92-1

Association for Professionals in Infection Control and Epidemiology (APIC) Major Educational Tasks Cited by Infection Control Professionals

Education and Research

Education

1. Assess needs, develop goals and measurable objectives, and prepare lesson plans for educational offerings
2. Apply principles of adult learning to educational strategies and delivery of educational sessions
3. Prepare, present, or coordinate educational workshops, lectures, discussion, or one-on-one instruction on a variety of infection prevention and control topics
4. Evaluate the effectiveness of education and learner outcomes (e.g., behavior modification and compliance rate)
5. Instruct patients, families, and other visitors about methods to prevent and control infections

Research

1. Apply critical reading skills to evaluate research findings
2. Incorporate research findings into practice through education and consultation

(From Fabrey LJ. *A practice analysis of the infection preventionist: executive summary*. Applied Measurement Professionals, Inc. and CBIC. Milwaukee, WI, 2010.)

course offered by the Centers for Disease Control and Prevention (CDC) in 1968 *(7)*. This course plus additional training courses were offered by the CDC for many years but were discontinued in 1988 *(8)*. In 1989, the Association for Professionals in Infection Control and Epidemiology (APIC) assumed responsibility for offering training courses for infection control, and education remains the organization's top priority *(9)*. In addition to APIC, sponsors of infection control conferences, webinars, and workshops include APIC chapters in states and regions and specialized training programs, such as at the University of North Carolina at Chapel Hill. Graduate education in infection prevention was limited to master's degree programs in public health and nursing until 2010 when the Health Resources and Services Administration funded the Infection Prevention and Environmental Safety track within the Doctor of Nursing Practice Program at Loyola University Chicago Marcella Niehoff School of Nursing. The Study on the Efficacy of Nosocomial Infection Control Project findings emphasized the need for physician training in infection control. In response, the Society for Healthcare Epidemiology of America and the CDC provide a training course in healthcare epidemiology for physicians *(10)*.

TABLE 92-2

Infection Prevention and Control Competencies

- Basic microbiology: Describe the role of microorganisms in disease
- Modes/mechanisms of infection/disease transmission: Describe how microorganisms are transmitted in healthcare settings
- Standard and transmission-based precautions: Demonstrate standard and transmission-based precautions for patient contact in healthcare settings
- Occupational health: Describe occupational health practices that protect the healthcare worker from acquiring infection
- Patient safety: Describe occupational health practices that prevent the healthcare worker from transmitting infection to a patient
- Emergency preparedness: Define the importance of healthcare preparedness for natural or man-made infectious disease disasters

(From Carrico et al. Infection prevention and control competencies for hospital-based health care personnel. *Am J Infect Control* 2008; 36:691—701.)

A survey by the National APIC Education Committee investigated the use of outdated infection control practices or rituals. Outdated practices were more likely to be used by persons who were not certified by the CBIC and who worked in long-term–care facilities or in smaller hospitals rather than larger hospitals. However, certified respondents were no more likely than noncertified respondents to be interested in changing any rituals (11).

The CBIC administers the process for Certification in Infection Control (CIC). APIC founded CBIC in 1981, and the first examination was administered in 1983. CBIC is a voluntary, autonomous, multidisciplinary board that provides direction for professionals in infection control and applied epidemiology. The principal purpose of CBIC is to provide public protection by providing and measuring a standard of knowledge desirable for practicing professionals, to encourage professional growth and individual study, and to recognize individuals who fulfill the requirements for certification. Eligibility requirements include a current license or registration as a medical technologist, physician, or registered nurse, or a minimum of a baccalaureate degree. To use the designation CIC, the professional must meet the eligibility requirements and pass an examination. To maintain certification, professionals must recertify every 5 years *(12)*. In 1999, The Joint Commission required that individuals who oversee infection control activities be "qualified in infection control practices through education, training, experience, or certification" *(13)*. As The Joint Commission standards change, it continues to require specific education (Table 92-3).

APIC provides numerous educational resources, most importantly the curriculum manual, *APIC Text of Infection Control and Epidemiology*, and *Certification Study Guide*, continuously updated online. In addition, webinars, toolkits, and prevention guides are available.

Infection control education begins in college programs for healthcare workers; however, this subject is inadequately presented before clinical experience. Instruction in microbiology (the basis for understanding transmission of infectious diseases) is not required in many schools of nursing, and when infection control material is presented, it is frequently presented by someone lacking the expertise of an IP *(14)*. Education of house officers on infection control is determined by individual training programs.

TABLE 92-3

The Joint Commission Accreditation Program—Education

Hospital National Patient Safety Goals, Effective July 1, 2010—NPSG.07.05.01 Elements of Performance

- Educate staff and licensed independent practitioners involved in surgical procedures about surgical site infections and the importance of prevention. Education occurs upon hire, annually thereafter, and when involvement in surgical procedures is added to an individual's responsibilities
- Educate patients, and their families as needed, who are undergoing a surgical procedure and surgical site infection prevention

HR Standards, Effective January 1, 2009

- HR.01.04.01—EP1: The hospital determines the key safety content of orientation provided to staff. Note: key safety content may include specific processes and procedures related to the provision of care, the environment of care, and infection control
- HR.01.05.03—EP1: Staff participate in ongoing education and training to maintain or increase their competency. Staff participation is documented

(From The Joint Commission, http://www.jointcommission.org.)

Survey responses from 158 of 381 (41%) internal residency programs in the United States showed that 79% of survey respondents relegate infection prevention to a general lecture for all new employees. Seventy-seven percent dedicated a lecture on infection control to new house staff. Only 34% reported using an online module for infection prevention education. Infection prevention training is not an integral part of medical education and thus does not translate into daily clinical practice activities. A standardized curriculum for ongoing infection prevention education should be developed (15).

Although manufacturers are not routinely classified as sources of educational programs for healthcare professionals, they provide information in marketing their products. Such information must always be critically examined as to whether it is reliable and supported by scientific evidence. Manufacturers also provide training for use of their equipment, provide grants to support lectures, and produce products designed specifically for educational purposes such as videotapes and slides. These materials should be carefully evaluated for completeness of information and evidence of objectivity.

Targeted Infection Control Education

Standard Precautions Misinformation and confusion about the transmission of blood-borne pathogens have given impetus to infection control education. Studies of human immunodeficiency virus/hepatitis B virus blood-borne pathogens have emphasized the difficulty of changing behaviors and have shown that knowledge does not necessarily translate into changed behaviors. Several studies have recognized that the desired outcome has not been achieved through in-service educational programs that provide the standard information on risk behavior and ways to reduce that risk *(16–18)*. A 5-year study found a decrease in the number of needlesticks through a combination of more convenient placement of needle disposal containers, communication, and education, but this study did not single out effectiveness of education *(19)*. A variety of interventions, tested on personnel in an emergency department, improved compliance with universal precautions, including making gloves and eyewear more accessible, signage reminders, and hands-on training *(20,21)*.

Tavolacci et al. (22) tested medical and nursing students' knowledge. Medical students' scores were highest in knowledge of hand hygiene and Standard Precautions and worst scores were in knowledge of healthcare-associated infections. To increase compliance, students must learn essential behaviors in medical school. Sax et al.'s *(23)* study showed that specific training for all individuals increases adherence to standard and isolation precautions. Specialized training must be received before healthcare students undertake any patient procedure involving sharps devices. Elliott et al.'s *(24)* studies of medical students showed that training and increased awareness of sharp injuries resulted in a significant reduction in needlestick injuries.

Hand Hygiene Compliance Larson et al.'s (25) study of 40 US hospitals before and after the publication of the CDC Hand Hygiene Guideline included site visits and surveys to measure healthcare-associated infection rates 1 year before and 1 year after the publication of the CDC guidelines. Site visits used direct observation of hand hygiene compliance and determined if facilities changed policies and procedures in compliance with guideline recommendations. Results showed that 90% of 1,359 staff members surveyed anonymously reported that they were familiar with the guideline but 44% of hospitals found no evidence of multidisciplinary programs to improve compliance, and hand hygiene rates remained low at 56.6% compliance. Rates of central line-associated bloodstream infections were significantly lowered in hospitals with higher rates of hand hygiene ($p > .001$), and there was no reported impact on other healthcare-associated infection rates (25).

A lack of compliance with the CDC hand hygiene standards has plagued infection control efforts using traditional strategies for education. In a longitudinal study of hospital workers, it was found that, despite a comprehensive educational and promotional campaign, hand washing frequencies returned to precampaign levels in 6 months. The authors concluded that a lack of motivation (failure to change attitudes), rather than a lack of education, was the most important cause of poor compliance *(26)*. Similarly, Larson and Killien *(27)* found that current methods of focusing on the benefits of hand washing with a public relations approach (i.e., signs, lectures, or posters describing the importance of hand washing) missed the significant reasons given for infrequent handwashing, such as being too busy. Two sequential studies of intensive care unit (ICU) personnel found that education alone did not have a sustained effect, but that maintaining education and providing feedback on hand washing performance were critical to having a continuing effect on motivation *(28,29)*.

A 2006 multihospital study found that a lack of IP time to implement hand hygiene educational tools, even when

provided a multimodal prepackaged educational tool by CDC, was the primary barrier (30). Significant improvement in hand hygiene was observed when senior healthcare workers were present and when educational promotion and feedback were made available (31).

A hospital-wide education program demonstrated that adherence to hand hygiene recommendations improved significantly (48–66%). The program involved using posters and other visual displays that promoted the use of bedside hand rubs. The posters featured messages submitted by healthcare workers that were then graphically illustrated in cartoons. The creativity of this program may be one reason for its success, giving recognition and ownership to local healthcare workers (32).

An evaluation of a patient-empowering model for increasing healthcare worker hand washing compliance on a 24-bed in-patient unit effectively increased compliance 56% and was sustained over 3 months. Compliance was measured through soap usage per resident day. The intervention was that patients asked their healthcare workers if they had washed hands before providing care. Interestingly, patients reported asking nurses 65% of the time to only 35% for doctors *(33)*.

Noncompliance with the basic tenets of healthcare is evident in other areas of infection control practice, including aseptic technique, isolation, and Standard Precautions techniques. Ching and Seto *(34)* found that patient care practices for urinary catheter care were significantly improved when a nurse from the ward was chosen to act as an infection control liaison, promoting control measures and providing teaching, as compared to nurses receiving only in-service lectures. Two studies report successful outcomes in reducing either ventilator-associated pneumonia or central intravenous catheter infections. Both used a multidisciplinary task force to develop self-study modules, lectures, pre- and posttesting, and posted fact sheets as posters through the ICU. The studies using a multi-intervention approach showed significant reductions of 50% (35) to 66% (36) in hospital infection rates. These reports suggest a variety of educational methods may be needed to achieve and maintain adherence (32).

In summary, successful hand hygiene compliance is achieved through a combination of many strategies including observation and feedback, administrative support, senior staff modeling, product selection, and educational campaigns such as posters.

Human Factors Engineering Well-trained and educated healthcare workers continue not to comply with infection control mandates. Alvarado has stated that the educational methods themselves are at fault. "Search for the individual bad actor keeps us from looking at the design of the overall system" *(37)*. The traditional way of "simply telling them" assumes that the healthcare workers have the information, that learning has taken place, and that they will change to the desired behavior. It may be time to consider multifaceted approaches that will achieve good and sustained results, for example, HFE, which has its origins in the Industrial Revolution *(38)*. HFE looks at the causes and effects of human error and was originally applied to the design of increasingly complex airplane cockpits *(39)*. It has been applied to numerous diverse systems such as software and computer control. In healthcare, HFE has been applied to the problem that 70% to 80% of adverse anesthetic events in the operating room involve human error *(39)*. Evaluating the differences between visual and manual activities using the HFE model removed the problems and reduced the errors *(40)*.

The goal of HFE is a systematic approach to designing safer processes and products rather than relying on education alone. It relies on communication; training; fatigue and scheduling; environment and equipment; rules, policies, and procedures; barriers (safeguards); and tasks and technology tools *(41)*. The human factors model is to write down the characteristic of each aspect of performance expectations and then consider the effect of each characteristic on the individual whose behavior needs changing and alter the model so that the desired outcome is reached (42). Ultimately, it has been demonstrated to reduce the need for training and seeks to achieve optimum performance.

A continuing problem in infection control is that healthcare workers do not consistently comply with critical practices such as proper hand washing, administering preoperative antibiotics at the appropriate time, precleaning and disinfecting endoscopes correctly, following isolation precautions, using aseptic practices, and wearing appropriate personal protective equipment. HFE focuses on the user interface. Bagian et al. *(41)* state, "It is essential to design and implement a system that takes into account the concerns of the frontline personnel and is aimed at being a tool for learning, not accountability." The objective of HFE is to design devices or procedures that users accept willingly and operate safely in realistic conditions *(39)*. An example is the improved compliance of healthcare workers with hand hygiene policies with the use of waterless hand agents as an alternative to soap and water under certain conditions.

Alvarado (42) suggests comprehensive blame-free programs to analyze near misses as well as crashes. Lapses in infection control reflect system flaws rather than human incompetence.

Education for Specific Groups of Healthcare Workers

Effective programs must be customized to meet the needs of the group for which they are given. Studying a specific group of healthcare providers or targeting a learner population can assist the educator in developing programs that meet the unique interests of the group based on professional experience, intellectual maturity, and group readiness *(43)*. Factors to consider, regarding the participants, include the general educational background, reasons for attending, current level of knowledge on topic, and level in the decision-making structure of the institution (44).

Seto (45) found that the differing responses to "social power" by nurses and housekeepers have implications for their training. Social power is defined as "the potential ability of an influencing agent to affect the cognition, attitudes, or behavior of another person (the target) in infection control." Studies found that nurses respond best to informational and expert power. This finding suggests that effective education for nurses should include relevant references and convincing information (e.g., surveillance rates) given by a perceived "expert" in the field. Housekeepers were

responsive to legitimate power (the target's acceptance of a role relationship that obligates the target to comply with the agent's request) and coercive power (ability of the influencing agent to mediate punishment for the target), but less responsive to informational power. It therefore would be prudent for this group to have acknowledgment of the supervisor's endorsement of the educational content (45).

Hospital personnel with academic preparation in healthcare begin their employment with varying educational backgrounds in infection control. In addition to providing on-the-job training, the challenge is for IPs to advocate changes in basic education in the curricula of schools of nursing and medicine, so that healthcare personnel enter their professions with basic knowledge of infection control *(46)*. Dembry and Hierholzer *(47)* consider changes in the role of the hospital epidemiologist over the years, and recommend that infectious diseases programs in medical schools should include training in infection control.

Reports have demonstrated significant benefits by focusing on the physician-in-training for specific educational interventions *(48,49)*. An observation that few physicians were using a full-size drape during central venous line insertion led to a nonrandomized pre- and postobservational trial in six ICUs and a stepdown unit. A 1-day didactic course on infection control practices and procedures for third-year medical students and first-year residents resulted in a significant increase ($p < .001$) of full-size drape use and a significant reduction in catheter-related infections *(49)*. Another report using stations for training house staff on safety issues (needlesticks, back injuries, and TB exposures) resulted in the reduction or elimination of each adverse outcome *(48)*.

Mah and Meyers (50) summarized the effectiveness of educational modalities in changing healthcare worker behavior using Cochrane Database System Reviews. A small to moderate result came from audit and feedback (47 randomized controlled trials). Moderate to moderately large effectiveness was achieved through continuing education meetings—a combination of interactive and didactive workshops. Didactive workshops alone were less effective. Improved practice resulted from training opinion leaders (two of seven comparisons), Internet-based learning (in 3 of 16 randomized controlled trials), printed educational materials (2 of 14 comparisons), computer-based clinical decision support systems (43 of 65 comparisons), and academic detailing (combination of written materials, conferences, reminders, and audio/feedback) (18 of 18 comparisons) (50).

LEARNING THEORY AND BEHAVIORAL SCIENCES

Knowledge of learning theory and relevant fields in the behavioral sciences should guide the educator in planning educational activities for infection control. Learning theories have some elements in common including the idea that learning produces a relatively permanent behavior change and is an internal process that varies from person to person. Both biologic factors (e.g., heredity and sensory structures) and the intelligence that results from experience, education, and cultural background influence learning *(51)*.

Seto (45) has investigated social psychology, a field of study in behavioral sciences that is relevant for infection control education. The reasoned action model assumes that people's behavioral intent is a good predictor of actual behavior. A study testing this theory on the infection control policy to stop recapping of needles divided nurses into three groups of three wards each, using an initial survey to categorize those who would comply with practice as "agreeables" and those who would not as "nonagreeables." The authors then utilized three methods to introduce the policy: (a) by announcement only, (b) by announcement and passive education (posters and pamphlets), and (c) by passive plus active education (e.g., in-service lectures). Behavioral change was assessed by another survey. The results suggested that the agreeables had significant improvement in compliance (85%) using the announcement and passive education method compared with the nonagreeables (21% compliance). The nonagreeables reached 83% compliance when passive plus active education methods were used. Before the introduction of a new policy or procedure, a survey can be used to assess the proportion of staff already with behavioral intent to comply. If these are the majority, then an in-service program is not needed and the passive method would be sufficient (45).

Research in another social psychology theory, consumer behavior, has found that there are individuals called opinion leaders who can exert significant influence over others within their social/work groups. These opinion leaders can also influence how effectively new information is accepted by the group. Direct observation of practice before and after was made on two groups of ward nurses using new urinary catheter care guidelines as the infection control monitor. After both groups received the standard in-service education, opinion leaders provided tutorial demonstration to one group. There was a significant difference ($p < .01$) in compliance by the group receiving the opinion leaders' additional training (45,*52*). IPs should consider whether ward staff opinion leaders may promote or assist education.

Mah and Meyers (50) advocate a new socioethical approach to behavior change based on four tenets. First, a Learning Innovation Team was formed of people interested in promoting safe behaviors among healthcare workers. Team members brought their individual areas of interest and expertise to the group. The team created behavior change at the local level, which could then diffuse throughout the facility and region. Second, because personal experience outweighs scientific evidence in today's world, educators must appeal to their audience by appearing to have high moral character, respect for commonly held values, and create empathy with their cause. Third, since excellence of practice does not guarantee a positive outcome, the healthcare worker is to do his or her utmost to advance the welfare of patients. Infection prevention in healthcare should be built on improvement and behavior change (*praxis*), which the authors suggest should not be one at the expense of the other. Fourth, improved behavior occurs when there is conversation and communication. Most education occurs in the form of a monologue (computer-based training, lectures, and videos) and must be replaced with dialogue if culture change is to occur (50).

PLANNING EDUCATIONAL PROGRAMS

The IP and other healthcare professionals are engaged in education in informal settings such as responding to questions on the telephone or in the hallway; however, scheduled programs that meet institutional requirements or specific needs necessitate planning that is based on teaching-learning principles. Planning an educational program, activities, or displays includes the following steps: (a) assess learner needs; (b) define goals or purpose; (c) formulate objectives; (d) develop a plan—determine the setting, organize the content, choose the format, choose teaching materials, and establish a climate conducive to learning; (e) prepare an evaluation; and (f) implement, evaluate, and revise the program *(53)*.

Needs Assessment

Planning for educational programs begins with determining what knowledge is needed (e.g., what the discrepancy is between the present and required levels of competency). This needs assessment may be based on the needs of the individual learner (e.g., a hospital employee who fears catching a communicable disease) or on the needs of the institution (e.g., passing The Joint Commission survey or implementing decisions of the infection control committee).

Methods of determining the educational needs include interviews (both structured and informal, such as asking nurses and doctors what is perceived to be harming their patients), surveillance, environmental rounds, questionnaires, tests, observations, group meetings for problem analysis (e.g., discussion of isolation techniques), and medical/hospital records and reports (e.g., healthcare-associated infection rates). Seto et al. *(54)* used a written survey and found that the educational needs for nurses were not the same as those for the entire hospital, and identified the specific needs of nurses in various units. Long-term–care facility IPs responded to Leinbach and English's *(55)* statewide needs assessment indicating that training is needed, especially if it is comprehensive, accessible, and focused on long-term care. Weinstein et al.'s *(56)* study made use of observation in a hands-on exercise for needs assessment in basic infection control practice. Observation was also used in Fernsebner's *(57)* study for educational needs assessment through the use of mock surgery for operating room staff to identify breaks in aseptic technique. Another way to identify needs is to review new infection control guidelines to focus on only the practices that require change and to evaluate barriers for staff compliance (58).

Goals and Objectives

Needs assessment determines the goal or purpose of the learning activity and leads to formulation of objectives that assist the educator and the learner in planning, conducting, and evaluating the learning process. Goals tend to be descriptive global statements, whereas instructional objectives describe a performance the learners will be able to exhibit in order to be competent. An objective is the specific observable, measurable behavioral outcome of instruction. Mager *(59)* identifies three characteristics of an instructional objective: performance, conditions, and criterion. For performance, the objective describes what a learner is expected to be able to do using specific action words. Any conditions or constraints are described in the objective. Finally, the criterion states how well the learner must perform or what the criterion level is for mastery *(59)*.

Objectives may be classified into categories using classification systems such as one developed by Benjamin Bloom identifying three domains (affective, cognitive, and psychomotor). The affective domain includes interests, values, and attitudes. The cognitive domain includes knowledge, intellectual skills, and problem-solving abilities. The psychomotor domain includes manipulations and motor skills. The value of such a classification system for the educator is that it assists in communicating objectives clearly to the learner and in understanding the level of difficulty of the objectives *(60)*.

A learning objective clarifies what will be learned, gives guidance to choosing appropriate formats and teaching methods, and specifies what is to be assessed in the evaluation of the learner *(59)*.

Instructional Formats

The objectives guide the educator in choosing the most appropriate instructional format or combination of formats, including large groups, small groups and seminars, individualized instruction, or experiential learning, to facilitate student learning.

Another consideration in choosing the format is the preferred teaching style of the instructor/facilitator and the preferred learning style of the participant. Teachers have a preference for teaching styles, such as formal lecture, small-group discussion, or a mentor role working individually with learners, but they frequently adapt to a less-preferred style, because the objectives and educational needs influence the format. Kolb's classification system of learning styles combines two of four learning processes (concrete experience [feeling], active experimentation [doing], abstract conceptualization [thinking], and reflective observation [watching]) for each of the four learning styles in his system. Goldrick et al.'s *(61)* study of nurses in three specialized groups (critical care, operating room, and infection control) found that 64% of the respondents preferred the abstract, reflective, self-directed, discovery approach. Rakoczy and Money's *(62)* study of nursing students' preferred learning style produced similar results; students preferred abstract/reflective learning. Another study examining the cognitive style preferences of staff registered nurses found that the majority expressed agreement with making decisions by rule or policy, preferred focusing on learning one task at a time, and rated high a commitment to a group of principles or set of values *(63)*.

Large Groups The lecture–discussion method has been widely used and accepted by the educational community and is useful for groups larger than 15 people. It is an efficient way to transmit material to a large group in a short time and provides a specialist as a role model. However, this method is inconsistent with some principles of adult learning, and its disadvantages include the following: the student's role is passive, feedback is slow, individual differences cannot be accommodated, and attitude changes and reasoning skills are not developed *(64)*.

The qualities of a good lecturer/instructor include more than knowing the subject well. The speaker must organize the presentation logically with an introduction, body, and summary, and then communicate that information effectively. Personal characteristics of the speaker such as a sense of humor, spontaneity, and even dramatic ability help to maintain the attention of the learners. Butler *(65)* found that the students perceive the traditional didactic lecture as the least effective learning method. However, varying the lecture format with handouts or experiential tasks that involve active participation by students greatly enhances student learning. Cooper et al.'s *(66)* study of infection control training needs of medical students found that the 30-minute lecture–discussion was not effective in teaching about infection control guidelines in relationship to perceived risks of acquiring human immunodeficiency virus. A comparison of traditional classroom lecture with computer-managed instruction and keypad questions in a nursing course found no statistically significant difference in achievement between the two groups *(67)*.

Small Groups and Seminars The small-group instruction format is useful for groups of 15 or fewer participants. The small group is called a "seminar" when led by an instructor. When the group is student-centered, eight should be the maximum number of participants, and the instructor should serve as a resource person. Small groups and seminars are effective for attitude change, developing collaboration and problem-solving skills, applying concepts, and promoting peer interaction. The disadvantages of this method are that the groups require a great deal of time for careful management and planning by a competent facilitator and evaluating individual progress is difficult *(64)*.

IPs can maximize time and individualize educational offerings for specialized departmental needs by using departmental liaisons who learn from the IPs and take messages and programs back to their departments. To save travel and meeting time for distant locations, the Internet or teleconferences can be utilized *(68)*.

Individualized Instruction Individualized instruction designed to meet the exact needs of the individual student is ideal in that it accommodates individual differences, provides immediate feedback, and allows the learner to be an active participant. However, this method is difficult to use with large groups of people and with students who are not motivated, and is less effective for learning that involves changes in attitude. Developing materials for individualized instruction can be extremely time-consuming. Individualized instruction is applied through the use of such methods as independent study, correspondence study, manuals or syllabuses, videotapes, programmed instruction, and computer-assisted instruction *(64)*. Lieb et al. *(69)* developed self-paced learning stations for TB respirator training that was effective and time-efficient.

Programmed instruction consists of a series of frames that are carefully sequenced, so that learners will proceed at their own pace toward the desired behavior. This method is useful for teaching facts and skills but is less appropriate for teaching concepts and relationships *(70)*. Studies by Goldrick *(71)* concluded that the programmed instruction unit (PIU) is an effective alternative to classroom lectures for teaching basic infection control principles and resulted in cost savings. Application to infection control was tested on a randomized population of senior nursing students. A comparison was made of those receiving a PIU in the basic principles of infection control with those given tests only or those given tests and another PIU that did not cover infection control material. The study reported significantly improved scores for those given a PIU in infection control and an additional finding that 68% of students preferred this type of learning to a lecture *(67)*. In addition, a study of nurses and a study of third-year baccalaureate nursing students indicated that those who took a PIU covering the basic principles of infection control scored higher on posttests than those who attended a lecture, regardless of their pretest scores, educational level, and experience *(72,73)*.

Experiential Learning Experiential learning includes internships, student-initiated projects, and student participation in scholarship or research. This method is time-consuming for the educator and requires a supervisor for each student, but it offers effective individualized and specialized learning *(74)*.

Teaching Aids

Materials and Media Media and teaching materials can assist in achieving the objectives of an educational program but should be used only if they serve an educational purpose. Comprehension and retention can be dramatically increased with visual aids because as much as 83% of the data people gather may be from sight *(75)*. Available media include print (e.g., handout, manual, and textbook), chalkboards or flip charts, computer-assisted instruction, overhead transparencies, slides, audiotapes, videotapes, films, television, games and simulations, and manipulative materials.

When selecting teaching materials, the educator determines whether the quality and potential effectiveness will enhance learning. The selection of materials must also be based on the availability of equipment and money and compatibility with the educational setting (e.g., format, staff, space, and time). A study in a low-resource setting found that healthcare staff preferred flipcharts (low cost and easily available) over videotapes. In addition, the patients and their families preferred flipcharts (76).

Guidelines for evaluating media include the following: (a) Is the information appropriate for the level of the learners? (b) Is the information accurate and current? (c) Is there consistency between the learning objectives and the material? (d) Is the material organized and presented in a logical sequence? (e) Is the visual and verbal information simple? and (f) Is the technical quality good?

Slide presentations provide colored visual stimuli, are appropriate for large groups, and are easily transported. The following principles should be applied when designing or using slides: (a) clarity—address one point and present limited information so that it is clearly visible; (c) focus—select data that fit the objectives and synthesize the data; (c) appropriateness—present information that is appropriate to the level of understanding of the audience; do not present highly detailed and complex information to a general audience and do not oversimplify for an advanced-level audience; (d) accuracy—the slides should present correct

information, using correct spelling; (e) purpose—select only those slides that match the focus of the presentation; eliminate information that is not directly relevant *(77)*.

Technologic Resources Technology is a powerful tool that enables the educator to provide a dynamic learning environment. The creative educator can facilitate learning using technologic resources such as computers and telecommunications. Computers provide software for learners to explore and gain information using nonlinear, nonsequential searching techniques to link facts and ideas in a way best suited to that person's needs. Technologic advances such as virtual reality systems (a computer-based platform using a helmet-like apparatus to project a video image that gives the illusion of reality) have potential for useful application in education in healthcare.

Computer-assisted instruction and interactive video are useful aids for educating healthcare workers. In computer-assisted instruction, the learner interacts with a computer program that presents information in small steps. This method provides immediate feedback and allows learners to advance at their own pace. Interactive video (controlling a video by the computer) allows the learner to respond and interact. One study showed that computer-assisted instruction resulted in marked improvement in universal precautions—related behaviors in nurses *(78)*. Cohen and Dacanay *(79)* conducted a meta-analysis on computer-based instruction (CBI). The majority of the studies favored CBI over traditional methods of instruction, although few studies reported on retention, attitudes, and time to learn. The authors found large positive effects for interactive video applications of CBI that simulates clinical settings, requires involvement, and gives immediate feedback. Jamison and Brannigan *(80)* suggest that people with medical knowledge, as well as computer specialists, are needed for the process of implementing interactive video in medical education to make it most effective.

Establishing an Environment Conducive to Learning

Principles of adult learning applied to educational programs result in an environment that is conducive to learning. In addition to a comfortable physical environment, the interpersonal and organizational climate influence learning *(81)*. Some guidelines that facilitate a positive learning setting include the following: (a) adults are generally participating voluntarily in educational activities and do not respond well to coercive practices; (b) effective education is based on the mutual respect of instructors and learners; (c) collaboration, not competition, contributes to effective adult education; (d) active involvement followed by reflection is essential; and (e) adult learning is most effective when it is self-directed *(82)*.

Evaluation

Evaluation is essential in the educational process in that its purposes are to improve the learner's performance, the instructor/facilitator's performance, and the educational program itself. Evaluation is accomplished in informal ways as well as through the use of formal evaluation instruments to collect data. No single evaluation method is suitable for all purposes, but available methods include anecdotal records, self-evaluations, checklists, rating scales, tests, questionnaires, and interviews.

The first step in the evaluation is to determine the purpose of the evaluation. Questions to consider to guide the establishment of an evaluation process include the following: (a) Who is to be evaluated (e.g., learner, instructor, or program)? (b)When is the evaluation to occur? and (c) What is to be examined (e.g., learners, instructors, instructional formats, or materials and teaching aids)?

When learners are to be evaluated, they need to know what is expected of them. The objectives for an educational program state what is to be accomplished and are the guide for constructing an instrument to measure the extent of learning. A pretest may be administered to assess the learner's level of competence at the beginning of an educational program, and then a posttest indicates the progress made. When instructors are to be evaluated, constructive feedback results in improvement in teaching. Evaluation of an educational program may be formative or summative, depending on the purpose. Formative evaluation occurs during the program and provides for modification of the program while it is being conducted. Summative evaluation occurs after the program is completed and focuses on accountability, indicating whether a program should be continued, modified, or discontinued *(83)*.

> *I believe that education is the principal component of infection control. Without education, every other activity of our specialty is just so much meaningless busy work.—Sandra J. Pfaff (46), Third Annual Carole de Mille Lecture*

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CHAPTER 93

Infection Control and the Employee Health Service

Pamela S. Falk

Hospitals, although traditionally a refuge for the sick and injured, not only are very dangerous environments for healthcare workers but also can be dangerous for patients. Hospital-based employee health programs are charged with diagnosing, treating, and preventing infectious diseases in healthcare workers. Because of this, a hospital-based employee health service plays an important role in the infection control program and is a key element in protecting patients from healthcare-associated infections.

Clear lines of communication need to be established between the employee health service and the infection control department. Infection control and employee health staff should meet on a routine basis and should communicate (telephone, notes, fax, e-mail) as needed for integration of activities. Protocols for triage, evaluation, prophylaxis, and follow-up after exposures should be developed and the roles and responsibilities of employee health and infection control should be carefully defined.

CONTROL AND PREVENTION OF SPECIFIC INFECTIOUS DISEASES IN THE HEALTHCARE SETTING

Varicella-Zoster Virus

The varicella-zoster virus (VZV) causes two diseases: varicella (chicken pox) and herpes zoster (shingles). Chicken pox is a common childhood disease. For the approximately 1% to 10% of adults who are susceptible to VZV *(1–7)*, exposure poses a significant risk of infection.

Assessment of Healthcare Workers' Immune Status A common goal of all infection control programs is to protect patients from healthcare workers who may be incubating infectious diseases after exposure in the community or in the hospital. All employees should, on their postoffer employee screening, be asked about a history of chicken pox. A healthcare worker with a positive history of chicken pox can be considered immune *(5–19)*. If the healthcare worker denies having had the disease or has an uncertain history for chicken pox, a serologic test, if deemed cost-effective by the institution, may be done to determine his or her immune status (see also Chapter 76).

Institutions should develop guidelines for managing healthcare personnel eligible for the varicella vaccine *(20)*. If the healthcare worker is not immune (either by history or serologic test), the varicella vaccine should be offered *(16–20)*. Serologic testing for postvaccination antibodies is not required *(16–19)*. Personnel who develop a rash after receiving the varicella vaccine must avoid contact with persons without evidence of immunity who are at risk for severe disease and complications until all lesions resolve (i.e., are crusted over or fade away) and no new lesions appear within a 24-hour period (*15*,21).

Nonimmune healthcare workers for whom the vaccine is contraindicated should be educated about the risk they pose to patients, should they be exposed to VZV and become infected. They should not be assigned to the care of any patient with chicken pox or herpes zoster.

Exposures to Varicella-Zoster Virus After a case of chicken pox has been confirmed in a patient or healthcare worker, infection preventionists should compile a list of personnel and patients exposed to the index case. The names of exposed employees are provided to the employee health service so that the immune status of those exposed can be determined. Exposed healthcare workers who are not immune should be furloughed. The period of contagiousness of infected persons is estimated to begin 1 to 2 days before the onset of the rash and to end when all lesions are crusted *(18)*. Thus, furlough should begin 8 days after the first day of exposure and extend through day 21 after the last day of exposure (*6*,*7*,*14*,*15*,*18*,*20*,21).

It is very important that nonimmune employees report chicken pox exposures whether they occur in the community or in the hospital. Employers should furlough healthcare workers with pay for exposures that occur within the institution. Without this policy, employees are reluctant to report their exposures. Although employees are strongly encouraged to report community exposures, few institutions furlough employees with pay after exposures in the community.

Although the risk of infection with VZV is less after exposure to a patient with herpes zoster than after exposure to a patient with chicken pox, the clinical manifestations

of chicken pox are the same after acquisition of infection by either type of exposure *(12)*. Nonimmune healthcare workers who have direct physical contact with draining vesicles of patients with herpes zoster should also be considered exposed and furloughed from work *(12)*. Nonimmune healthcare workers should refrain from working with patients with herpes zoster *(12)*.

Often, the source of exposure to VZV is a healthcare worker. One of the most important functions for the employee health service during the investigation of a VZV exposure episode is to confirm VZV infection in the index case. Once VZV infection has been confirmed, the employee must be furloughed until all lesions are crusted *(12)*. Although the furlough may be instituted by either the infection control department or the employee health service, the employee must return to the employee health service to be cleared before returning to work.

Prophylaxis using varicella-zoster immune globulin should be considered for nonimmune exposed healthcare workers who are at high risk for complications of varicella-zoster infection (pregnant and immunosuppressed employees) (*22*,23) (see also Chapters 43, 75, and 76).

Tuberculosis

The American Thoracic Society issued a statement in 1967 recommending that all hospitals have a "consistent program of tuberculin testing … of all employees who may be subject to exposure" *(24)*. By 1983, the Centers for Disease Control and Prevention (CDC) recognized that all healthcare workers were not at equal risk for acquiring tuberculosis (TB) and recommended skin testing based on individual classification of risk for a facility and the location and prevalence of untreated TB in the community, in the institution, and among personnel *(25,26)*.

Because of these recommendations, many hospitals in the late 1980s discontinued or restricted their purified protein derivative (PPD) skin testing program. However, since 1988, there has been a dramatic increase in TB in the United States that is largely related to the human immunodeficiency virus (HIV) epidemic *(26–28)*. Hospitals have had to reassess their TB surveillance plans and develop mandatory skin testing policies for healthcare workers. These programs should include baseline TB skin tests upon employment, periodic retesting for at-risk employees, postexposure evaluation, preventive therapy as indicated, and employee education (*26*,29) (see also Chapter 38).

Healthcare workers with a positive TB skin test on initial testing or with a skin test conversion after exposure should be evaluated for active TB by the employee health service. Persons with symptoms suggestive of TB should be evaluated regardless of skin test results. If TB is diagnosed, appropriate therapy should be instituted. Healthcare workers with a reactive skin test but without disease should be educated about the signs and symptoms of disease and instructed to report immediately to the employee health service for evaluation, should they develop any of these signs and symptoms.

Healthcare workers who have active pulmonary or laryngeal TB, endobronchial or tracheal disease, or a draining TB skin lesion pose a risk to patients and staff. Therefore, the CDC recommends that the healthcare worker be excluded from work until adequate treatment has been instituted, cough has resolved, and sputum has been found free of acid-fast bacilli on smears from three consecutive specimens collected at 8- to 24-hour intervals with at least one sample from an early morning specimen (because respiratory secretions pool overnight) (29).

Healthcare workers who cannot take or do not accept or complete a full course of preventive therapy should be counseled about the risk of reactivation of infection and development of disease and should be instructed to seek evaluation promptly if symptoms develop that may be due to TB.

Annual and postexposure tuberculin skin test results should be monitored routinely. Results of skin tests should be placed in the healthcare worker's medical records and recorded in an aggregate form for analysis of skin test conversion patterns in various areas of the hospital. The aggregate data set should include information about each skin test conversion such as job classification, work location, date of first PPD, and date of positive PPD. Analysis of the aggregate data set is done by the infection control department to determine whether personnel in any area or service in the hospital have an increased incidence of skin test conversions. An increased incidence of skin test conversions in a given area or service may indicate that the infection control procedures to prevent transmission of TB in that area or service need to be improved.

Seasonal Influenza

Since 1984, the recommendations of the Advisory Committee on Immunization Practices (ACIP) for immunization against influenza have included healthcare workers as a group because they may transmit influenza to patients *(30)*. The annual recommendations for adults were published in the 2008 ACIP guidelines. Annual vaccination against influenza is recommended for any adult who wants to reduce the risk for becoming ill with influenza or of transmitting it to others. Vaccination is also recommended for all adults in the following groups because these persons are either at high risk for influenza complications or are close contacts of persons at higher risk:

- Persons aged 50 years or older
- Women who will be pregnant during the influenza season
- Persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes mellitus)
- Persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- Persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function, or the handling of respiratory secretions or that can increase the risk for aspiration
- Residents of nursing homes and other chronic-care facilities
- Healthcare personnel
- Household contacts and caregivers of children younger than 5 years and adults older than 50 years, with

particular emphasis on vaccinating contacts of children younger than 6 months
- Household contacts and caregivers of persons with medical conditions that put them at high risk for severe complications from influenza (31)

All healthcare institutions should develop a policy to enhance the delivery of influenza vaccine to healthcare workers for the following reasons *(32)*: (a) healthcare-associated outbreaks occur during the influenza season, and a well-immunized workforce is less likely to transmit influenza to the patients under their care; (b) immunizations should minimize absenteeism during influenza outbreaks; and (c) influenza can be a serious disease and should not be confused with a cold or "intestinal flu." Immunization provides the best personal protection for each employee.

The vaccine should be offered beginning in October of each year. The employee health service and the infection control department need to collaborate in the education of healthcare workers about the importance of immunization against influenza. Measures should be taken to provide all healthcare workers, regardless of shift or work location, convenient access to influenza vaccinations at the work site, free of charge, as part of the employee health program *(20)*. The risk of introducing influenza into high-risk groups, such as those with compromised cardiopulmonary or immune systems or infants in the neonatal intensive care unit, should be reduced by targeted vaccination programs of these medical personnel.

In addition to a vaccination program, monitoring the community for influenza activity and monitoring healthcare workers for influenza may help prevent healthcare-associated transmission of influenza. When healthcare workers have signs and symptoms of influenza, they should be evaluated by the employee health service, and if possible, viral cultures and serologic tests for antibodies to influenza should be obtained.

To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status *(32)* (see also Chapter 42). In addition, the employee health service would be responsible for education of healthcare workers about the side effects of the prophylactic drugs and for evaluation of healthcare workers for possible side effects of these medications. Healthcare workers with active disease should be relieved from duty because it is estimated that viral shedding in the nasal secretions usually continues up to 5 days after the onset of illness *(13,15)*. Healthcare workers should be cleared by the employee health service before returning to work.

Blood-Borne Diseases

All healthcare institutions should have a plan to follow-up all occupational exposures to blood-borne pathogens *(33)*. Healthcare workers must be educated about the importance of promptly reporting exposures. Ideally, each institution should have a triage system available by telephone 24 hours a day. Such a triage service could be provided by the infection control department, by the employee health service, or jointly by both services. This system provides immediate triage, initial evaluation, and early prophylaxis if needed. It also permits early counseling for anxious healthcare workers after exposure. If the exposed healthcare worker is seen in urgent care or the emergency department at night or on weekends or holidays, he or she should be instructed to report to the employee health service on the next business day (34).

The interval within which postexposure prophylaxis for HIV should be started for optimal efficacy is unknown. An occupational exposure should be regarded as an urgent medical concern and postexposure prophylaxis started as soon as possible after the exposure (i.e., within a few hours rather than days) (34,*35*). In the author's hospital, the policy is to start prophylaxis within 2 hours of exposure.

Prompt reporting of all exposures is necessary for the timely administration of postexposure prophylaxis. Source patients should be evaluated for a history of high-risk behavior and should have serologic tests performed for viral hepatitis and HIV as soon as possible after the exposure. Infection control personnel should conduct the risk assessment. Once the risk assessment has been completed, the information should be shared with the employee health service so that postexposure prophylaxis can be administered as soon as possible after exposure (*15*,34) (see also Chapters 73 and 74).

Measles, Mumps, and Rubella

Healthcare workers are considered at a higher risk of acquiring measles (rubeola), mumps, or rubella than are the general population because of their chance exposure to either ambulatory or hospitalized patients being treated for these diseases *(36)*. An effective immunization program for healthcare workers can markedly reduce this risk. In addition to protection for healthcare workers, such immunization programs can be expected to have institutional benefits, such as prevention of transmission of infectious diseases to patients and visitors, reduction of workers' sick days, and improved efficiency in the management of outbreaks and exposures.

When developing a measles, mumps, and rubella (MMR) vaccination program, the most accessible population for vaccination is the healthcare workers who are being seen for their postoffer evaluations. All healthcare workers who do not have documentation of physician-diagnosed measles, laboratory evidence of measles immunity, or contraindications to the MMR vaccine and who have not already received two doses should be vaccinated with MMR before starting work. All healthcare workers should be assessed during their annual physical visit to the employee health service. If a healthcare worker had a contraindication to MMR vaccine during the last employee health service visit, that healthcare worker should be reassessed and the vaccine given, if possible. If patients or personnel are exposed to measles, mumps, or rubella, the following should be considered (*36*,37):

1. If the index case is an employee, the infection should be confirmed by the employee health service. Serum

should be obtained for acute and convalescent antibody titers to help establish the diagnosis. However, results of serologic tests are usually not immediately available, and the response to most exposure incidents must be based on a clinical diagnosis. It must be remembered that MMR are no longer common childhood diseases, and each can be easily misdiagnosed by relying on clinical signs alone. Consultation with a physician experienced in the diagnosis of measles, mumps, or rubella, such as a dermatologist, pediatrician, or infectious diseases specialist, should be considered if the diagnosis is unclear.

2. The activities of the index case, such as contact with coworkers on his or her unit and social contact with other healthcare workers in areas in which the employee has worked (e.g., nursing units, various departments, clinics), should be documented. A list of exposed healthcare workers should be sent to the employee health service.
3. Exposed healthcare workers with documentation of immunity by vaccination or positive serologic tests should be considered immune and not at risk for clinical disease.
4. Those without documented immunity should be vaccinated as soon as possible, if there are no contraindications, and furloughed as necessary. Exposure to measles requires a furlough from 5 days after the date of first exposure to 21 days from the date of last exposure *(15–20,38,39)*. Those exposed to rubella should be furloughed from the 7th day after the first exposure to the 21st day after the last exposure *(15,20,40)*, and those exposed to mumps should be furloughed from the 12th day after the first exposure to the 26th day after the last exposure (*12*,*13*,*15*,21).
5. Exposure to measles or rubella is not a contraindication to vaccination. An emergency MMR vaccination program may be implemented if there is evidence that many employees are susceptible to the disease in question. Such an emergency program may be needed to prevent an outbreak of infections among employees.
6. During an outbreak of measles, all healthcare workers with direct patient contact who were born after 1957 should receive one dose of measles vaccine unless they can provide proof of immunity or document previous receipt of two doses of the measles vaccine *(39)* (see also Chapter 51).

Pertussis

Multiple outbreaks of pertussis in healthcare facilities have been reported in the literature. These outbreaks have resulted from failure to recognize and isolate infected infants and children and failure to recognize and treat the disease in staff members. Healthcare-associated acquisition of pertussis by healthcare workers has occurred during several outbreaks (41).

Investigation and control measures to prevent pertussis after unprotected exposure in healthcare settings are labor-intensive, disruptive, and costly, particularly when the number of exposed contacts is large. Such measures include identifying contacts among healthcare workers and patients, providing postexposure prophylaxis for asymptomatic close contacts, and evaluating, treating, and placing symptomatic healthcare workers on administrative leave until they have received effective treatment. Despite the effectiveness of control measures to prevent future transmission of pertussis, one or more cycles of transmission with exposures and secondary cases can occur before pertussis is recognized. This might occur regardless of whether the source case is a patient or healthcare worker, the age of the source case, or the setting (e.g., emergency department, nursery, or any other inpatient unit).

Infrastructure for screening, administering, and tracking vaccinations exists in occupational health or infection prevention and control departments in most hospitals, and hospitals should implement Tdap vaccination programs. New personnel can be screened and vaccinated with Tdap when they begin employment. As Tdap vaccination coverage in the general population increases, many new healthcare workers will have already received a dose of Tdap.

To achieve optimal Tdap coverage among personnel in healthcare settings, healthcare facilities are encouraged to use strategies that have enhanced healthcare worker participation in other hospital vaccination campaigns. Successful strategies for hospital influenza vaccine campaigns have included strong proactive educational programs designed at appropriate educational and language levels for the targeted healthcare worker, vaccination clinics in areas convenient to healthcare worker, vaccination at worksites, and provision of vaccine at no cost to the healthcare worker. Some healthcare institutions might favor a tiered approach to Tdap vaccination, with priority given to healthcare workers who have contact with infants aged 12 months or younger and other vulnerable groups of patients (41).

Therapy of infected patients and chemoprophylaxis of exposed healthcare workers has been successful in terminating outbreaks in healthcare institutions. Erythromycin has been the antibiotic of choice for both treatment and prophylaxis. More recently, the CDC has recommended that azithromycin be used for both treatment and postexposure prophylaxis for pertussis (42) (see also Chapters 75 and 76).

Meningococcal Exposure

Healthcare workers may be exposed to the meningococcus. Source patients with *Neisseria meningitidis* in their blood, spinal fluid, or respiratory secretions can be considered to be colonized with the microorganism in their oropharynx. Transmission is probably by way of large droplets. Exposure in a healthcare setting should be defined as an individual who has had close contact with the source patient with meningococcal disease. Close contact is defined as exposure to the patient's respiratory secretions (i.e., mouth-to-mouth resuscitation, endotracheal intubation or endotracheal tube management) but not as routine patient care activities (e.g., making beds and taking blood pressures) *(43)*.

In the microbiology laboratory, care should be taken whenever droplet formation or aerosolization is possible (subculturing and serogrouping). It is recommended that all work manipulations be done in a biologic safety cabinet. Some states are now requiring those who perform testing on this microorganism "to" receive the quadrivalent meningococcal polysaccharide vaccination for *N. meningitidis* types

A, C, Y, and W-135 (*44*,*45*,46). However, the meningococcal tetravalent conjugate vaccine is preferred for persons 11 to 55 years of age (46).

Infection control personnel should investigate every possible exposure, interview healthcare workers regarding possible exposure, and refer healthcare workers with exposures to the employee health service for prophylaxis (see also Chapters 47 and 76).

Herpes Simplex Virus

Personnel with active herpes simplex virus infections pose certain problems for infection control. Healthcare workers with draining oral lesions need to be educated about the importance of good hand washing, use of barrier protection for the infected site (e.g., mask), and avoiding care of high-risk patients (e.g., immunocompromised patients and newborns). Healthcare workers with herpetic whitlow may transmit the virus even when wearing gloves *(47)*. These healthcare workers should be excluded from patient care until the lesions are healed *(2,15)*. There is no evidence that healthcare workers with genital herpes need work restrictions.

All healthcare workers should be educated about the need to seek evaluation at the employee health service for diagnosis, treatment, and potential reassignment or furlough for herpetic lesions. It is the responsibility of the infection control department to educate healthcare workers about their risk of acquiring and transmitting the herpes simplex virus and the importance of hand washing after contact with herpetic lesions in patients (see also Chapter 44).

Ectoparasites

The most difficult part of dealing with healthcare workers who have been exposed, or presumably exposed, to an ectoparasite is contending with their hysteria. The employee health service and infection control department should work together and follow a consistent protocol for prophylaxis. In general, prophylaxis is not recommended for exposure to lice (sans bedmates). Healthcare workers who have had prolonged skin-to-skin contact with patients with scabies may benefit from prophylactic treatment (i.e., permethrin 5%, lindane 1%, or crotamiton) *(15)*. All healthcare workers must be made aware of the signs and symptoms of infestation, regardless of source of exposure, and should be instructed to report to the employee health service for treatment if such manifestations appear.

SYNDROMES THAT MAY BE DUE TO INFECTIOUS DISEASES

Diarrhea

An employee health policy should be developed that requires all employees with diarrhea to report to the employee health service for evaluation and clearance before reporting for work. Any employee with acute diarrhea should be relieved from work until it is determined whether there is an infectious etiology. The elements of good hand washing, especially after using the restroom, must be stressed.

Diarrhea in a food handler may be cause for concern. Because of the fecal-oral route of transmission for many bacterial and viral pathogens, the food handler may be the source of a hospital outbreak. It is very important that all food handlers report to the employee health service when they have diarrhea. They should comply with the hand washing policy after using the restroom and before handling food. They should also understand the proper use of gloves.

Skin Eruptions of Undetermined Cause

Many viral diseases such as chicken pox, measles, and rubella present with the sudden onset of a rash. Healthcare workers with a new-onset skin eruption should be instructed to report to the employee health service for diagnosis and clearance before reporting for work. Hospital-based outbreaks may be caused by a healthcare worker who does not report an eruption to the employee health service and continues to work, exposing patients and other healthcare workers.

The employee health service should play a pivotal role in the triage of all healthcare workers who have a rash. Healthcare workers should be seen in the employee health service in a timely manner and evaluated by an experienced practitioner. Employees who have a communicable disease should be furloughed from work. All employees who have a rash that may be a manifestation of a communicable disease should be reported to the infection control department so that postexposure control measures may be instituted. Employees with skin eruptions may be sources of exposure for diseases associated with significant morbidity and mortality in hospitalized patients.

DERMATITIS

Frequent hand washing is stressed extensively in infection control educational programs. One consequence of this is development of dermatitis of the hands. It is probably more risky to provide patient care with weeping dermatitis than it is to forgo hand washing all together. Furthermore, transient microbial flora on the hands acquired by contact with patients and environmental surfaces cannot be removed by hand washing when healthcare workers have dermatitis of their hands.

Dermatitis can be caused by a variety of factors, but in healthcare workers it is most commonly caused by excessive hand washing, harsh hand soaps, and use of gloves. Healthcare workers who scrub for operative procedures often react to the harshness of the scrub brushes. In addition, the unavailability of moisturizing lotion can lead to dry and cracked skin, especially during the cooler winter season.

Infection preventionists should encourage not only good hand washing but also good hand maintenance. When employees develop hand dermatitis, they should be instructed to report to the employee health service. Protecting the hands of healthcare workers from dermatitis is important for the health of the healthcare worker and for patients. The employee health service can help prevent healthcare-associated infections by consulting with the infection control department regarding reported cases of hand dermatitis and offering healthcare workers education and alternatives regarding daily hand maintenance.

Latex Allergy

Latex is liquid sap from the commercial rubber tree. Latex contains naturally occurring impurities (e.g., plant proteins and peptides), which are believed to be responsible for allergic reactions. Latex is processed to form natural rubber latex (NRL) and dry natural rubber. Dry natural rubber and NRL might contain the same plant impurities as latex but in lesser amounts. NRL is used to produce medical gloves, catheters, and other products. Dry natural rubber is used in syringe plungers, vial stoppers, and injection ports on intravascular tubing. Synthetic rubber and synthetic latex also are used in medical gloves, syringe plungers, and vial stoppers. Synthetic rubber and synthetic latex do not contain natural rubber or natural latex and therefore do not contain the impurities linked to allergic reactions *(48)*.

Reactions Associated with Latex Exposure

1. *Contact irritant dermatitis:* This is the most common type of reaction. It is not an allergic reaction that involves the immune system. Symptoms often present as skin irritations (e.g., dry, itchy, cracked, and reddened). Latex allergens may be absorbed through the openings in the skin and could progress to a true allergy *(49)*.
2. *Type IV delayed hypersensitivity (allergic contact dermatitis):* This is the second most common type of reaction reported due to latex exposure. This type of allergic reaction is mediated by T cells and is typically characterized by swelling, burning, itching, and rashes on hands when using gloves containing NRL. The reaction can occur in as little as 6 hours and up to 48 hours after an exposure to the offensive allergens. Allergic contact dermatitis associated with poison ivy exposure is an example of a type IV reaction. Generally, allergic contact dermatitis may spread beyond the area that has been exposed to the offensive allergen. Conversely, irritant contact dermatitis generally does not extend beyond the area of contact. Type IV reactions can progress to type I reactions with repeated exposure *(49)*.
3. *Type I immediate hypersensitivity:* This is the least common type of reaction but is the most serious and potentially life-threatening. It is an immune response to a foreign substance (latex protein) and produces such symptoms as edema of the exposed site(s), nausea, vomiting, sneezing, nasal congestion, or systemic reactions. Reactions typically begin within minutes, but may take several hours to manifest. The airways can close down, which may result in respiratory arrest. If not handled properly by medical personnel during such a reaction, anaphylactic type reactions can be fatal. Fatal reactions have been reported from exposure to NRL even when patients have no history of latex allergy *(49)*.

Recognized Routes of Latex Exposure

1. *Cutaneous* exposure can occur while wearing latex gloves or touching other latex products.
2. *Percutaneous* exposure can occur if the latex protein gets under the skin as with dry, irritated, and cracked skin.
3. *Mucosal* exposure occurs when touching a latex balloon to one's lips and mouth while blowing it up or having a dental procedure with a rubber dental dam.
4. *Parenteral* exposure occurs when medications are injected through a latex IV port or with a syringe with a dry rubber latex–tipped plunger. In this way, allergens are injected into the body or bloodstream.
5. *Aerosol* exposure may occur when an individual enters a room in which someone has donned powered latex gloves (causing proteins to be airborne) and protein particles are inhaled into the lungs.

At-Risk Healthcare Workers

Healthcare workers may be at increased risk of developing a latex allergy if they work in a clinical environment where latex products are frequently used. Healthcare workers with a history of multiple allergies, especially foods such as bananas, chestnuts, kiwi, avocados, or other tropical fruits, are also at risk. Asthma, allergic rhinitis, and hand dermatitis in a latex glove wearer also raises the risk of developing latex allergy.

The American Academy of Allergy and Immunology (AAAI) determined that because there is no known cure for this allergy, it would be beneficial to implement regulations early to prevent the allergy from becoming widespread. On September 30, 1997, the Food and Drug Administration ruled that "[a]ll medical devices containing latex [must] be labeled as such and [must] carry a caution that latex can cause allergic reactions" *(50)*.

The National Institute of Occupational Safety and Health issued comprehensive recommendations regarding latex in 1997. The recommendation was aimed at the employer and the employee. The healthcare facility was encouraged to use nonlatex gloves when latex was not absolutely necessary. It also encouraged education about latex allergies and periodic screening of high-risk employees. It was recommended that the employees take the initiative to rid the work environment of latex containing dust *(50)*.

In studies of healthcare workers, self-reported hypersensitivity is fairly common and closely associated with the use of medical gloves. There are no diagnostic tests or standardized criteria to diagnosis latex allergy. It is recommended that each institution assess the use of latex products and try to minimize it. Also, education is recommended for all healthcare workers about their personal risk and the risk they pose to their patients.

SPECIAL EMPLOYEE POPULATIONS

Day-Care Centers Associated with Hospitals

As competition among healthcare institutions grows, more institutions are offering on-site day-care centers for the children of healthcare workers. Employees in day-care centers may be exposed to a greater variety of infections compared with their counterparts in the main healthcare facility (see also Chapter 53). Infection control departments and employee health services are frequently charged with providing services for associated day-care facilities.

Diseases Commonly Encountered in Day Care

Enteric Diseases Fecal-oral transmission of pathogens such as *Salmonella*, *Shigella*, *Escherichia coli*, *Campylobacter*, hepatitis A, rotavirus, and a variety of parasites is common in day-care centers. It is imperative that the infection

control department educate the staff frequently on proper hygienic practices such as hand washing, diapering, and infant feeding. Employees in this area must understand the importance of reporting to the employee health service for any gastrointestinal signs and symptoms and/or diarrhea to avoid spread of disease in this highly susceptible population.

Respiratory Infections Children with respiratory infections may shed viruses before the onset of symptoms, making control of infections due to respiratory syncytial virus, parainfluenza virus, adenovirus, and other respiratory viruses difficult. Although infection preventionists need to educate the employees on hand washing, the employee health service can also help prevent the spread of diseases by diagnosing communicable diseases in employees and furloughing them during the infectious stage of their illness. Because the day-care center employees are asked to report to the employee health service for symptoms of any respiratory infection, the employee health service should document each case and share data on respiratory infections with infection control. In the event a higher than expected rate of disease is discovered in the day-care center, infection preventionists can investigate and implement control measures.

Skin and Cutaneous Infections As in the hospitalized population, lice and scabies pose a unique problem to employees in the day-care center. Employees or day-care center attendees may also contract and expose others to herpes simplex virus or bacterial pathogens such as group A β-hemolytic streptococci. It is important that both the infection control department and the employee health service are notified in the event of a case of cutaneous infection. The infection control department should investigate the exposure, and the employee health service should evaluate employees, provide treatment, and determine whether employees can continue to work or should be furloughed.

Day-Care Center Employee Health Policies Policies for the prevention of infections in the day-care setting and adherence to these policies are important for effective infection control in day-care centers. The policies must be in compliance with the appropriate regulatory agency guidelines. The policies relating to employee health should require (a) documented evidence of immunity to tetanus, measles, mumps, rubella, diphtheria, and poliomyelitis in caregivers by either immunization or serologic evidence of prior infection; (b) TB screening within 1 month of starting work and then annually, and appropriate follow-up protocols for PPD skin test converters; (c) annual updating for immunizations; and (d) guidelines for work restrictions if an employee has a communicable disease (i.e., furloughed from direct child care or excluded from work until the disease is no longer contagious).

Prehospital Healthcare Workers

Today, firefighters, emergency medical technicians, police officers, and others often are exposed to infectious diseases during patient care and transport to the hospital. The receiving hospital is often called on to triage and treat these prehospital healthcare workers or at least to ensure that their exposures are managed appropriately.

For the most part, prehospital healthcare workers transport patients with undiagnosed diseases. Therefore, when a patient has a disease transmitted by the airborne route, such as TB or chicken pox, or by large droplets, such as meningococcal disease, prehospital healthcare workers may be inadvertently exposed. It is important that infection preventionists include prehospital healthcare workers in investigations of exposures. Prehospital healthcare workers may be evaluated, prophylaxed, and followed up by the hospital employee health service just as the hospital's healthcare workers are evaluated, prophylaxed, and followed up after exposures to communicable diseases. If a separate healthcare provider has been established for the prehospital healthcare workers, the infection control department should communicate directly with that provider.

Prehospital healthcare workers are most at risk for exposures to blood and body fluids via needlesticks and splashes to mucous membranes. A system of reporting such exposures must be developed and included either in the hospital employee health program or by the outside healthcare provider. Education of the prehospital healthcare workers about reporting all exposures is important to the success of such programs. All prehospital healthcare workers need to know the mechanism for reporting exposures and fully understand the importance of postexposure evaluation, prophylaxis, and follow-up (see also Chapter 78).

Emergency Department: An After-Hours Employee Health Service

Traditionally, employee health services operate during the day Monday through Friday. However, employees who sustain an exposure after hours, on weekends, or on holidays usually report to the emergency department. Thus, the emergency department is often an extension of the employee health service, and communication between the emergency department and the employee health service and interaction with the infection control department is important to provide continuity of care for exposed employees.

Protocols for meningococcal exposure prophylaxis, hepatitis B vaccination and hepatitis B immune globulin administration, prophylaxis for exposure to HIV, and diagnosis of diseases such as chicken pox and measles are extremely helpful to emergency room doctors and nurses who are triaging an employee. Consistency in delivering care is the goal. Although the initial diagnosis or prophylaxis may occur in the emergency department, employees receive their follow-up care at the employee health service and their records are permanently filed in that location.

Although protocols outline the various interventions that are needed postexposure, it is important that emergency department physicians document the following: (a) complete description of the exposure; (b) completed employee occurrence report; (c) type of prophylaxis administered (e.g., hepatitis B vaccine and hepatitis B immune globulin) and schedule of additional doses if required; (d) clear communication to the employee regarding furlough status (after communication with the infection control department); and (e) referral to the employee health service, as soon as possible, to arrange follow-up care for any exposed or ill employee.

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CHAPTER 94

Epidemiology and Prevention of Healthcare-Associated Infections Related to Animals in the Hospital

David J. Weber and William A. Rutala

Americans keep a wide variety of animals as household pets. Common pets include cats, dogs, birds, and fish; however, increasingly more exotic animals are being kept as pets, including other felines, ferrets, monkeys and other primates, rabbits, reptiles, rodents, and wolves. In addition, a variety of farm animals may be kept as pets, such as cattle, chickens, horses, pigs, and sheep. In 2006, 37.2% of households owned a dog, 32.4% owned a cat, 3.9% owned a pet bird, and 1.8% owned a horse *(1)*. The total number of animals owned was 72.1 million dogs, 81.7 million cats, 11.2 million birds, and 7.3 million horses. An estimated 9 million American homes had an aquarium. The average veterinary expenditures per household for all pets was $366 *(1)*. Retail trade in pet food alone totaled $41.2 billion in 2007 *(2)*.

Hospitalized patients may come into contact with animals for two main reasons: the use of animals for animal-assisted interventions (also known as pet therapy or pet-assisted therapy) and the use of service animals, such as guide dogs for the blind and primates for persons with impaired motion. This chapter focuses on the benefits and potential risks of animal use in the hospital, especially pet therapy. This chapter covers only the most common animals kept as pets and the major zoonotic diseases. Readers interested in a comprehensive review of zoonotic diseases or in rare and exotic zoonotic diseases are referred to several comprehensive monographs (*3,4*,5, *6–9*,10,*11*,12,*13,14*,15) and review articles *(16–18)*. Several excellent reviews of infections associated with pets have appeared in the general medical literature (19,*20–32*,33). The frequency of type of allergic reactions to pets has also been reviewed *(26,27,34–36)*. Finally, the infectious hazards associated with the use of animals in medical research have also been reviewed *(37–39)*. The clinical diseases associated with specific zoonotic agents and their therapy are well covered in infectious diseases textbooks *(40,41)*.

Multiple recent outbreaks of zoonotic diseases that have occurred as a result of petting zoos have called attention to the risks of human–animal contact, especially for young children (42,*43–45*). Recommendations to prevent such outbreaks have recently been published (46). In recent years, there has been a growing appreciation that most emerging infectious diseases are of zoonotic origin (*47–50*,51,52). Finally, with the exception of smallpox, virtually all potential bioterrorist agents are zoonotic pathogens including *Bacillus anthracis* (anthrax), *Coxiella burnetii* (Q fever), *Francisella tularensis* (tularemia), and *Yersinia pestis* (plague) *(53–62)*. Bioterrorist agents are discussed in Section XVII Bioterrorism. In the future, zoonotic pathogens may be introduced into humans via the use of xenotransplantation (*63–66*,67,*68*).

POTENTIAL HAZARDS OF ANIMALS IN THE HOSPITAL

A comprehensive literature survey of human pathogens listed more than 1,400 infectious agents capable of causing human infection *(47)*. Of these, more than half are known to be zoonotic (i.e., able to infect other host species). However, strictly speaking, zoonoses refer only to those diseases that are transmitted from vertebrate animals to humans. In most cases, humans are accidentally infected and are dead-end hosts. Other pathogens also share maintenance of their life cycle with both animals and humans. In addition, the ectoparasites of some domestic animals carry pathogenic microorganisms, which may spread to humans through close association with infested animals.

Humans may come into contact with animals through many activities, including pet ownership; leisure pursuits such as camping, hunting, and hiking; travel to remote regions; and via occupations such as animal husbandry, medical research, veterinary medicine, animal control, and handling of agricultural products or animal hides. This chapter reviews only the diseases most likely to be transmitted by domesticated animals that serve as pets or service animals, because these animals are most likely to be encountered in the hospital (Table 94-1). These common pets include birds; cats; dogs; rodents such as mice, rats, gerbils, and hamsters; and fish, turtles, snakes, and rabbits. Nonhuman primates that may be used to aid disabled persons are also discussed.

Potential Pathogens

Animals commonly used as pets can serve as the reservoir or source for a significant number of diseases that potentially could be transmitted to humans in the healthcare

TABLE 94-1

Diseases Potentially Transmitted by Pets in the Healthcare Setting

Infectious Disease	*Cats*	*Dogs*	*Fish*	*Fowl/Birds*	*Primates*	*Rabbits*	*Reptiles*[a]	*Rodents*[b]
Viral								
Simian herpes B virus					+			
Influenza A (avian)				+				
Lymphocytic choriomeningitis								+++
Monkeypox					+	+		+
Rabies	+	+						
Simian immunodeficiency virus					+			
Bacterial								
Aeromonas			+				+	
Anthrax	+	+						
Brucellosis		+						
Campylobacteriosis	+	++		++			++	++
C. canimorsus sepsis	+	+++						
Cat scratch disease	+++	+						
Ehrlichiosis		+						
Erysipeloid			+	+				+
Leptospirosis		+		+		+		+
Listeriosis		+		+		+	+	
Murine typhus								+
Mycobacteriosis (*M. marinum*)			+++					
Pasteurellosis	+++	++			+	+++		+
Plague	+							+
Psittacosis				+++				
Q fever	++							
Rat bite fever								+++
Rocky Mountain spotted fever		++						
Salmonellosis	+	+		+++	+	+++	+++	+++
Tuberculosis	+	+			+	+		
Tularemia	++	+				++		+
Vibriosis			+					
Yersiniosis				+	+	++	++	++
Parasites								
Cryptosporidiosis	+	+			+			
Dipylidiasis		+						
Dirofilariasis		+						
Echinococcosis		+						
Fleas	+	+						
Giardia lamblia		+			+			
Mites (scabies)	+	+						
Toxocariasis	++	+						
Toxoplasmosis	+++							
Mycotic								
Dermatophytosis	+	++				+++		+++

[a]Reptiles include lizards, snakes, and turtles.
[b]Rodents include hamsters, mice, and rats.
+, rare zoonoses; ++, occasional zoonoses; +++, most common zoonoses.
(Adapted from references *4,16,18*,19,*20*.)

setting (Table 94-2). These animals are also involved in the life cycles of an even wider variety of diseases in which healthcare-associated transmission is either rare or impossible (e.g., echinococcosis, leishmaniasis, schistosomiasis, and trypanosomiasis). New zoonotic pathogens continue to be recognized either because the microbial agent is newly isolated or because its potential to cause human disease is newly recognized *(47–52)*. Newly discovered zoonotic pathogens discovered outside the United States include Nipah virus *(69)*, Hendra virus *(70)*, and SARS-coV *(71)*, whereas newly discovered pathogens in the United States include Sin Nombre virus *(72)* and Southern Tick–Associated Rash Illness *(73)*. Zoonotic diseases endemic outside the United States may spread to the United States,

TABLE 94-2

Medically Important Zoonotic Diseases

Pathogen	*Disease*	*Medical Illness(es)*
Viral		
Coronavirus	SARS	Pneumonia (mortality 10–15%)
Herpesvirus simiae (B virus)	B virus infection	Erythema, vescicles, ulcers, and local pain at site of inoculation Rapidly progressive ascending neuropathy and encephalitis
Lymphocytic choriomeningitis (LCM)	LCM meningitis	Influenza-like illness and occasional meningitis
Orbivirus	Colorado tick fever	Biphasic disease: sudden onset of fever, prostration, headache, photophobia, muscle and joint pains; followed by 2- to 3-d remission; then second episode of fever and rash (10%)
Orthopoxvirus	Monkeypox	Variola-like skin eruption with lymphyadenopathy (mortality ~10%)
Rhabdovirus	Rabies	Encephalitis (mortality ~100%)
Rotavirus	Rotavirus	Enteritis
Bacterial		
Aeromonas spp.	Aeromonas	Gangrenous wound infection, gastroenteritis, and pneumonia
Bacillus anthracis	Woolsorter's disease	Localized skin lesions; mediastinal or intestinal infection (rare) leading to sepsis
Borrelia burgdorferi	Lyme arthritis	Three stages: (a) localized characterized by skin rash (erythema chronicum migrans); (b) disseminated characterized by musculoskeletal symptoms, neurological, or cardiac abnormalities, arthritis; (c) persistent infection with chronic skin, nervous system, or joint involvement
Borrelia spp.	Relapsing fever	Systemic disease marked by periods of fever alternating with afebrile episodes; erythema, petechia, jaundice may occur
Brucella spp.	Brucellosis	Systemic disease with acute or insidious onset, characterized by fever, headache, weakness, sweating, chills, arthralgia, and weight loss
Campylobacter jejuni	Campylobacteriosis	Gastroenteritis
Capnocytophaga canimorsus	Septicemia	Sepsis with multiorgan failure and cutaneous gangrene
Rochalimaea henselae	Cat scratch disease	Lymphadenitis, Parinaud's syndrome, meningo-encephalitis, and bacillary angiomatosis in HIV-infected patients
Chlamydia psittaci	Psittacosis	"Atypical" pneumonia
Ehrlichia spp.	Ehrlichiosis	Multisystem disease; may have rash
Erysipelothrix insidiosa	Erysipeloid	Skin infection (localized pain, erythema, edema surrounding wound); arthritis; and sepsis (rare)
Francisella tularensis	Tularemia	Indolent ulcer and adenopathy (ulceroglandular); pneumonia; systemic symptoms (typhoidal); pharyngitis, abdominal pain, diarrhea, and vomiting (gastrointestinal); conjunctivitis; and adenopathy (oculoglandular)
Leptospira interrogans	Leptospirosis	Variable disease; biphasic illness—sudden onset with fever, headache, severe myalgias, conjunctival suffusion, rash, meningitis, hepatorenal failure, and CNS involvement
Listeria monocytogenes	Listeriosis	Variable disease, meningitis, and abortion
Mycobacterium marinum	Skin granulomas	Local ulcerative disease
Mycobacterium tuberculosis	Tuberculosis	Pneumonia, disseminated infection, and meningitis
Pasteurella multocida	Pasteurellosis	Cellulitis, septic arthritis, osteomyelitis; pneumonia; meningitis; endocarditis; sepsis; and intra-abdominal infection
Pseudomonas pseudomallei	Melioidosis	Fever, pneumonia, gastroenteritis; chronic cases may have necrotic and granulomatous soft tissue or bone lesions
Coxiella burnetti	Q fever	Variation in severity and duration; onset may be sudden with chills, headache, weakness, and malaise; pneumonitis and endocarditis may occur
Rickettsia rickettsii	Rocky Mountain spotted fever	Systemic illness with fever, headache, rash, meningitis, multiorgan failure
Salmonella enteriditis	Salmonellosis	Gastroenteritis, sepsis (occasionally), and osteomyelitis
Staphylococcus aureus	Staphylococcal infection	Skin and soft tissue infections, osteomyelitis, endocarditis, toxic shock syndrome, and gastroenteritis (toxin mediated)

(*Continued*)

TABLE 94-2

Medically Important Zoonotic Diseases (*Continued*)

Pathogen	*Disease*	*Medical Illness(es)*
Streptococcus pyogenes	Streptococcal infection	Pharyngitis and cellulitis; streptococcal toxic shock syndrome
Streptobacillus moniliformis	Haverhill or rat bite fever	Systemic illness characterized by sudden onset fever and chills, headache and muscle pain, followed by rash, polyarthritis, and rarely endocarditis
Vibrio parahemolyticus	Vibriosis	Acute gastroenteritis
Yersinia enterocolitica	Yersiniosis	Acute ileitis; peritonitis may occur; rarely septicemia, reactive arthritis
Yersinia pestis	Plague	Systemic disease with multiple manifestations: lymphadenitis (bubonic), pneumonia (pneumonic), and sepsis
Fungal		
Dermatophytes	Ringworm	Skin disease (ringworm)
Parasitic		
Babesia microti	Babesiosis	Sepsis with fever, shaking chills, headache, gastrointestinal symptoms, and arthralgias; hemolytic anemia
Cryptosporidia spp.	Cryptosporidiosis	Gastroenteritis (self-limited in normal host, may become chronic in immunocompromised host)
Ehrlichia risticii	Ehrlichiosis	Systemic illness similar to Rocky Mt. spotted fever without rash
Giardia lamblia	Giardiasis	Chronic diarrhea
Toxoplasma gondii	Toxoplasmosis	Usually asymptomatic, lymphadenopathy, chorioretinitis, and encephalitis (immunocompromised host)

(Adapted from references *4-6,8,9,27,28.*)

leading to sporadic infections or outbreaks such as dengue *(74)*, monkeypox *(75)*, and West Nile disease *(76)*.

Healthcare-Associated Hazards of Animals in the Hospital

Zoonotic diseases can be transmitted to humans through animal trauma (bites, scratches, and stings); direct contact; arthropod vectors; aerosols; and contamination of food, water, or milk *(4,77)* (Table 94-3). Physicians should be aware of the major clinical syndromes associated with zoonotic diseases and their potential to cause healthcare-associated infection (*78*,79,80) (Table 94-2).

Hospitalized patients often have altered host defenses that may increase their susceptibility to a zoonotic infection and/or increase the severity of clinical disease *(81–86)* (Table 94-4).

In addition to direct transmission from animal to human, healthcare epidemiologists and infection preventionists should be aware that some zoonotic diseases may be transmitted from human to human, whereas others may represent a hazard in the microbiology laboratory (Table 94-4) (see Chapter 77). Several recent papers have provided recommendations for the management of animals in public settings and healthcare facilities (46,*87–89*,90).

Unfortunately, few scientific studies have addressed the potential risks of animal-to-human transmission in the healthcare setting. Furthermore, because animals have, in general, been excluded from hospitals, experience gained by means of case reports and outbreak investigations is minimal. However, Lefebvre et al. *(91)* assessed 102 healthy visitation dogs for the presence of zoonotic pathogens. Zoonotic agents were isolated from 80% of animals including toxigenic *Clostridium difficile* (40.1%), *Salmonella* spp. (3%), extended spectrum β-lactamase (ESBL)- or cephaloporinase-producing *Escherichia coli* (4%), *Pasteurella* spp. (29%), *Malassezia pachydermatis* (8%), *Toxocaria canis* (2%), and *Ancylostoma caninum* (2%). Scott et al. *(92)* described an epidemic of methicillin-resistant *Staphylococcus aureus* (MRSA) on a rehabilitation geriatric ward. The paws and fur of a cat that roamed the ward were heavily colonized by MRSA, and the cat was considered to be a possible vector for the transmission of MRSA. Lyons et al. *(93)* described an outbreak of *Salmonella heidelberg* in a hospital nursery that was traced to infected calves on a dairy farm where the mother of the index patient lived. An outbreak of *Rhodococcus (Gordona) bronchialis* sternal surgical site infections after coronary artery bypass surgery was linked to a nurse whose hands, scalp, and vagina were colonized with the epidemic pathogen *(94)*. Although cultures of neck-scruff skin of two of her three dogs were also positive, whether the animals were the source for colonizing the nurse or whether both the animals and nurse were colonized from an environmental reservoir could not be determined. An evaluation of a large outbreak of *M. pachydermatis* in an intensive care nursery discovered that the isolates from all 15 case patients, 9 additional colonized infants, 1 healthcare worker, and 3 pet dogs owned by healthcare workers had identical patterns of restriction fragment length polymorphisms *(95)*. The authors believed that *M. pachydermatis* was likely introduced into the intensive care nursery from the healthcare worker's hands after being colonized from pet dogs at home and then persisted in the nursery through patient-to-patient transmission. Patient infections were not benign and included eight bloodstream infections, two urinary tract infections, one case of meningitis, and four asymptomatic colonizations. Multiple healthcare-associated outbreaks of

TABLE 94-3

Transmission of Important Zoonotic Diseases

Disease	*Aerosol*	*Ingestion*	*Contact*	*Animal Trauma*	*Arthropod-Vector*
Viral					
B virus infection		Saliva		Primate bite	
LCM meningitis	Infected aerosols	Food, water			
Colorado tick fever					Tick
Rabies	Probably bat caves, laboratory		Secretions, corneal tranplant	Wild animals, dog, cat	
Bacterial					
Aeromonas spp.	Fresh water drowning	Food, water	Water	Fish, reptile	
Anthrax	Spores in hides, spores in raw wool	Spores in contaminated meat	Spores in hides or environment	Contact with lesions on animals	
Brucellosis	Inhalation while handling animals or products	Goat cheese and milk products	Animal and food products		
Campylobacteriosis		Meat, poultry, milk, water	Puppies with diarrhea		
C. canimorsus sepsis				Dog bite	
Cat scratch disease				Cat scratch	
Ehrlichiosis					Tick
Erysipeloid			Fish slime, shellfish	Lobster or crab pinch	
Leptospirosis	Secretions, wild and domestic animals	Water, milk	Contaminated water		
Listeriosis		Vegetables, water, cheese			
Lyme arthritis					Tick
Melioidosis				Rodents	
Monkeypox	From infected animals		Primates, rodents		
Mycobacteriosis *(M. marinum)*			Water, fish tanks		
Pasteurellosis	Respiratory secretions		Cat, dog secretions	Feline bites and scratches, dog bites	
Plague	Inhalation-infected material		Infected animals	Cat scratch	Rodent flea
Psittacosis	Dried excreta from birds				
Q fever	Endospores from animal-contaminated soil, cat afterbirth		Infected animals		
Rat bite fever		Water, milk contaminated by infected urine		Lab and wild rodents	
Rocky Mountain spotted fever	Laboratory accident		Engorged tick		Tick
Relapsing fever					Tick
Salmonellosis		Food esp. poultry, eggs, shellfish, water	Fecal material reptile/amphibians		Cockroaches, bed bugs

(*Continued*)

TABLE 94-3

Transmission of Important Zoonotic Diseases (*Continued*)

Disease	*Aerosol*	*Ingestion*	*Contact*	*Animal Trauma*	*Arthropod-Vector*
Tuberculosis	Respiratory secretions	Milk (*M. bovis*)			
Tularemia	Droplet particles, dead birds, animals	Food including meat	Dressing squirrels, muskrats, etc.	Cat bite (rare)	Tick
Vibriosis		Shellfish			
Yersiniosis		Milk, water	Farm animals		
Fungal					
Dermatophytes			Dogs, cats		
Parasitic					
Babesiosis					Tick
Cryptosporidiosis		Cysts in water, ice			
Ehrlichiosis					Tick
Giardiasis		Cysts in water			
Toxoplasmosis		Oocysts from cat feces, tissue cysts from uncooked meat			

(Adapted from references *4,30,37,41*.)

Microsporum canis (ringworm) with person-to-person transmission have been described in newborn nurseries *(96,97)* or neonatal intensive care units *(98)*. In the latter case, the source of infection was a nurse, likely infected from her pet cat.

Outbreaks of Q fever have been described in a secondary school in which infected goats were maintained for teaching purposes *(99)*, in a psychiatric institution in which patients and staff worked with goats on a farm *(100)*, and in a university department in which sheep placentas were used for fetal respiratory studies *(101)*. There are two reports of postmortem examinations that lead to the transmission of *C. burnetii* to pathologists, mortuary technicians, doctors, and a medical student *(102,103)*. Person-to-person transmission of Q fever within a family that affected five members has been reported *(104)*. Healthcare-associated transmission has also been reported. There have been several reports of hospital staff who acquired Q fever via exposure to infected patients *(102,105,106)*. In the latter case, Q fever developed in an obstetrician 7 days after he cared for a woman undergoing a spontaneous abortion at 24 weeks. *C. burnetii* was identified in the fetal spleen and kidney, and the placenta, but not the lung. Probable patient-to-patient transmission has also been described *(107)*.

ANIMAL USE IN THE HOSPITAL

Service Animals as Aids for Disabled Persons

The Americans with Disabilities Act (ADA) of 1990 is a federal civil rights law that protects persons with disabilities from discrimination in areas of employment, public services, public accommodations, services operated by private entities, and telecommunications *(78)*. Title III of the ADA mandates that persons with disabilities accompanied by service animals generally must be allowed access with their service animals into places of public accommodation, including restaurants, public transportation, and healthcare facilities. The responsibilities of healthcare institutions under the Act have been extensively reviewed in a guidance document by the Association for Professionals in Infection Control and Epidemiology *(78)*. *Disability*, as defined in the ADA, is any physical or mental impairment that substantially limits one or more major life activities such as breathing, hearing, or caring for oneself. *Service animal* is a legal term defined in the ADA. A service animal is a dog individually trained to do work or perform tasks for the benefit of a person with a disability. A service animal is not considered a "pet," because it is specially trained to help a person overcome the limitations caused by his or her disability *(78)*.

Dogs are most often trained for service work *(78)*. In the United States, an estimated 5,000 working dogs guide the visually impaired, more than 2,500 working dogs assist the hearing impaired, and more than 2,500 working dogs aid the physically challenged persons *(108)*. Service animals provide several valuable services, including enhanced mobility, dignity, decreased anxiety, improved confidence, and independence *(109)*. Not surprisingly, visually challenged persons have a close relationship with their dogs. The importance of guide dogs is well recognized, and they are often exempt from public health regulations governing dogs in general. Animals may also be used to aid the hearing disabled and physically disabled patient; however, these uses are less well described than those of guide dogs.

TABLE 94-4

Zoonotic Diseases with Special Healthcare-Associated Concern

			Compromised Hosts with Increased Susceptibility[a]	
Disease	*Human-to-Human Transmission*	*Important Laboratory Hazard*	*At-Risk Population*	*Disease*
Viral				
LCM meningitis	Not described	Yes	Not described	
Colorado tick fever	Not described	No	Not described	
Rabies	Anecdotal reports; corneal transplants	Yes	Not described	
Bacterial				
Aeromonas infection	Yes (contact, fecal–oral)	No	Not described	
Anthrax	Yes (contact)	Yes	Not described	
Brucellosis	Not described	Yes	Not described	
Campylobacteriosis	Yes (fecal–oral)	No	Not described	
C. canimorsus sepsis	Not described	No	Asplenia	Sepsis
Cat scratch disease	Not described	No	HIV infection	Bacillary angiomatosis, Bacillary peliosis
Erysipeloid	Not described	No	Not described	
Leptospirosis	Not described	Yes	Not described	
Listeriosis	Not described	No	Organ transplant	Sepsis, meningitis
			Chemotherapy	Sepsis, meningitis
Lyme disease	Not described	No	Not described	
Melioidosis	Yes (contact)	No	Not described	
M. marinum granuloma	Not described	No	Not described	
Monkeypox	Yes	Yes	Not described	
Pasteurellosis	Not described	No	Lung disease	Pneumonia
			Prosthetic joint	Septic arthritis
Plague	Yes (aerosol)	Yes	Not described	
Psittacosis	Yes (aerosol)	Yes	Not described	Chronic infection
Q fever	Yes (aerosol during birth)	Yes	Cancer	
Rat bite fever	Not described	No	Not described	
Relapsing fever	Not described	Yes	Not described	
Rocky Mountain spotted fever	Not described	Yes	G6PD deficiency	Death from infection
Salmonellosis	Yes (contact, fecal–oral)	Yes	Achlorhydria	Sepsis
			HIV infection	Prolonged infection, sepsis
			Hemoglobinopathy	Osteomyellitis
Tuberculosis	Yes (aerosol)	Yes	Organ transplant	Pneumonia, disseminated disease
			HIV infection disease	Pneumonia, disseminated disease
Tularemia	Not described	Yes	Not described	
Vibriosis	Yes (fecal–oral)	No	Cirrhosis (*V. vulnificus*)	Sepsis
Yersiniosis	Yes (fecal–oral)	No	Not described	
Fungal				
Dermatophytes	Yes (contact)	Yes	Not described	
Parasitic				
Babesiosis	Yes (transfusion)	No	Asplenia	Sepsis (death)
Cryptosporidiosis	Yes (fecal–oral)	No	HIV infection	Chronic gastroenteritis
Ehrlichiosis	Not described	No	Not described	
Giardiasis	Yes (fecal–oral)	No	Not described	
Toxoplasmosis	Yes (transfusion)	Yes	Organ transplant	Pneumonia
			HIV infection	Encephalitis

[a]Lack of a described risk should not be taken to imply that immunocompromised patients are not in fact at higher risk for disease acquisition or progression.

Healthcare facilities as places of public accommodation are required to permit the use of service animals by a person with a disability as defined by the ADA, unless doing so would create a fundamental alteration or a direct threat to the safety of others or the facility *(78)*. It is not permissible to require that a service animal wear special equipment or tag nor is it permissible to require "certification" or proof of an animal's training or a person's disability.

To ensure compliance with the ADA, healthcare facilities should have a written policy regarding the use of service animals by employees, patients, and visitors. This policy should ensure that service dogs and their owners have general access to the institution. The service animal policy should include the following topics *(78,110)*. First, the locations in the hospital from which the service animal is prohibited. Such areas would include those that pose a risk to patients, especially areas that require the use of sterile or clean precautions such as operating rooms, pharmacy, and kitchens. Also, the service animal should be prohibited from areas that pose a risk to the animal such as pathology and radiology. Second, facilities should not permit handlers with service animals to act as self-appointed animal-assisted therapy (AAT) ("pet therapy") providers. Third, employees, visitors, and patients should be educated to understand that service animals should not be allowed to come in contact with any patient's nonintact skin (e.g., surgical wounds and drainage tube). Fourth, there should be a mechanism to screen persons other than the handler (e.g., roommate) who may come into contact with the service animal for allergies or fears regarding the service animal. Fifth, the policy should define conditions on which the service animal may be removed, restricted, or denied access to an area. Such conditions might include aggressive behavior (i.e., biting), inability to contain excretions, or apparent illness. Evaluation of a potentially ill animal should be made by a veterinarian. Sixth, care and feeding of the service animal should be the responsibility of the owner or the handler or their designee rather than healthcare personnel. The facility may elect to provide temporary care such as during a short operative procedure but would need to have available trained personnel. Legal services should be consulted regarding any formal consent needed when the handler transfers responsibility for service animal stewardship to a facility representative. Finally, a mechanism should be in place for determining the appropriate use of a service animal on a case-by-case basis.

Differences Between Service Animals and Therapy Animals

Therapy animals and their handlers are trained to provide specific human populations with appropriate contact with animals *(111)*. They are usually personal pets of the handlers and accompany their handlers to the sites they visit, but they may also reside at a facility. Animals must meet specific criteria for health, grooming, and behavior. Therapy animals are usually not service animals. Federal law, which protects the rights of qualified persons with disabilities, has no provision for people to be accompanied by therapy animals in places of public accommodation that have "no pets" policies. AAT is a goal-directed intervention in which an animal is incorporated as an integral part of the clinical healthcare treatment process. Animal-assisted activities (AAAs) provide opportunities for motivational, educational, and/or recreational benefits to enhance a person's quality of life. Both AAT and AAA are delivered by a trained person.

Animal-Assisted Therapy

AAT is designed to promote improvement in the physical, psychosocial, and/or cognitive function of people who are being medically treated *(112)*. Other terms used in the literature for AAT are "pet therapy" or "pet-facilitated therapy." In a review of pet-facilitated therapy as an aid to psychotherapy, Draper et al. *(113)* noted that a literature review conducted in 1987 revealed more than 1,000 articles on the human–animal bond. As of 1983, however, only six studies of the therapeutic value of pets in which controls were used had been reported. They concluded that the benefits of pet therapy rely heavily on anecdotal reports and the widespread attachment of persons with animals. More recently, Allen *(114)* performed a critical appraisal of the literature from 1986 through 1997 and concluded that most reports describing the effects of human–canine interactions fell into the lowest category of scientific studies (i.e., descriptive studies and expert opinion). Newer research, sometimes using controlled trials, has provided evidence that companion animals provide health benefits in the home setting *(115)*. However, there continues to be a paucity of well-designed clinical trials evaluating the benefits of AAT in the hospital.

The benefits of AAT have been reviewed *(116–122)*. AAT has been most commonly reported to be beneficial among the chronically mentally ill *(118,123–125)*, geriatric patients *(126–130)*, patients with hypertension or coronary artery disease *(131,132)*, and human immunodeficiency virus–infected persons *(133)*.

Several recent articles have reviewed the potential risks associated with AAT in healthcare facilities *(87,134–136)*. Risks fall into four general areas: reservoir of multidrug-resistant human pathogens, animal bites or scratches, allergies, and transmission of a zoonotic infection. The potential risks of bites or acquisition of a zoonotic disease are reviewed later. However, to date, there have been no reports of illness or disease among hospitalized patients associated with a well-designed program that provides AAT.

ANIMALS USED IN HOSPITALS AS RESERVOIRS OF MULTIDRUG-RESISTANT PATHOGENS

Since the last revision of this chapter, there has been a growing literature that animals commonly used as pets or for AAT may be colonized with multidrug-resistant pathogens and that these animals may transmit such pathogens to human contacts (*137*,138,139). Of particular concern are MRSA, *C. difficile*, and ESBL-producing gram-negative bacilli *(140)*.

MRSA first emerged as a serious pathogen in human medicine in the late-1970s and has been increasingly reported in animals in the last 10 years *(141)*. Human strains of MRSA have increasingly been described in cats, dogs,

horses, and pigs. A cross-sectional study demonstrated a high prevalence of concurrent MRSA colonization as well as identification of indistinguishable strains in humans and pet dogs and cats in the same household *(142)*. Owners of MRSA-colonized dogs are more likely than owners of non-MRSA-colonized pets to be colonized with MRSA *(143)*. A positive correlation has been demonstrated between the presence of a cat in the home and isolation of MRSA from surfaces *(144,145)*. Recently, 2 of 11 resident cats of a long-term care facility were found to be colonized with MRSA *(146)*. It appears that humans are generally the vector for animal colonization *(141)*. For example, a pet therapy dog appears to have been colonized by MRSA after visiting the geriatric wards *(147)*. In a longitudinal study of dogs involved in AAT in healthcare facilities, Lefebvre et al. *(148)* demonstrated a rate of MRSA acquisition that was 4.7 times higher than in dogs involved in other animal-assisted interventions. However, animal-to-human transmission has been suggested. For example, Manian reported recurrent MRSA infection in a patient with diabetes and in his wife. The nares of the family dog were colonized with an identical strain of MRSA. Recurrence of MRSA infection and nasal colonization in the couple was halted only following successful eradication of MRSA from the dog's nares *(149)*. Similarly, Cefai et al. described a colonized dog that was implicated as reservoir for reinfection of two nurses after their treatment to eliminate MRSA carriage *(150)*. To date, the available data on MRSA transmission between humans and companion animals are limited, and the public health impact of such transmission needs to be the subject of more detailed epidemiologic investigations *(151)*.

The incidence of *C. difficile* infection in the United States has been noted to be increasing over the last decade in association with the emergence of a new, hypervirulent stain (NAP1/BI/O267) *(152)*. *C. difficile* is both a commensal microorganism and a pathogen in domestic and food animals *(153)*. Recent studies have found considerable overlap among bovine, equine, porcine, canine, and human isolates *(153,154)*. Toxigenic strains of *C. difficile* have been isolated from companion dogs, and dog colonization with *C. difficile* was associated with living with an immunocompromised individual *(155)*. Human strains of *C. difficile* have been isolated from the stool *(156)* and paws *(157)* of pet therapy dogs.

ESBL-producing gram-negative bacilli have been isolated from animals *(140)*. Recently, acquisition of a multidrug-resistant *E. coli* from a dog bite was reported *(158)*.

DISEASES TRANSMITTED BY ANIMAL BITES

Animal bites are a major public health problem *(159,160)*. National estimates based on a 1994 national telephone survey of randomly selected households revealed 4.7 million dog bites, of which approximately 799,700 necessitated medical attention *(161)*. These numbers corresponded to an annual incidence rate of 18 per 1,000 and bites requiring medical attention 3 per 1,000 (adults 2 per 1,000 vs. children 6.4 per 1,000). A follow-up survey from 2001 to 2003 revealed that an estimated 4.5 million people were bitten each year *(162)*. Compared with 1994, the incidence of dog bites among adults remained relatively unchanged whereas the incidence among children declined by 47%. Overall, 19% of dog bites required medical attention. Although most bite wounds are trivial and most victims do not seek medical attention *(162)*, bite wounds have been reported to account for approximately 1% to 2% of all emergency department visits in the United States *(162–167)*. More precise population-based estimates are available from a 1992 to 1994 National Center for Health Statistics survey, which reported that 334,000 dog-related injuries were seen in US emergency departments for a rate of 129 per 100,000 persons *(164)*. More recent data from the National Electronic Surveillance System-All Injury Program for the year 2001 revealed that an estimated 368,245 persons were treated in US emergency departments for dog bite–related injuries (rate: 129.3 per 10,000 population) *(168)*. This is slightly lower than the rate of 158 per 10,000 population reported from the 2001 to 2003 national cross-sectional telephone survey *(162)*. Although most bites produce only minor injury, at least 10% require suturing *(169)*, and 1% to 5% required hospitalization *(164,167,169–173)*. An estimated 5,991 hospitalizations resulted from dog bites in 1994 *(173)*. Between 1991 and 1998, 6,676 hospitalizations in California resulted from dog bites *(174)*. Attacks by dogs resulted in at least 25 deaths between 1995 and 1996 *(175)* and 27 deaths between 1997 and 1998 *(176)*. Between 1979 and 2005, an average of 19 deaths were reported annually from dog bites *(177)*. In summary, dog bites result annually in an estimated 17 to 19 deaths, 6,000 to 13,000 hospitalizations, and more than 330,000 emergency department visits, with the total costs of treating these injuries being $235,600,000 to $253,700,000 *(173,177)*. Because of its medical importance, the epidemiology, clinical management, and prevention of bite wounds have been extensively reviewed *(165,171,178–190)*.

Epidemiology

Only the epidemiology of bites relevant to risks associated with the use of animals in the hospital is reviewed here. Dog bites account for 70% to 93% of animal bites, and cat bites account for 3% to 15% *(165,171,191–193)*. Dog bites more commonly involve the lower extremities, followed by the hands, arms, face, and trunk *(165,171,179,193)*. A survey of dog bite wounds treated in the emergency department in 2001 revealed that 45% of injuries occurred to the arm and hand but that injuries to the extremity increased with age and accounted for 86.2% of injuries treated in persons 15 years of age *(168)*. Cat bites more commonly involve the hands, followed by the arms, lower extremities, face, and trunk *(165,179,194)*. The peak incidence of bites occurs in persons 5 to 9 years of age *(164,168–170,193)*. Compared with older children and adults, young children have a higher risk of being bitten and of suffering fatal injuries from bites *(172,175,195–197)*; bites are more likely to involve the face, head, or neck *(164,168,195,198,199)*; bites are more likely to occur at home and to be caused by the child's pet *(164,172,196)*; and the attacking dog is less likely to have a history of biting *(172)*.

About two-thirds of bites occur when interacting with a dog (e.g., petting, feeding, and playing) or when on the dog owner's property *(193,200)*. Only about 25% of victims, however, report direct interaction with the dog, such as

feeding, playing, or petting *(193)*. Only a small proportion of bites occur when the dog has been teased or abused. Large dogs are more commonly involved than small dogs in attacks. Shepherds and mixed breeds are most commonly named as the biting animal *(165,198,199,200)*. During 1995 to 1996 and 1997 to 1998, Rottweilers were the most commonly reported breed involved in fatal attacks *(175,176)*.

Etiologic Agents of Infection

The infection rate from penetrating dog bites has generally been reported in the range of 5% to 15% *(165,166,181,201)*. Cat bites are more likely to become infected than dog bites *(165,202)*. Factors that increase the risk of infection after a dog or cat bite include (a) full-thickness puncture; (b) hand or lower extremity wounds; (c) wounds requiring surgical debridement; (d) wounds involving joints, tendons, ligaments, or fractures; and (e) wounds in patients who are high-risk hosts *(181)*.

A large number of aerobes and anaerobes have been isolated from the gingival flora of cats and dogs *(203,204)*. Pathogenic microorganisms derived from the normal oral flora of cats and dogs can be isolated from approximately 90% of clinically infected wounds *(205,206)*. Most infections that develop after a cat or dog bite are polymicrobial *(206–208)*. Goldstein, Talan, and associates *(207–211)* have studied the microbial agents associated with animal bite infections. The most common aerobic microorganisms isolated from infected dog bites were *Pasteurella* species 50%, *Streptococcus* species 46%, *Staphylococcus* species 46%, and *Neisseria* species 16% *(208)*. The most common aerobic microorganisms isolated from infected cat bites were *Pasteurella* species 75%, *Streptococcus* species 46%, *Moraxella* species 35%, *Staphylococcus* species 35%, and *Cornyebacterium* species 28% *(208)*. Anaerobic microorganisms are commonly isolated from both cat bite and dog bite wounds. In addition to these microorganisms, others included *Enterococcus* species, *Eikenella corrodens*, EF-4a and 4b, *Micrococcus* species, *Acinetobacter actinomycetemcomitans*, and *Haemophilus aphrophilus*. Rarely, gram-negative bacilli, such as *Proteus mirabilis*, *Enterobacter cloacae*, and *Pseudomonas fluorescens*, have been isolated from infected wounds. Of particular importance is *Capnocytophaga canimorsus*, which has been associated with severe sepsis and a high case–fatality rate. Unusual infections following dog bites have included blastomycosis *(212)*, leptospirosis *(213)*, brucellosis *(214)*, and salmonellosis *(215)*. Unusual infections transmitted by cat bites or scratches have included tularemia *(216–228)* and plague *(229–232)*.

The anaerobic bacteria isolated from dog bite wounds may include species of *Actinomyces*, *Bacteroides*, *Fusobacterium*, *Peptostreptococcus*, *Eubacterium*, *Veillonella*, and *Leptotrichia*. The constituents of the oral flora of animals may occasionally be β-lactamase producers *(205)*.

A large number of pathogens may occur in infections that complicate the bites of animals other than dogs and cats *(178)*; however, a few generalizations may be made. All felines, including lions, cougars, panthers, and tigers, may transmit *Pasteurella multocida. P. multocida* may also be transmitted by other animals, including pigs, rabbits, rats, opossums, and wolves. The agents of rat bite fever, *Streptobacillus moniliformis* and *Spirillum minor*, may be transmitted by several small rodents, such as the rat, mouse, and gerbil *(233)*. Bites inflicted in the water or by aquatic animals or reptiles (alligators, snakes, and piranhas) may become infected with *Aeromonas hydrophila*, *Vibrio* species, or *Edwardsiella tarda*. Although most cases of tularemia follow the handling of rabbits, infection may be transmitted by bites from other animals, such as the cat, coyote, pig, and squirrel. Ferrets have become a popular pet in recent years. Ferret attacks are common and may lead to severe injury and even death, especially among young infants *(234,235)*. Ferrets have been the source of viral influenza *(236)* and *Mycobacterium bovis* chronic wound infection *(237)*. Potential zoonotic diseases include leptospirosis, listeriosis, salmonellosis, campylobacteriosis, tuberculosis, rabies, cryptosporidiosis, dermatophytosis, scabies, and various helminth infections (visceral larva migrans, cutaneous larva migrans, dipylidiasis, and dirofilariasis) *(238)*.

More than 80 strains of aerobic bacteria have been isolated from the mouths of rhesus monkeys *(239,240)*. Nonhuman primate bites can result in infection with herpes B virus, *E. corrodens*, *Corynebacterium* species, α-hemolytic streptococci, and occasionally *Enterobacteriaceae (241)*. Nonhuman primates may become infected with bunyaviruses (Marituba fever, Caraparu fever, and Oropouche virus), poxviruses (tanapox and monkeypox), rhabdoviruses (Marburg disease), togaviruses (Kyasanur forest virus, yellow fever, and Zika fever), hepatitis A, hepatitis B, *Campylobacter*, *Salmonella*, *Shigella*, *Mycobacterium tuberculosis*, *Yersinia* species, *Giardia*, *Cryptosporidia*, filaria (*Brugei malayi*), flukes (*Paragonimus westermani*), and flatworms (*Schistosoma japonicum*). Transmission to humans for some pathogens (e.g., *B. malayi*) may require the presence of specific arthropod vectors. Other agents may be transmitted by the respiratory route (e.g., *M. tuberculosis*) or the fecal–oral route (e.g., hepatitis A). Of these pathogens, laboratory personnel have acquired Marburg virus, Ebola virus, monkeypox, hepatitis A, *Shigella*, tuberculosis, and herpes B virus infection. To date, more than 25 cases of herpes B virus infection in humans have been reported *(242–246)*, with a case–fatality rate of >50%. A guideline designed to prevent herpes B virus infection in monkey handlers has been published *(247)*.

PATHOGENS OF SPECIAL IMPORTANCE

Pasteurella Species

Epidemiology and Microbiology *Pasteurella* spp. are small, nonmotile, nonspore-forming, gram-negative coccobacilli. On gram-stained smear, the microorganisms generally appear as a single bacillus but may occur in pairs or chains. They frequently show bipolar staining. The microorganisms are aerobic, facultatively anaerobic, and grow well at 37°C on blood, chocolate, and Mueller–Hinton agar but not on MacConkey's agar. Growth is facilitated by enriched media and increased CO_2. More than 17 species of *Pasteurella* are known; *P. multocida* subspecies *multocida*, *P. multocida* subspecies *septica*, *P. canis*, *P. stomatis*, and *P. dogmatis* are the most common pathogens in humans *(248)*. One author noted that *P. multocida* subspecies *septica* was more likely to be isolated from wounds and

P. multocida subspecies *multocida* from the respiratory tract *(248)*. However, a larger study reported that for both cat- and dog-associated bite wounds, *P. multocida* subspecies *multocida* was more commonly isolated than *P. multocida* subspecies *septica (208)*.

P. multocida has been isolated from the digestive system or respiratory tract of domestic cats and dogs, rats, mice, rabbits, cattle, sheep, swine, horses, and monkeys. Carriage rates of *P. multocida* in the oral or nasal secretions of various apparently well animals are high: 70% to 90% in cats, 50% to 66% in dogs, 51% in pigs, and 14% in Norway rats.

Most human infections result from direct inoculation by bites or scratches. Infections following animal exposure in the absence of bites or scratches probably stem from contact with animal secretions. *P. multocida* infections are frequently associated with impaired host defenses and include the following localized infections (host defense defects): septic arthritis (prosthetic joints or joints damaged by degenerative or rheumatoid arthritis), meningitis (infants younger than 1 year of age or elderly persons), spontaneous bacterial peritonitis (cirrhosis), sepsis (alcoholism and diabetes mellitus), lower respiratory tract infections (chronic obstructive pulmonary disease and bronchiectasis), urinary tract infections (underlying structural and/or functional alterations), and endocarditis (prosthetic valve). Human-to-human spread of infection has not been documented, and contaminated food or water has not been implicated as a source of infection.

Clinical Features of Disease and Diagnosis Infections with *P. multocida* may be divided into three categories *(249)*. First, soft tissue infections may follow animal bites or scratches *(250–253)*. Rapidly spreading cellulitis is the most common presentation. Joint or bone penetration may lead to septic arthritis or osteomyelitis *(254)*. Prosthetic joints may be seeded by more distal injury with infection *(255,256)*. Second, *P. multocida* may cause respiratory tract colonization or infections such as acute pneumonia, chronic pneumonitis, or empyemas *(250,252,257–259)*. Most infected patients have underlying pulmonary diseases, including bronchitis, chronic obstructive pulmonary disease, or bronchiectasis. A history of animal contact is common, but actual bites or scratches are rare. Finally, *P. multocida* may cause serious systemic diseases such as endocarditis *(260,261)*, meningitis *(262–264)*, intra-abdominal infection *(252,265,266)*, urinary tract infection *(267)*, and sepsis *(268–270)*.

Definitive diagnosis requires isolation of the microorganism. However, *P. multocida* should be considered a potential pathogen in any skin or soft tissue infection after an animal bite, especially that of a cat or a dog.

Capnocytophaga Canimorsus

Epidemiology and Microbiology *C. canimorsus* (dysgonic fermentor-2 [DF-2]) is a fastidious, gram-negative, opportunistic pathogen that can cause serious multiorgan disease in humans. More than 100 cases have been described in recent reviews *(270–280)*.

C. canimorsus is a thin nonspore-forming rod 1 to 3 μm long. The microorganism exhibits gliding motility and is oxidase- and catalase-positive but negative for nitrate reduction, urease, and indole. It is a fastidious, slow-growing microorganism that, depending on the culture method used, may take from 3 to 11 days to form mature colonies.

C. canimorsus has a worldwide distribution. Studies suggest that it is part of the normal gingival flora of cats and dogs. Although infected patients have ranged from infants to persons older than 75 years, 60% of infections have been reported in adults older than 50 years.

Approximately 80% of patients reported in the literature have a predisposing condition, most commonly splenectomy. Other predisposing conditions have included Hodgkin's disease, trauma, idiopathic thrombocytopenic purpura, alcohol abuse, steroid therapy, and chronic lung disease. Forty percent of the cases of sepsis, however, have occurred in persons with no predisposing condition. Sepsis is the most common clinical infection. *C. canimorsus* infections range from mild to fulminant, with shock, respiratory distress, and disseminated intravascular coagulation. Meningitis may occur *(281,282)*. Dermatological lesions (maculopapular rash and purpura) or gangrene are common. The overall mortality is approximately 30%.

Infection is strongly associated with dog bites. More than 50% of patients have reported dog bites before clinical infection. Infections have also followed cat bites or scratches *(278,283,284)*, scratches from dogs, and contact with wild animals. An additional 20% of patients have reported exposure to dogs without a history of an actual bite or scratch.

Clinical Features of Disease and Diagnosis The clinical syndrome in humans is characterized by disseminated intravascular coagulation, cellular necrosis in certain organs such as kidneys and adrenal glands, cutaneous gangrene, thrombocytopenia, hypotension, hemorrhagic diathesis with purpuric skin lesions and petechiae, and renal failure with oliguria and anuria. The case–fatality rate is approximately 25%. Death has not been confined to immunocompromised patients.

Infection with *C. canimorsus* should be considered in patients who have a compatible clinical syndrome with a history of a dog bite or animal exposure. Definitive diagnosis requires isolation of the microorganism from blood or other body fluids or tissues. Empiric therapy should be instituted based on the clinical presentation. In patients who show high-grade bacteremia, the microorganism has been demonstrated in peripheral blood smears *(285,286)*. Therefore, all patients suspected of having *C. canimorsus* sepsis, especially splenectomized patients, should have a Gram stain of their buffy coat.

Cat Scratch Disease

Epidemiology and Microbiology Multiple species of *Bartonella* have now been demonstrated to be pathogenic for humans *(287,288)*. Clinical syndromes caused by these bacteria (etiologic agents) include the following: Oroya fever and verruga peruana (*B. bacilliformis*), bacteremia and endocarditis (*B. quintana* and *B. henselae*), bacillary angiomatosis (BA) and peliosis (*B. quintana* and *B. henselae*), HIV-associated neurologic syndromes (*B. quintana*), and cat scratch disease (CSD) (*B. henselae*, *B. clarridgeiae*, and *Afipia felis*) *(289–296)*. *B. henselae* is considered the primary agent of CSD *(297)*.

The syndrome of regional lymphadenopathy after a cat scratch was first described in 1932 by Lee Foshay in the United States and Robert Debre in France. Debre and Lamy provided the definitive description of CSD in 1950. A clinical diagnosis of CSD was established by the presence of three of four criteria including (a) a history of animal (in 99% of cases, a cat or dog) contact with an abrasion, scratch, or ocular lesion; (b) a positive cat scratch skin test result; (c) negative results of laboratory studies for other causes of lymphadenopathy; and (d) characteristic histopathology of the lymph node.

Infection with *Bartonella* species results in disease syndromes of variable severity, ranging from lymphadenopathy only (CSD) to systemic disease. As noted by Anderson and Neuman *(294)*, the severity and presentation of disease are related to immune status. In general (excluding *B. bacilliformis*), immunocompetent patients who are otherwise healthy tend to present with classic CSD when infected with *B. henselae*. Patients who are immunocompromised by having AIDS, chronic alcoholism, immunosuppression, or other serious health problems tend to have systemic disease; however, there have been rare reports of systemic disease, including BA, in immunocompetent persons *(298)*.

Clinical Features of Disease and Diagnosis CSD most commonly occurs among children and adolescents. Typically, it begins 4 to 6 days after animal contact (most commonly a scratch by a cat, especially a kitten) with the formation of a 2- to 3-mm macule at the site of inoculation, which progresses to a papule or pustule. Inoculation papules are described in 50% to 76% of reports *(299)*. Approximately 3 weeks after inoculation, regional adenopathy develops (range 5–50 days). About 80% of involved nodes are located in the head, neck, or upper extremities. The node is tender in 80% of patients and suppurates in 15% of patients. Fever and malaise each accompany the illness in about 30% of patients. Resolution occurs spontaneously in 2 to 6 months. Less common clinical findings include rash, hepatosplenomegaly, lytic bone lesions, granulomatous conjunctivitis, pneumonitis, endocarditis, and central nervous system involvement *(300)*. *B. henselae* has been shown to be the third most common cause of fever of unknown origin in children, accounting for approximately 55% of cases.

Manifestations of *Bartonella* infection in the immunocompromised patient include cutaneous BA, extracutaneous lesions, bacillary peliosis hepatitis, and fever with bacteremia *(301–303)*. BA is the most common clinical manifestation of *Bartonella* infection in the immunocompromised person. Clinical findings associated with BA include elevated, friable, firm, bright red papules (67% of cases); subcutaneous nodules (50%); and cellulitis plaques (5–10%). Extracutaneous manifestations may be present and include visceral lesions in the respiratory or gastrointestinal mucosa, heart, liver, spleen, bone marrow, muscles, or lymph nodes.

CSD is diagnosed by its distinctive clinical picture and the characteristic histology of lymph node biopsies. Similarly, BA is diagnosed by its clinical syndrome and characteristic histology of skin or liver biopsies. Serologic tests (indirect fluorescence assay and enzyme immunosorbent assay) for the diagnosis of *B. henselae* are now widely available. In addition, polymerase chain reaction tests are now commercially available using tissue or blood.

Prevention of Animal Bites in the Hospital

Hospital personnel and owners of seeing-eye dogs should be notified to discourage the petting of such dogs. Petting and playing with dogs distracts them from their primary responsibility and might lead to injury.

Animals used for pet therapy should be carefully screened, and all encounters should be carefully supervised. Patients who might benefit from pet therapy should be carefully screened as well. Toddlers, patients with psychiatric difficulties, and active children are probably at higher risk for bites and should either be excluded from pet therapy or carefully supervised. Guidelines for the prevention of animal bites have been published *(304,305)*. Immunocompromised patients, including functionally asplenic patients and HIV-infected patients, also should not interact directly with animals. All patients bitten or scratched in the hospital should be appropriately evaluated.

DISEASES TRANSMITTED BY DIRECT CONTACT

Ectoparasites

Animals may be infested with ectoparasites, which harbor microorganisms potentially pathogenic for humans, either transiently or chronically. Animals that are allowed outdoors, such as cats and dogs, are at special risk for becoming infested. Once infested, close contact with humans may allow transmission of infection. Of most concern are tick-borne diseases, which in the United States include babesiosis, Colorado tick fever, ehrlichiosis, anaplasmosis, Lyme disease, relapsing fever, Rocky Mountain spotted fever, southern tick–associated rash illness, and tularemia *(306–312)*. In general, the reservoirs for these diseases are small animals, such as rodents or rabbits. Only in the case of ehrlichiosis is the dog believed to be a possible reservoir. In other cases, the dog acts as a passive carrier of the infected tick. Pets may become ill with leptospirosis, Rocky Mountain spotted fever, and tularemia.

As with humans, pets should be inspected twice daily for ticks. Removal is best accomplished by grasping the head of the tick with a forceps and gently pulling until it is removed *(313)*. Care should be taken to avoid crushing attached ticks, spraying blood from engorged ticks, and excoriating the area. After removal, the area should be cleansed with soap and water or a disinfectant.

Cats and dogs could also be agents for transmitting plague to humans via its rodent flea vector. Plague causes a self-limited disease in dogs, but cats are susceptible to severe and often fatal infection. Animal fleas are best eradicated by flea dips. Pets should not be allowed to forage in areas where *Y. pestis* is prevalent.

Scabies is caused by a subspecies of the mite *Sarcoptes scabiei (314)*. The subspecies that infects cats and dogs can occasionally be transmitted to humans. These mites can cause intensely pruritic, papular, excoriated lesions but do not cause burrows, because the animal subspecies cannot complete its life cycle in humans. Hence, disease

is a manifestation of hypersensitivity in the human host. Diagnosis is by clinical presentation because skin scrapings are negative. Multiple healthcare-associated outbreaks of scabies have been reported *(315–317)*. Control measures have been described *(316,317)*.

Fleas from infested animals, as well as those in the environment, will feed on humans *(314)*. They also carry the intermediate stage of the tapeworm, *Dipylidium caninum* (human infestation occurs via ingestion of infected fleas).

Pathogenic Bacteria

In addition to harboring *Staphylococcus* spp. *(318)*, animals may rarely harbor pathogenic *Streptococcus* species in their eyes *(319)*, on their fur, or in their pharynx. Occasionally, humans may become infected as a result of animal contact. For example, a household cat or dog has occasionally served as the reservoir for household infections with the group A *Streptococcus (320)*.

Dermatomycoses

Zoophilic dermatophytes occasionally cause disease in humans. *M. canis* (less commonly *M. gypseum* and *Trichophyton mentagrophytes*) produces most superficial fungus infections of dogs and cats and may cause tinea capitis or ringworm in humans *(19,321)*; however, cats, the major reservoir for *M. canis*, often have inconspicuous or subclinical infections. These infections may not be suspected until lesions appear on human contacts. Ten percent to 30% of cases of human dermatophytoses in urban settings are estimated to be of animal origin.

The spectrum of disease is variable and can include circular alopecia, scaling and crusting lesions, or ulcers and nodules. Ringworm is characterized by an annular, expanding, erythematous area with central scaling, crusting or healing, and surrounding follicular papules. An exudative secondary bacterial infection may occur. Wood's light examination of hairs demonstrates *Microsporum* infection by showing blue-green fluorescence. Zoophilic fungal infections may also be demonstrated by scraping the lesions followed by examination with 20% potassium hydroxide. Exact identification of pathogens requires culture on fungal media.

Aquariums and Water-Related Diseases

A large number of bacterial infections may be acquired by trauma sustained in water or by injuries caused by water-dwelling animals *(322–324)*. The most important of these pathogens are *A. hydrophila*, *E. tarda*, *Erysipelothrix rhusiopathiae*, *Mycobacterium marinum*, *Vibrio cholerae* non-O1, *V. parahaemolyticus*, and *V. vulnificus*. Aquarium-acquired *Plesiomonas shigelloides* infection has been reported in a 14-month-old girl *(325)*. Cercarial dermatitis occurred in a 33-year-old man who stocked his aquarium with local snails *(326)*.

M. marinum causes granulomatous, papular cutaneous lesions in humans. Deep tissue infections may also occur and include tenosynovitis, septic arthritis, and osteomyelitis. Many cases result from injuries sustained while cleaning fish tanks *(327–336)*. Rarely, infections due to other *Mycobacterium* spp. have been associated with care of an aquarium *(337)*. A public aquarium was reported to be the source of an outbreak of Legionnaires' disease *(338)*. Pet turtles *(339)* and frogs *(340)* that are often maintained in home aquariums have been responsible for multistate outbreaks of salmonellosis.

Other potential infections that could be acquired by maintaining an aquarium include erysipeloid and gangrenous soft tissue infections. Erysipeloid is a skin infection of pig handlers, abattoir workers, and fish workers worldwide. Infection usually results when the microorganism contaminates cuts and abrasions. Infection is characterized by erythema with pain and edema of skin spreading peripherally. Septic arthritis may develop. Severe cellulitis, including gangrenous soft tissue infection, may result from infection with *A. hydrophila* or *V. vulnificus. Aeromonas* infection has also followed the use of medicinal leeches (see following section).

A large number of marine animals may injure humans via bites or stings or when humans ingest them *(341–346)*.

Because aquariums may harbor the aforementioned pathogens, aquariums, if present in a medical facility, should be cleaned only by trained medical personnel. In addition, because water may serve as a reservoir for multiple antibiotic-resistant gram-negative bacilli, aquariums should not be maintained in areas frequented by immunocompromised or intensive care patients.

Francisella tularensis

Epidemiology and Microbiology *F. tularensis* is capable of infecting more than 100 species of wild and domestic animals and more than 100 species of invertebrates *(347)*. The diversity of both biological and mechanical vectors is also high (>15 ticks, >10 mosquitoe species, tabanid flies, mites, fleas, and lice) *(348,349)*. Natural foci of infection are found in the Northern Hemisphere. Both sporadic *(350)* and epidemic cases occur *(351)*.

Tularemia may be acquired via multiple routes including (a) direct contact with infected animals, including bites, scratches, and contact with nonintact skin or mucous membranes; (b) arthropod bite (most commonly an infected tick); (c) inhalation of contaminated animal products in the laboratory; and (d) ingestion of contaminated food or water *(348,349,352–361)*. Crushing of infected ticks living on dogs may also lead to infection *(362)*.

Clinical Features of Disease and Diagnosis The incubation period is 3 to 5 days (range 1–21 days). Multiple clinical forms have been described; they are determined principally by the agent's route of entry *(348,349,356–362)*. Tularemia usually starts abruptly, with onset of fever, chills, headache, anorexia, malaise, and fatigue. Other symptoms include myalgia, cough, vomiting, pharyngitis, abdominal pain, and diarrhea. Fever typically lasts several days, remits for a brief period, and then recurs *(363,364)*. Presentations of tularemia include the following:

1. Ulceroglandular (21–78% of cases)—The most common presentation of tularemia is the ulceroglandular form, which accounts for about 85% of cases in the Western Hemisphere. A local lesion is seen at the site of entry (an arthropod bite or an injury inflicted by a contaminated sharp), which progresses to a necrotic ulceration accompanied by swelling of the nearby lymph node. The node frequently suppurates, ulcerates, and becomes sclerotic.
2. Oculoglandular (0–5% of cases)—This form develops when infective material comes into contact with the

conjunctiva. The primary lesion consists of an ulcerated papule on the lower eyelid that is associated with regional adenopathy *(365)*.

3. Glandular (3–20% of cases)—Occasionally, lymphadenopathy may occur in the absence of an ulcerative local lesion. The course is similar to ulceroglandular fever.
4. Pulmonary (7–20% of cases)—Pneumonia may result from inhalation of an infected aerosol from handling dead animals or examining pets that are ill with respiratory infections and when laboratory workers attempt to isolate the pathogen on agar plates *(366–370)*. During septicemia, the microorganisms can lodge in pulmonary tissues and give rise to secondary tularemic pneumonia. Symptoms include cough and high fever, occasional pleurisy, and rarely dyspnea. The chest radiograph may demonstrate disproportionately extensive disease compared with the physical examination.
5. Typhoidal (5–30% of cases)—The typhoidal form, which is uncommon, results from ingestion of contaminated food (usually rabbit meat) or water. Symptoms include fever, prostration, and gastroenteritis. Ulcerative lesions are found in the mucosa of the gastrointestinal tract.
6. Miscellaneous—Uncommon forms of tularemia include oropharyngeal (0–12% of cases), caused by ingestion of contaminated food or water, and meningitis (rare) *(371)*. Infection of a central nervous system shunt has been reported *(372)*.

Tularemia may be a serious disease. The case–fatality rate in untreated patients for the pneumonic and typhoidal forms is between 40% and 60%.

The diagnosis is often suspected on the basis of an appropriate exposure history or with an eschar at the site of an arthropod bite; it may be confirmed by serologic testing. Since the microorganism is fastidious, routine cultures of blood, lymph nodes, sputum or pharynx, and skin lesions are usually negative.

RESPIRATORY INFECTIONS TRANSMITTED FROM ANIMALS

The diagnosis of a lower respiratory tract infection is relatively simple in most cases. The major symptoms are fever, productive or nonproductive cough, chest pain that may be pleuritic, and shortness of breath. Headache and myalgias are common. Physical examination and chest radiography can confirm the diagnosis. Despite the relative ease of diagnosis, defining the etiologic agent of pneumonia remains difficult. Etiologic agents are commonly grouped into "typical" and "atypical" agents. Typical agents include *S. pneumoniae*, *Streptococcus* species, *S. aureus*, and *H. influenzae*. Atypical agents most commonly include respiratory viruses, mycoplasma, *Chlamydia pneumoniae*, and *Legionella pneumophila*; however, a variety of zoonotic pneumonias that are community acquired must be considered in the differential diagnosis of "atypical pneumonia" *(373,374)*.

Etiologic Agents and Epidemiology

Several zoonotic agents transmitted from pets may produce significant respiratory symptoms. Diseases transmitted by the aerosol route include anthrax, brucellosis, plague, psittacosis, Q fever, and tularemia. Other zoonotic agents that may involve the lungs include CSD, dirofilariasis, echinococcosis, ehrlichiosis, leptospirosis, melioidosis, pasteurellosis, Rocky Mountain spotted fever, toxocariasis, and toxoplasmosis. Of these, the pathogens most likely to be transmitted during pet therapy would be *Chlamydia psittaci* from infected birds, *C. burnetii* by infected cats, and *P. multocida* by close animal contact.

Pets, especially dogs, can develop fungal pneumonia following exposure to an environmental source with *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Cryptococcus neoformans*. Common-source outbreaks involving humans and dogs of histoplasmosis and blastomycosis have been described. In general, animal-to-human transmission does not occur; however, animal-to-human transmission of blastomycosis has been reported after dog bites.

The etiologic agents of mammalian tuberculosis (*M. tuberculosis*, *M. Bovis*, and *M. africanum*) can infect animals, and, rarely, animal-to-human transmission has been described. The main reservoir of *M. bovis* infection in mammals is cattle, but badgers, foxes, nonhuman primates, bison, and opossums have been found to be infected *(375–377)*. Transmission to humans is usually via milk from infected cattle. In developed countries, such as the United States, the pasteurization of milk and the testing and culling of infected cattle have resulted in steep decreases in *M. bovis* infection *(378)*. For example, a recent analysis revealed that 1.4% of US cases of tuberculosis were due to *M. bovis (378)*. The main reservoir for *M. tuberculosis* is the human, but other animals including monkeys, large apes, elephants, and dogs can become infected. Rarely, animal (e.g., elephant)-to-human transmission of *M. tuberculosis* has been documented *(379)*.

M. avium complexes are of most consequence for birds, but are also pathogenic for swine, cattle, sheep, dogs, cats, and humans. Other mycobacterial species, such as *M. fortuitum*, *M. chelonae*, *M. kansasii*, and *M. marinum*, have been only infrequently isolated from exotic and cold-blooded animals.

Prevention Of the zoonotic agents that may cause pneumonia, only plague *(380)*, *M. bovis (381)*, Q fever, and possibly psittacosis *(382)* may be transmitted between humans. Patients with respiratory infections with these agents, therefore, should be placed on Airborne Precautions. Birds, especially psittacine birds, should be excluded from the hospital. Patients with respiratory infections consistent with tuberculosis should be maintained on Airborne Precautions and be prohibited from interacting with animals.

Q Fever

Epidemiology and Microbiology Q fever is the only rickettsial microorganism spread primarily by the aerosol route rather than by an arthropod intermediate *(383–404)*. In the United States, a variety of domestic farm animals may be infected, including goats, sheep, and cattle. Microorganisms are shed with placental tissues, feces, urine, and uterine discharges. Domestic animals may become infected from contact with contaminated tissues during parturition *(409)*. Parturient cats have been the source of

multiple outbreaks *(405–407)*. A parturient dog has also been reported as the source of an outbreak *(408)*. Person-to-person transmission of *C. burnetii* is rare but has been reported from patients to hospital staff and to attendants during autopsies *(388)*. It has also been transmitted via bone marrow transplantation and via blood transfusion *(384)*. As noted previously, an obstetrician was infected while attending a pregnant woman, with vertical transmission also occurring in that case. Sexual transmission probably occurs.

Clinical Features of Disease and Diagnosis Most patients with Q fever are asymptomatic, and disease is usually self-limited. The spectrum of Q fever includes isolated fever, flulike illness, atypical pneumonia, hepatitis, fever and rash, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy *(409)*. Pneumonia is highly variable, occurring in up to 90% of cases *(410,411)*. Acute disease typically manifests as a pneumonitis with malaise, anorexia, muscular pain, and usually an intense preorbital headache and fever; defervescence usually occurs within 1 or 2 weeks. Extrapulmonary complications include granulomatous hepatitis, pericarditis, myocarditis, uveitis, meningitis, and subacute bacterial endocarditis. Of these, endocarditis is the most common complication *(412)*. Infection of vascular grafts has been reported *(413)*. Chronic infection in patients with cancer has been described *(414)*. As in animals, infection in pregnant women may result in maternal illness, prematurity, or abortion *(415,416)*. Epidemiologic clues and serologic testing are the keys for proper diagnosis *(417)*. Polymerase chain reaction has been successfully used for clinical diagnosis.

Prevention Immunization with inactivated vaccine prepared from *C. burnetii* (phase I)-infected yolk sac is available in Australia and Eastern European countries. It has proven useful in protecting laboratory workers and should also be considered for use by abattoir workers and others in hazardous occupations. An acellular vaccine is available in the United States for persons conducting research with pregnant sheep or viable *C. burnetii*.

Chlamydophila psittaci

Epidemiology and Microbiology *C. psittaci* is pathogenic for most avian species and is capable of widespread dissemination to humans who have pet birds, who visit pet shops, or who care for birds *(418–422)*. During the 1980s, approximately 70% of the psittacosis cases with a known source of infection resulted from human exposure to caged pet birds *(423)*. Other persons at risk include employees in poultry slaughtering and processing plants, veterinarians, laboratory workers, farmers, and zoo workers. Spread to humans occurs by inhalation of microorganisms persisting in dried feces, contact with bird feather dust, and exposure to birds flapping their wings for exercise. Outbreak investigations suggest that human-to-human transmission occurs in addition to animal-to-human transmission *(424)*. Healthcare-associated outbreaks have been reported *(282,425)*, but the accurate identification of the causative agent as *C. psittaci* has been questioned, because serologic tests may cross-react with *C. pneumoniae (426)*. Infection with feline *C. psittaci* has been reported in a man with a cat *(427)*.

Clinical Features of Disease and Diagnosis

C. psittaci causes infections in humans ranging from a severe systemic illness to an asymptomatic infection *(428–436)*. Symptomatic psittacosis is characterized by high fever, chills, headache, myalgias, dry cough, and, sometimes, respiratory compromise. Extrapulmonary manifestations are common and include cardiac, neurological, hematologic, hepatic, and renal changes. Case–fatality rates as high as 40% have been reported, but with treatment mortality is usually <1%.

As in Q fever, the diagnosis is suggested by an epidemiologic exposure and compatible disease course and is confirmed by serology.

Yersinia pestis

Epidemiology and Microbiology Most cases of plague result from humans coming into contact with sylvatic sources of disease and being bitten by an infected flea. Pneumonic plague may occur following hematogenous spread of bacteria during bacteremia in patients with bubonic or septicemic plague, or by inhalation of bacteria after coming into contact with a person or animal (most commonly a cat) with plague pneumonia. Acquisition of pneumonic plague via droplet transmission from an infected cat has been reported *(437–441)*. Pneumonic plague in humans is believed to be highly contagious via droplet transmission. However, the last case of secondary pneumonic plague in the United States was reported in 1925 *(442)*.

Clinical Features of Disease and Diagnosis Inhalation plague pneumonia begins with a painless cough and shortness of breath *(443–449)*. Pathologically, plague pneumonia is a bronchiolitis and alveolitis causing lobar consolidation and evolves into lobar consolidation with areas of hemorrhage. Patients with hematogenous plague pneumonia present with fever, lymphadenopathy, cough, hemoptysis, and chest pain. Diagnosis is via isolation of the causative pathogen from sputum.

GASTROINTESTINAL INFECTIONS ACQUIRED FROM ANIMAL RESERVOIRS

Many gastrointestinal pathogens of humans have animal reservoirs. These pathogens may then be acquired by humans via ingestion of contaminated surface waters, raw milk, and uncooked or undercooked foods, such as shellfish, fish, poultry, and meat. Enteric bacterial pathogens acquired from pets include *A. hydrophila*, *P. shigelloides*, *Campylobacter jejuni*, *E. tarda*, *Salmonella*, *Y. enterocolitica*, and *Y. pseudotuberculosis (450)*. Parasites include *Cryptospordium*, *D. caninum*, *Giardia*, *Isospora belli*, and *Strongyloides* species *(450)*.

Of the zoonotic infections, *Salmonella* is the greatest public health concern. Nontyphoidal *Salmonella* have been isolated from many domestic animals, including cats, dogs, birds, reptiles, hamsters, and monkeys. In the recent past, turtles were recognized as an important source of human

salmonellosis *(451)*. Pet turtles caused an estimated 14% of all cases of *Salmonella* infections in the United States for a total of 2,000,000 cases per year. Reptiles continue to be a source of human salmonellosis *(452,453)*. Multiple outbreaks of *Salmonella* have been reported in hospitals involving person-to-person transmission, common-source outbreaks (e.g., food), and the use of contaminated instruments (e.g., gastrointestinal endoscopes) *(454)*.

Bacterial gastroenteritis linked to pets has been demonstrated for *A. hydrophila*, *P. shigelloides*, *Y. enterocolitica (455)*, and *C. jejuni (456–458)*. All these pathogens have been isolated from many animals, including dogs, cats, reptiles, hamsters, and monkeys. In humans, all these pathogens may cause gastroenteritis characterized by fever, chills, nausea, vomiting, and diarrhea.

Cryptosporidia is now recognized as an important gastrointestinal pathogen. In normal hosts, it generally causes an episode of self-limited diarrhea. However, in patients immunocompromised by HIV infection, it may cause chronic diarrhea with severe fluid losses and malnutrition. Multiple outbreaks among veterinarians have been described. Hospital *(459–462)* and veterinary school outbreaks *(463)* have also been described. Cats and dogs can likely transmit infective oocysts to humans.

Although most dogs and cats harbor *D. caninum*, human infections are uncommon. Infections are acquired by ingestion of an infected flea, which acts as an intermediate host. Infection may be asymptomatic or associated with abdominal pain, diarrhea, irritability, and anal pruritus. Passage of proglottids that resemble grains of rice in the stool may lead to presentation to a physician *(464)*.

Toxocara canis and *Toxocara cati* are helminth parasites that affect dogs and cats, respectively. Animals may be infected *in utero* and transplacentally or may become infected by ingestion of infested feces. Once passed in animal feces, the ova take several weeks to mature but can remain viable for months. Humans are infected by ingestion of the ova. This situation usually occurs in children younger than 6 years who play in areas where cats and dogs defecate. Contamination of sandboxes used by daycare centers has been demonstrated. In humans, most infections are asymptomatic but may present as cough and wheezing from pulmonary migration, or with abdominal pain, hepatomegaly, and peripheral eosinophilia.

The reservoir for *Giardia* is wild animals. The role of pets in the transmission of giardiasis to humans has not been well defined; however, there have been isolated reports of giardiasis related to dog or cat exposure.

Fang et al. *(450)* have summarized several rules to help prevent the acquisition of enteric infections from pets. These rules include (a) wash hands after handling an animal, (b) keep cages and pens clean to avoid attracting fleas, (c) do not use waste material from pets as fertilizer, (d) cover children's sandboxes when not in use, (e) consult a veterinarian regarding illness in a pet, (f) deworm dogs and cats regularly and do not allow them to defecate on playgrounds, (g) remove animal feces from a lawn frequently, (h) dispose off cat litter daily, (i) treat affected pets and their areas with powders and sprays on alternate weeks for effective flea control, and (j) do not keep turtles as pets.

GUIDELINES FOR THE PREVENTION OF TRANSMISSION OF ZOONOTIC DISEASES

Service Animals

Service animals such as guide dogs provide an important health service for the disabled. Prohibiting service animal's access to a public facility violates the ADA. Recommendations for the use of guide dogs in hospitals have been published *(88,465)*.

Pet-Facilitated Therapy

An extensive literature supports the use of pet-facilitated therapy. Benefits cited by advocates include improved self-esteem, increased knowledge and practice of caring from pets, increased socialization by sharing animal experiences, increased empathy, production of feelings of being liked unconditionally, enhanced nurturing behaviors, increased feelings of control, increased independence, and increased ability to follow directions. Unfortunately, these reported benefits are almost entirely based on anecdotal reports rather than on controlled clinical trials. Additional research is required to determine scientifically which patients would benefit from pet-facilitated therapy and the best form of animal–human interaction.

Animals within the hospital pose a potential risk; however, with the use of a carefully developed and implemented policy, animals can probably be used with minimal risk, provided current recommendations are followed *(89,90)*. Infection control guidelines for AAAs and AAT are also available from the Delta Society *(111,120)*. Similar to the perceived benefits of pet therapy, the risks have been incompletely assessed. However, one study of 2,361 visits to 1,158 patients by dogs under "strict guidelines" reported no incidents of zoonotic infections or evidence that the dogs acted as fomites in the transmission of microorganisms from patient to patient *(466)*. Additional studies are warranted, especially before immunocompromised patients are allowed contact with animals. The Delta Society provides a directory listing of AAT and AAA programs in hospitals (*www.deltasociety.org*).

More detailed guidelines regarding the evaluation of patients suitable for AAT, medical clearance procedures for animals considered for pet therapy, and protocols for the management of pet therapy in healthcare facilities have been published *(88–90)*.

OTHER USES OF ANIMALS IN HOSPITALS

Medicinal Leeches

Leeches have been used in medicine for centuries. The word *leech* is likely derived from the Old English *laece* meaning physician (*467*,468). Medicinal leeches (hirudotherapy) were introduced by Avicenna in "Canon of Medicine" in 1020. They were reintroduced by Abd-el-latifal-Baghdadi in the 12th century (468). Leeches continue to be used in modern medicine in the management of acute problems related to vascular congestion in patients with reimplantation of digits and ears and in reconstruction using cutaneous or muscle flaps *(469–473)*. Leeches are

useful in reducing vascular congestion because they are capable of ingesting up to 10 times their body weight in blood. The process of absorbing blood is aided by the production of hirudin, which inhibits the thrombin-catalyzed conversion of fibrinogen to fibrin, hyaluronidase, proteinase inhibitors, and a vasodilator.

The most common leech used is *Hirudo medicinalis*. Wound infections are an important hazard with the use of medicinal leeches. The most common pathogen is *A. hydrophila (474–477)*, but infection with *V. fluvialis* has also been reported *(478)*. The incidence of wound infections has been reported to be 7% *(474)* and 20% *(479)*. Multiple potential pathogens have been isolated from *H. medicinalis*, including *A. hydrophila*, *Staphylococcus* species, *Alcaligenes* species, *Pseudomonas putida*, and *Fusobacterium varium (480)*. *A. hydrophila* obtained from the gut of *H. medicinalis* has been found to be susceptible to third-generation cephalosporins and tetracycline *(481)*. Treatment of leeches with ciprofloxacin has been reported to eliminate carriage of *Aeromonas* spp. *(482)*. Systemic antibiotics administered to patients have been found to penetrate into leeches and to significantly reduce the rate of *A. hydrophila* isolation compared with controls (i.e., 12% vs. 100%) *(483)*. For this reason, suppression of leech enteric bacteria by antibiotic administration has been recommended as possibly an effective strategy to prevent invasive infection with *A. hydrophila*. Additional clinical trials have been recommended, however, to assess the efficacy of prophylactic antibiotic administration *(483)*.

Medicinal leeches should not be reused between patients because of the risk of cross-infection. Syphilis, puerperal fever, and erysipelas have occurred from the reuse of medicinal leeches *(467)*. Furthermore, laboratory studies have indicated that many parasites, such as *Toxoplasma gondii* and *Trypanosoma brucei*, not only survive but also multiply inside the gut of the leech *(484)*. Once used, medicinal leeches are a biohazard and should be discarded in a manner consistent with Occupational Safety and Health Administration guidelines.

CONCLUSIONS

The use of service animals provides a valuable function for the disabled. Adherence to the ADA with regard to service animals can be safely managed in the hospital setting. The benefits of a well-managed AAT program remain inadequately demonstrated by scientific studies. However, the risks have proved largely theoretical. Pets have been associated with healthcare-associated infections and should be prohibited from hospitals. All healthcare facilities should have policies regarding service animals and the visitation by personal pets.

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CHAPTER 95

Role of the Microbiology Laboratory and Molecular Epidemiology in Healthcare Epidemiology and Infection Control

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In the late 19th century, early microbiologists such as Pasteur and Koch demonstrated that infections were due to specific microorganisms and that these microbes could be isolated by appropriate cultures. Another early microbiologist, Lister, recognized the principle that certain chemicals antagonized microbes. Lister then applied this principle to infection control by using phenol to sterilize surgical instruments and dressings to reduce the morbidity and mortality associated at that time with surgery *(1)*. Thus began the association of microbiology with antibiosis and infection control.

The relationship of microbiology with infection control was formally recognized in the early 1970s by the Centers for Disease Control and Prevention (CDC), which developed standard definitions for nosocomial infections and methods for infection surveillance (2). Infection control committees incorporated these CDC recommendations into practice at that time. The result was a shift from unproductive environmental sampling *(3)* to more directed surveillance and intervention when established baseline endemic rates of infection were exceeded. However, unless these baseline endemic rates of infection were exceeded, the surveillance process was, for the most part, passive.

As humans and medicine complete the first decade of the 21st century, infection control strategies continue to evolve. First, microbiologic surveillance has shifted away from general categories of medical service, infection site, and hospital-wide infection rates and is focusing instead on problem categories (4,5). These focused categories include high-risk areas such as intensive care units (ICUs) (*6,7*), preventable high-risk infections such as intravascular device–related infections *(8,9)*, the surveillance and control of microbial resistance (10,11,*12–14*,15,*16*), and emerging pathogens (10,17,*18*). Second, infection control strategies today are more proactive, which simply means that active intervention for prevention of infections and control of resistance has an equal priority to simply monitoring for changes in these parameters *(6*,*8*,*19–21)*. Third, it is now recognized that a key component in this proactive strategy is the need for ongoing and constant education of healthcare and infection control personnel as well as education of residents, pathologists, infectious disease fellows, and clinical microbiology fellows *(22–26)*. Such educational efforts are becoming important functions of an infection control committee with the assistance of the microbiology laboratory. Fourth, implementation of efficient infection control requires the construction of a computerized information network that ideally includes the hospital, the community, the state, the nation, and other countries (27,*28–33*). Such networks that eventually would include guidelines, microbiologic surveillance data, and full-text references (i.e., PDFs) available on the Internet ultimately will become the cornerstone of infection control.

The interaction of the microbiology laboratory with healthcare epidemiology and infection control continues to evolve as an integral part of a nationwide concerted effort to develop and improve infection control practices and programs. This process began with the National Nosocomial Infections Surveillance (now the National Healthcare Safety Network) system developed by the CDC. This system provides risk-specific infection rates for use by hospitals and national healthcare planners to set priorities for their infection control programs and to evaluate the effectiveness of their effort *(31)*. The Division of Healthcare Quality Promotion at the CDC through National Healthcare Safety Network continues to provide relevant surveillance information on healthcare-associated infections *(34,35)*. In addition, the Division of Healthcare Quality Promotion is expanding to provide relevant information for other healthcare facilities such as dialysis centers *(29)*. The Study on the Efficacy of Nosocomial Infection Control conducted by the CDC in the 1970s found that hospitals had lower rates of healthcare-associated infections if levels of surveillance activities were increased *(36)*. Thus, many infection control programs received additional support to increase the number of infection preventionists (IPs).

Meanwhile, the focus and procedures of microbiology laboratories were changing because of multiple factors that included increasing resistance, emerging pathogens, and new technology (10,17,37). For example, the need for clinical microbiology laboratories to detect emerging antimicrobial resistance (*38*,39,40,41) has resulted in new approaches and technology for this purpose *(42–44)*. All of these factors have resulted in important changes in the role of the microbiology laboratory in healthcare epidemiology and infection control.

The microbiology laboratory has always been recognized as an essential element in the control of healthcare-associated infection *(3)* and has long served as an early warning system for healthcare-associated infections by identifying clusters of microbes with unique phenotypic characteristics and communicating this information to IPs (*45*,46). In the past, such healthcare epidemiology and infection control activities did not place a great demand on the microbiology laboratory.

Today, however, the work done by the microbiology laboratory is increasingly complex and demanding. Much of this has direct implications on healthcare epidemiology and infection control. Microbiology laboratories now must be able to detect, identify, and characterize an expanded array of microbes, including newly emerging pathogens (10,40). Some of these pathogens, such as fungal microorganisms, may be important causes of healthcare-associated infections but difficult to detect *(47–49)*. Fortunately, traditional methods using cultures for isolation, identification, and susceptibility testing of pathogens have been supplemented by highly sensitive, rapid, and specific molecular biologic techniques in which unique DNA or RNA sequences can be directly detected (10,*12*,17,*18*,*43*,*44*,*50*,*51*,52,*53*,*54*,55,56,*57*,*58*). These and other molecular techniques have enabled microbiology laboratories to "fingerprint" microbes, thereby facilitating studies of healthcare-associated transmission *(58,59)*. Finally, the microbiology laboratory's role in monitoring and controlling resistance has become critical because of the increasing frequency with which resistant pathogens are causing healthcare-associated infections (10,*12–14*,*21*,*38*,*42*,*60*). This role today may include not only the accurate detection of resistance *per se* but also the determination of the molecular epidemiology of the resistant isolates. The amount of work by the microbiology laboratory to support healthcare epidemiology and infection control has greatly increased.

The role of the microbiology laboratory in healthcare epidemiology and infection control continues to expand. For example, IPs today often augment their surveillance efforts by the use of computer-generated focused microbiologic surveillance reports from the microbiology laboratory. Problems thus detected may require molecular methods as a part of their evaluation. If the problems involve resistance, additional susceptibility testing and molecular methods may be required. Finally, the microbiology laboratory has become recognized as an important resource for the microbiologic training and education of healthcare and infection control personnel. Indeed, the interactions of infection control committees with the microbiology laboratory are now so complex and important that most committees require that a representative of the microbiology laboratory serve as an active member to ensure the appropriate advice, education, coordination, and technical support. This chapter examines these various facets of the changing and increasingly critical role of the microbiology laboratory in healthcare epidemiology and infection control.

SURVEILLANCE

The key to an effective infection control program continues to be effective surveillance, which the Study on the Efficacy of Nosocomial Infection Control has defined as an IP using basic epidemiologic techniques to perform surveillance on clinical ward rounds, to analyze rates of infection, and to incorporate the data generated in decision making *(31)*. Such surveillance for healthcare-associated infections involves identifying patients who are colonized or infected, assessing the risk of transmission of infection between patients, proving transmission of a given strain from one patient to another, and, more generally, detecting healthcare outbreaks *(61)*. However, to recognize the existence of an outbreak, baseline endemic rates of infection must be determined for each type of infection within a given institution.

Defining endemic rates (the number of infections divided by the number of patient-days or patients at risk) for services, sites of infection, microorganisms, and procedures can be accomplished in each hospital by an active surveillance system coordinated by the IP and the microbiology laboratory. Clusters and epidemics can be investigated when endemic threshold rates are exceeded, when unusual or new microorganisms are isolated, and when new sites of infection are identified. Collection of surveillance data, usually by the IP, consists of reviewing microbiology reports generated by the laboratory. If trends of increasing or unusual infection rates are discovered, then chart review and discussion with personnel involved in patient care should follow to determine the significance of these isolates. The importance of active surveillance is seen with the recent outbreak of the pandemic H1N1 influenza *(62)*. Pandemic influenza is an example of emerging and reemerging infectious diseases that must be monitored with ongoing surveillance strategies and new diagnostic methods (40,*43*,55,56,57,*63*,*64*) (see also Chapters 101 and 102).

With increasing resistance and the fact that many healthcare-associated infections are caused by resistant microbes, surveillance and control of resistance have become critical (10,*12–14*,*21*,*38*,*42*,*60*). Susceptibility patterns can be monitored for emergence of resistant microorganisms; when resistant microorganisms are identified, appropriate isolation precautions should be instituted. Moreover, control of antimicrobial use has become important for controlling resistance (10,*12–16*). For this reason, the antibiotic subcommittee of the pharmacy and therapeutics committee should be included as a part of the infection control program for preventing resistance. One practical way to do this is for a representative of the microbiology laboratory to be a voting member of both the infection control committee and the antibiotic subcommittee. In addition, one or more members of the antibiotic subcommittee should be a member(s) of the infection control committee.

Today, all microbiology laboratories have a computerized reporting system known as the laboratory information system *(65)*. Computer-generated microbiology reports are usually sorted by site of isolation, type of microorganism, and location of the patient, but they can be programmed to focus on any particular problem. Reports are generated daily and cumulatively. These reports are used to detect trends of increasing infection rates or increasing resistance and are reviewed daily by the IP. In addition, the IP often participates in daily clinical microbiology rounds in which new positive cultures at each bench station are reviewed.

The microbiology laboratory receives appropriate hospital demographic information on any culture request and often is able to use this information to recognize clusters of similar isolates. In addition, the availability of laboratory computer systems allows specific types of patients (e.g., transplant patients) or specific locations (e.g., ICUs) to be easily grouped and reviewed. When such focused microbiologic surveillance is desired, the microbiology laboratory should have the capability to provide such reports. In the past, a computerized reporting system did not necessarily mean that focused surveillance reports could be easily obtained. Often, some degree of computer programming was needed; therefore, this programming capability should be readily available. Once obtained, these focused surveillance reports for specific units should be incorporated as a routine surveillance method with these reports also provided to the medical director of the specific unit(s) (5,*6–8*).

Once the microbiology reports have been reviewed and prioritized, charts of the patients with the microorganisms of interest should be analyzed to evaluate the significance of the isolates as potential causes of healthcare-associated colonization and infection. Susceptibility trends should be analyzed. By defining baseline endemic rates for various infections and resistance problems through effective surveillance, unusual disease and resistance activity will trigger disease control and prevention efforts (10,*12–14*,*21*,*38*,*42*,*60*). In summary, an active surveillance system assists the clinician in making an accurate diagnosis and prescribing therapy by providing the knowledge of disease occurrence and antibiotic resistance patterns.

IDENTIFICATION OF OUTBREAKS

An investigation of a potential outbreak of healthcare-associated infections must first determine if these infections are related in any way (*31*,41,46). Most often, this determination involves recognition of the microbial pathogen causing the outbreak and differentiation from those microorganisms of the same genus or species that, although isolated from some patients, are not involved in the outbreak (*31*,41,46,55,*59*,*66*). However, an outbreak may involve resistance rather than an increased incidence of infections. For example, an outbreak might actually consist of only one strain of vancomycin-resistant *Staphylococcus aureus* because of the implications of such an isolate *(67)*. If the outbreak can be linked to infection by a single strain (also called a clone), exposure to a common source or reservoir or transmission from patient to patient would be inferred.

Traditionally, the epidemic strain has been defined with phenotypic methods, which include genus, species, biotype, serotype, phage type, bacteriocin production, and antimicrobial susceptibility patterns *(68)*. Phenotypic methods reflect genetic traits and may be quite specific. When a given phenotype is rarely found in a microbial strain, that phenotype alone may provide convincing evidence of transmission between patients (e.g., *Escherichia coli* O157:H7). However, microorganisms with commonly expressed phenotypic characteristics may require additional subtyping (37). Sometimes, isolates share phenotypic markers but are actually genotypically different; this implies the presence of two separate strains and infection from two different sources. The limitations of phenotypic techniques are presented in Table 95-1.

TABLE 95-1

Limitations of Phenotypic Methods

Influenced by environmental selective pressure
Unstable antigenic traits may be altered by random mutation
Resistance patterns are strongly influenced by the selective pressure of antibiotic use
Bacteria predictably alter the expression of the characteristic being assessed
Necessary reagents may not be commercially available, which limits the number of tests available for phenotypic testing
Phenotypic traits may not have sufficient discriminatory power to distinguish each strain of a species

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; Diekema DJ, Pfaller MA. Infection control epidemiology and clinical microbiology. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:118–128; Versalovic J, Lupski JF. Molecular detection and genotyping of pathogens: more accurate and rapid answers. *Trends Microbiol* 2002;10(suppl):S15–S21; Gilbert GL. Molecular diagnostics in infectious diseases and public health microbiology: cottage industry to postgenomics. *Trends Molec Microbiol* 2002;8:280–287; Nolte FS, Caliendo AM. Molecular detection and identification of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:218–244; Procop GW. Molecular diagnostics for the detection and characterization of microbial pathogens. *Clin Infect Dis* 2007;45(suppl):S99–S111; Weile J, Knabbe C. Current applications and future trends of molecular diagnostics in clinical microbiology. *Anal Bioanal Chem* 2009;394:731–742; and Eisenstein BI. New molecular techniques for microbial epidemiology and the diagnosis of infectious diseases. *J Infect Dis* 1990;161:595–602.)

When microbial pathogens are nontypeable by phenotypic methods or have only a few types, the poor discriminatory power precludes the use of these typing methods. This has led to the use of genotypic methods for typing. This approach has been extremely successful and is now termed *molecular epidemiology* (37,46,55,56,57,*58*,*59*,*66*,69). These molecular epidemiologic methods most often involve genotyping of microbial plasmid or chromosomal DNA and go far beyond the current limitations of phenotyping and provide more accurate data during outbreak investigation (37). Moreover, outbreaks of viruses *(70)* and free-living microorganisms can now be adequately studied with current molecular epidemiologic methods.

However, combining methods of microorganism identification provides stronger evidence for the presumed relationship between isolates. Such was the case with an outbreak of neonatal meningitis caused by *Enterobacter sakazakii (71)*. Biotypes, plasmid DNA profiles, and antibiograms of isolates from patients and the environment were identical,

establishing the means of transmission from a powdered milk preparation. On the other hand, multiple typing systems may show dissimilarity among strains, casting uncertainty on the relatedness of isolates. This was illustrated when widespread colonization of personnel with methicillin-resistant coagulase-negative staphylococci (MRCNS) at a Veterans Affairs hospital was investigated *(72)*. Antimicrobial susceptibility profiles, biotyping, phage typing, plasmid profiles, restriction fragment length polymorphism (RFLP), and plasmid hybridization with a DNA probe showed dissimilarity among strains. Because of the absence of strain similarity that has been found using the various methods, the role of human reservoirs of MRCNS as a source for infections in hospitalized patients remains obscure *(72)*.

Identification of a microorganism by any means requires thorough knowledge of the unique attributes of the microorganism to distinguish it from the large background of nonepidemic, nonpathogenic strains (55,56,57,*58*,*59*,69). Specific strain identification can be critical in identifying outbreaks of infection (55,56,57,*58*,*59*,69). This can be seen with the speciation of coagulase-negative staphylococci. *S. schleiferi* is a species of coagulase-negative staphylococci that is pathogenic in animals and humans, causes pyoderma and abscesses, and has been described in an outbreak of wound infections *(73)*. Isolation and speciation of this pathogen from a cluster of surgical site infections would have far greater impact than the isolation and report of coagulase-negative staphylococci from the same cluster, as the latter would be interpreted as likely representing various coagulase-negative species and thus skin contaminants. As the ability to characterize strains improves, the number of differences detected between strains will likely increase. This will allow better characterization of the pathogenesis of coagulase-negative staphylococci *(74)*.

An important feature of an epidemiologic evaluation is the determination of clonality of the suspected pathogen regardless of the mode of transmission. A clone is a set of isolates that have been recovered independently from different sources, in different locations, and possibly at different times but that show so many identical phenotypic and genetic traits that the most likely explanation for this identity is a common origin (69,*75*). Clonality among isolates in an outbreak must be established before it can be concluded that the outbreak originated from a common source (69). Successful clone identification requires knowledge of the genetic stability of the microorganism, the selective pressure of the environment, and the discriminatory power of the given procedure used to characterize the isolate (69). The judgment of nonclonality eliminates an isolate from consideration as one involved in a particular chain of transmission (69). A judgment of probable clonality strengthens the case for either a common-source outbreak or an outbreak resulting from person-to-person transmission in proportion to the rareness of that clone in the environment (69). Following a given clone throughout its travels by surveillance methods has documented the worldwide spread of multiresistant strains of penicillin-resistant *Streptococcus pneumoniae (76)*, methicillin-resistant *S. aureus* (MRSA) *(77)*, and community-acquired MRSA *(78)*.

Host responses to invading microorganisms may also be used to identify and track infections that are difficult to investigate using current phenotypic and genotypic methods. For instance, serology may be used to determine infection rates during outbreaks, particularly when cultures have not been obtained or are obtained after initiating treatment or when routine cultures may not detect infection (e.g., pneumonia). This was seen with group A *Streptococcus* (GAS) infections in a nursing home *(79)*. Nine (56%) of the 16 cases of GAS disease or infection in residents were confirmed by serologic testing (anti-DNase B titers) alone *(79)*. The identification of a single serotype (M-1, T-1) from the four available isolates and epidemiologic correlation suggested that a single strain of GAS was introduced into the nursing home by the index patient, with subsequent person-to-person transmission. Similarly, pulsed-field gel electrophoresis (PFGE) has been used to document a community outbreak of invasive GAS infection in Minnesota *(80)*. Field inversion gel electrophoresis is another electrophoretic typing method similar to PFGE that has been developed for GAS *(81)*. These electrophoretic methods are able to identify differences between and within M types of GAS. Another molecular method for distinguishing GAS is fluorescent amplified fragment length polymorphism (AFLP) analysis *(82)*. Finally, the *emm* gene for the M protein has proven useful for typing GAS *(83)*.

When investigating a possible outbreak, the healthcare epidemiologist or IP, who formulates a hypothesis based on clinical and epidemiologic evidence, must collaborate with a microbiology laboratory to provide microbiologic data to either support or refute the hypothesis (27,*45*,46,*59*). Isolates from multiple patients are examined to determine whether the infections are related. Establishing similarities or differences among epidemic isolates is not always sufficient to determine the source or the mode of dissemination *(84)*. Data derived from epidemiologic studies are also needed. Cultures and molecular typing without an epidemiologic study often lead to uninterpretable results. However, when molecular typing is combined with an epidemiologic study, the two methods are complementary in confirming transmission of a single or multiple strains *(85)*.

EPIDEMIOLOGIC TYPING

Currently, there are a vast number of epidemiologic typing systems available (37,55,56,57,*58*,*59*,69,*86–88*,89,90,*91*,92). These include molecular methods that are clearly useful for the epidemiologic analysis of infectious disease outbreaks (52,89,*90*,*91*,92). However, to gain acceptance and be routinely applied in clinical situations, molecular epidemiologic methods must be easy to perform, rapid, reproducible, and cost-effective and provide additional information not obtained from traditional typing techniques (*84*,*85*,*87*,89,*90*,*91*,92). Also, it is important with high-resolution typing systems to distinguish between comparative epidemiologic typing systems that are used in outbreak investigations and library epidemiologic typing systems that are used in surveillance systems *(87)*. Most of the currently available molecular typing systems are comparative methods that are reproducible in single assay, have high discrimination ($D > .95$), and are used to compare isolates from a suspected outbreak and distinguish them from sporadic isolates. Such comparative methods include RFLP, PFGE, and arbitrarily primed and randomly

amplified polymorphic polymerase chain reaction (PCR) analysis. Library typing systems, in contrast, are reproducible over time and between laboratories, have discrimination power balanced against evolutionary stability, and are used for long-term surveillance. Library methods include serotyping, insertion sequence fingerprinting, ribotyping, PFGE, AFLP, infrequent-restriction-site amplification PCR, interrepetitive element PCR typing (rep-PCR), and PCR-RFLP of polymorphic loci. Finally, a typing method cannot be considered valid unless it is capable of discriminating among randomly chosen isolates (*84–91*,92).

The basic premise inherent in any typing system is that epidemiologically related isolates are derived from the clonal expression of a single precursor and share characteristics that differ from epidemiologically unrelated isolates (52). The utility of a particular characteristic for typing is related to its stability within a strain and its diversity within the species *(93)*. The most clinically relevant isolates are those with characteristics that provide for increased virulence or resistance and are often the most difficult to differentiate *(93)*. The strength of typing depends on the discriminatory power of the method used *(93)*. When strains are nontypeable or have only a few serotypes, such poor discriminatory power precludes the use of certain typing methods. Ideally, a typing method will recognize each unrelated isolate as unique. In practice, the technique is considered useful if the most common type it detects occurs in <5% of the population *(93)*. There is currently no gold standard or definitive typing system or even an authoritatively validated collection of isolates against which a new method can be evaluated *(93)*. Nevertheless, bacterial typing systems are applied clinically to address one fundamental question: Are two isolates the same or different? *(93)*

One of the earliest phenotypic methods used in hospitals for outbreak investigations was biotyping. Biotyping refers to establishing the pattern of activity of cellular enzymes. Most microbiology laboratories identify bacteria with an automated biotype system *(94)*. The ability of biotyping to differentiate among unrelated strains (discriminatory power) is poor. However, Maki et al. *(95)* successfully used biotyping to implicate contaminated intravenous fluid preparations as the means of transmitting *E. agglomerans* to patients. However, if the same strain differs in one or more biochemical reactions because of mutations in gene expression or a random mutation, then the strains may be mistakenly reported as unrelated *(93)*. Also, specific testing reagents are often difficult and expensive to develop and characterize or are not available in most microbiology laboratories *(93)*. Because of these limitations, new methods to characterize epidemic strains were developed. The different but complementary epidemiologic typing techniques are reviewed in the chronologic order of their development.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

Antimicrobial susceptibility testing (AST) is an inexpensive, easy to use, and readily available means that often is used to characterize microorganisms. The IP frequently reviews daily and cumulative antimicrobial susceptibility reports (antibiograms) for emerging patterns of resistance *(96–99)*. A new or unusual trend of antibiotic resistance from isolates from different patients may raise the suspicion of an outbreak. For example, the rate of ampicillin resistance in *Haemophilus influenzae* isolates from adults was higher than expected in a Georgia community when all isolates were analyzed over a given time, alerting local physicians to the possibility of treatment failure *(100)*.

AST has been used successfully in the investigation of several outbreaks. For example, review of antimicrobial susceptibility patterns implicated vancomycin-resistant *Enterococcus faecium* as the cause of an outbreak in a cardiothoracic surgery ICU *(101)*. AST is frequently all that is required in the investigation of an outbreak of MRSA in a hospital where the microorganism is not endemic. However, this has become the exception rather than the rule. In an era of multidrug-resistant pathogens, AST has become less sensitive. The shortcomings of AST for epidemic typing are well known. The use of AST is limited in epidemiologic studies because of phenotypic variations and because changes in antibiotic resistance occur frequently under the extraordinary selective pressure caused by the extensive use of antimicrobials in hospitals today.

BACTERIOPHAGE AND BACTERIOCIN TYPING

Bacteriophages are viruses capable of infecting and lysing bacterial cells. When used in epidemiologic investigations, their susceptibility or resistance to lysis characterizes isolates by each member of a panel of bacteriophages *(102)*. For *S. aureus* and *Salmonella* species, phage typing was the mainstay of strain discrimination in the past *(102)*. The problem with this method is that it is very demanding, subject to biologic variability, and available only at reference laboratories because of the need to maintain stocks of phages and control strains *(102)*. Phage typing is still used for *Salmonella* surveillance *(103)*. However, DNA-based techniques have, for the most part, replaced bacteriophage typing as the authoritative system.

Bacteriocin typing depends on the susceptibility of the test microorganism to toxins produced by other bacteria. This method has limitations similar to those of phage typing and is rarely used today.

PLASMID PROFILE ANALYSIS

The first genotypic method applied to epidemiologic study involved the analysis of plasmids. Plasmid profile analysis (PPA) or plasmid fingerprinting involves the extraction of plasmid DNA followed by the separation of plasmid molecules by agarose gel electrophoresis *(104)*. Initially, the isolation of plasmid DNA required liters of bacterial broth cultures and relied on sophisticated ultracentrifugation techniques *(105)*. Currently, PPA is simple to perform, requires a minimum of equipment and expense, and is well suited for the study of outbreaks of infection (37). This technique has been used successfully for the isolation of plasmid DNA from most *Enterobacteriaceae*, *Streptococcus* species, *Staphylococcus* species, *Legionella*, *Vibrio* species, *Plesiomonas*, *Pseudomonas* species, and *Campylobacter* species (37,*105*).

Plasmid fingerprinting by agarose gel electrophoresis is a useful means of identifying epidemic strains in outbreaks of healthcare-associated infections and following endemic antibiotic resistance patterns and the spread of specific resistance genes *(104)*. PPA has been used to identify epidemic strains of gram-negative bacilli In one study, PPA for all epidemic isolates of gram-negative bacilli was the same, whereas coisolates (controls) showed different DNA patterns, although the antibiograms failed to show a difference (106). Plasmid profiles were found to be better than antibiograms in identifying epidemic strains of *Salmonella typhimurium* and slightly better than phage typing *(105)*. An epidemic of *Pseudomonas aeruginosa* causing wound and peritoneal infections in hemodialysis patients was traced with PPA to an iodophor solution *(107)*. Two outbreaks of infection resulting from *Enterobacter cloacae* that occurred 6 years apart in the same burn unit were attributed to two different strains by plasmid fingerprinting *(108)*. An outbreak of infections caused by an aminoglycoside-resistant strain of *Acinetobacter calcoaceticus* in an intensive care setting was investigated with plasmid fingerprinting *(109)*. All isolates from patients and the environment were identical, thus suggesting a common means of transmission *(109)*.

Because plasmids can spread from one bacterial species or strain to another by conjugation, it is occasionally the plasmid rather than the bacterial strain that is epidemic *(110)*. An epidemic plasmid may be found in several different bacterial species or serotypes *(110)*. These epidemic plasmids can enter a hospital in one or a few strains and subsequently spread by conjugation to other strains present in the flora of hospitalized patients *(110)*. Whenever possible, it is extremely important for one to compare epidemic strains with nonepidemic control strains (37,*105*). However, the presence of one or more plasmids may be unique to a particular strain of a pathogen and, therefore, be used to incriminate that microorganism in an epidemic, especially if the plasmid is stable through time and environmental stress *(23,105)*.

PPA has significant limitations inherent in the fact that plasmids are mobile, extrachromosomal elements rather than the chromosomal genotype that defines the host microorganism. Moreover, plasmids can exist in different molecular forms such as supercoiled (closed circle), nicked (open circle), and linear; each form migrates differently during gel electrophoresis. Both the reproducibility and discriminatory power of plasmid analysis can be greatly improved by digesting the plasmids with restriction endonuclease enzymes. The resulting restriction fragments are then analyzed by electrophoresis. Restriction enzyme analysis (see later discussion) *(111)* of plasmids is now the method of choice when plasmid analysis is desired. Tables 95-2 and 95-3 show the advantages and limitations of PPA, respectively. Usually, PPA is most effective in studies that are restricted in time and place (e.g., an acute outbreak at one institution) *(112)*.

TABLE 95-2

Advantages of PPA

Applicable to many bacterial strains
Entire analysis can be completed in 1 d
Twenty-four or more cultures can be processed at one time
Gene expression (i.e., production of surface antigen or specific protein) is not necessary
Cultures too "rough" to serotype are easily analyzed
Microtechniques conserve reagents and space
Rapid, inexpensive, and reproducible

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; and Eisenstein BI, Engleberg NC. Applied molecular genetics: new tools for microbiologists and clinicians. *J Infect Dis* 1986;153:416–430.)

RESTRICTION ENDONUCLEASE ANALYSIS

Restriction endonuclease analysis (REA) relies on enzymes that recognize unique plasmid or chromosomal DNA sequences and cleaves the double-stranded DNA at specific sites within the target (37,*113*). The separation of these fragments by size in agarose gel produces a restriction endonuclease profile *(114)*. Unlike PPA, small differences in bacterial strains with identical profiles can be detected with REA, as can acquisition of a new plasmid. If two plasmids are of the same size and yield identical fragment patterns on REA, especially if two or more restriction enzymes are used, they may be assumed to be identical or nearly so *(110)*. Thus, two plasmids may be of the same size but produce different patterns of fragments, identifying two different strains. Such was the case when large plasmids of similar size were found in both strains of *Klebsiella pneumoniae* causing infection in an intensive care nursery a year apart, suggesting they were similar strains *(114)*. However,

TABLE 95-3

Limitations of PPA

The epidemic strain may contain no plasmid DNA or a plasmid that is difficult to isolate
Strains unrelated to the outbreak may contain the epidemic profile
The presence of a plasmid does not provide evidence that it codes for a specific factor (i.e., toxin, antigen, or resistance)
Many plasmids (especially R-plasmids) are readily lost or acquired
Plasmids are subject to rearrangements
As extrachromosomal elements, plasmids do not reflect the stable genotype of the microorganism

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; Eisenstein BI. New molecular techniques for microbial epidemiology and the diagnosis of infectious diseases. *J Infect Dis* 1990;161:595–602; Lupski JR. Molecular epidemiology and its clinical application. *JAMA* 1993;270:1363–1364; and Eisenstein BI, Engleberg NC. Applied molecular genetics: new tools for microbiologists and clinicians. *J Infect Dis* 1986;153:416–430.)

REA showed that the two plasmids were from two different strains causing two separate outbreaks *(114)*.

REA of plasmid DNA was used to implicate rectal probes of electronic thermometers in the transmission of vancomycin-resistant *E. faecium* between patients during an outbreak *(115)*. In another study using REA, spread of MRSA in a hospital was traced to a healthcare worker (HCW) with chronic sinusitis *(116)*. The plasmid DNA of isolates from affected patients and a respiratory therapist yielded the same pattern on restriction endonuclease digestion. Epidemiologic methods led to the control of the outbreak without extensive culturing of specimens from patients, personnel, or environmental surfaces or requiring other expensive and labor-intensive resources.

The role of asymptomatic fecal excretors treated with antibiotics in the epidemiology of healthcare-associated *Clostridium difficile* diarrhea was clarified with REA typing of the strains cultured from stool specimens. Johnson et al. *(117)* found that asymptomatic fecal excretion of *C. difficile* was transient in most patients. Treatment with metronidazole was not effective. Although treatment with vancomycin was temporarily effective, it was associated with a significantly higher rate of *C. difficile* carriage 2 months after treatment. In five instances, the recurrent *C. difficile* excretion represented acquisition of new strains (reinfection) based on REA typing of the isolates, and three patients began excreting the same REA strain after initial eradication with vancomycin. In another study, the epidemiology and relatedness of *C. difficile* isolates in two geographically separated hospitals in a large city were studied using REA *(118)*. A high degree of similarity among isolates from these different hospitals suggested the possibility of an extended outbreak with subsequent genetic drift at the two different institutions. Comparisons of REA typing with other methods such as immunoblot, bacteriophage and bacteriocin, ribotyping, protein profile analysis, arbitrarily primed polymerase chain reaction (AP-PCR), and toxinotyping for *C. difficile* have noted that REA (along with AP-PCR and toxinotyping) is among the most discriminating of the techniques in establishing strain differences *(119–121)*. The REA for *C. difficile* strains is among the most reliable typing methods for current use by clinical laboratories.

Molecular epidemiology can also be used to study resistance patterns resulting from selective pressure from antibiotics. REA of chromosomal DNA has been used to demonstrate that resistance to ciprofloxacin in strains of *Serratia marcescens* and *Proteus mirabilis (122)* and to imipenem in strains of *E. aerogenes (123)* arose from endemic susceptible strains.

REA can be combined with other methods to strengthen the association between isolates during outbreak investigations. PPA and REA were used to trace an outbreak of multiresistant *Salmonella newport* infections to animals fed subtherapeutic doses of antibiotics *(124)*. Another example involved the use of plasmid profiles and restriction endonuclease digestion to show that an MRSA outbreak was caused by a single strain introduced by an employee 15 months before an outbreak on a vascular surgery service *(104)*. Strains from patients and employees were found to be identical with this technique.

In addition to plasmid DNA, reproducible REA patterns of chromosomal DNA can be detected. REA is especially useful for examining viruses, protozoans, and bacterial strains that lack plasmids *(125)*. REA recognizes specific sites on the chromosome, and the pattern is unique for each isolate *(125)*. Different strains of the same bacterial species can be shown to have different REA profiles. Despite phenotypic dissimilarity, REA of chromosomal DNA of group B *Neisseria meningitidis* identified isolates from the throat that were genetically similar to an epidemic strain *(126)*. However, if, genotypically, all strains appear similar, including the random endemic isolates (controls), then additional restriction digestions with at least two other enzymes that are able to discriminate outbreak strains from endemic strains are likely to be useful in typing isolates *(84)*. The outbreak strains can be considered to belong to the same clone if a second enzyme shows identity among the outbreak strains *(84)*.

RFLP produced by restriction endonucleases has proved useful for strain identification of mycobacteria, for detecting cross-contamination, and for tracing epidemics *(127,128)*. For example, RFLP was used effectively to study an outbreak of tuberculosis with accelerated progression among human immunodeficiency virus (HIV)-infected patients *(129)*. An outbreak of 60 cases of tuberculosis in the Netherlands associated with one physician's office was successfully investigated using RFLP *(130)*. Ongoing uses of RFLP include determining whether the emergence of a multidrug-resistant tuberculosis isolate is clonal or whether reinfection occurs with different RFLP types and analyzing strains on a geographic basis *(131)*. The results of such studies are changing the traditional concepts of tuberculosis transmission. For example, tuberculosis in elderly persons has been generally thought to be the result of reactivation. However, two recent studies have found that a high proportion (30% or more) of tuberculosis cases in elderly people appear to be due to recent infection rather than reactivation *(132,133)*. This has important implications for control of tuberculosis.

The limitation of having enough DNA to analyze (which requires 6 or more weeks of growth of the isolate) can now be overcome by combining RFLP with PCR (which requires short periods of growth by amplifying small quantities of DNA) *(131)*. However, the expense and the labor-intensive and time-consuming requirements of RFLP limit its use to research facilities.

Invasive aspergillosis is a well-known infection with a high mortality that affects immunosuppressed patients. Healthcare-associated outbreaks have been associated with contaminated ventilation systems and construction within or near hospitals that have immunosuppressed patients *(134)*. Although airborne transmission has been suggested by epidemiologic studies, an accurate typing system, until recently, has not existed to confirm this hypothesis. Biotyping methods are unreliable in differentiating strains because of variable phenotypic expression under different environmental conditions. RFLP of total DNA, digested by particular restriction enzymes, is able to discriminate strains of *Aspergillus fumigatus* to some degree *(135)*. Girardin et al. *(136)* used Southern blot hybridization of moderately repeated DNA sequences to fingerprint strains of *A. fumigatus* isolated from patients with invasive aspergillosis and from their hospital environment. They

demonstrated that some strains persist in the hospital environment for at least 6 months and found suggestive evidence of healthcare-associated spread of *A. fumigatus* in two patients *(136)*. Thus, the healthcare-associated origin of infection can be demonstrated if environmental strains identical to the strains from patients are isolated in a prospective survey a few days before the patient's aspergillosis is diagnosed *(136)*. More recent studies done by other molecular methods *(137,138)* have confirmed this link.

The major advantage of REA is that it allows for differentiation of one strain from another without relying on the expression of a given phenotype *(139)*. The major limitation of REA has been that the number of chromosomal bands produced (~103) is so large and overlapping that the specific bands are difficult to identify; thus, it does not lend itself to a comparison of various isolates *(139,140)*. This limitation of REA has largely been overcome by using PFGE instead of agarose gel electrophoresis(see later discussion).

PULSED-FIELD GEL ELECTROPHORESIS

PFGE of chromosomal DNA is a variation of agarose gel electrophoresis that allows analysis of bacterial DNA fragments over and above conventional REA *(88)*. Although it is more expensive and demanding than conventional REA, a highly reproducible restriction profile is provided with PFGE that shows distinct, well-resolved fragments representing the entire bacterial chromosome in a single gel. PFGE banding patterns can readily discriminate among endemic and epidemic strains, especially for *E. coli* and *Mycobacterium avium-intracellulare* but not for MRSA and *H. influenzae* serotype b. RFLP patterns of *Mycobacterium* species can be easily interpreted with PFGE, unlike the pattern obtained with routine electrophoresis *(127)*.

Back et al. *(139)* investigated a recurrent epidemic of erythromycin-resistant *S. aureus* infection in a well-baby nursery. Initial traditional epidemiologic techniques suggested that these were two separate outbreaks. However, REA of plasmid DNA along with genomic DNA typing by PFGE of the isolates demonstrated that the two epidemics resulted from the same strain. A nursing assistant was assumed to be responsible for the first epidemic, because she carried a *S. aureus* strain with the same antibiogram. However, she was infected with an unrelated strain, as assessed by REA with PFGE. Instead, a physician who attended on the unit during both epidemics had the same epidemic strain and was the most likely source of the outbreaks. The authors concluded that traditional epidemic investigations might engender misleading conclusions that can be avoided with molecular epidemiologic techniques. The cost for epidemiologic typing of this outbreak was $1,000 for REA and $1,500 for REA with PFGE.

REA of genomic DNA with PFGE provides DNA fingerprinting of various microorganisms, especially *S. aureus*, which is highly discriminatory and stable enough to reliably characterize many strains *(140,141)*. Such molecular typing has been used recently to identify and characterize the clonal expansion of community-acquired MRSA in a Native American community *(142)*. This technique identified 31 or 32 isolates of MRSA from the community that were highly related, yet distinguishable from 32 hospital-acquired MRSA strains.

In another study, endemic MRSA in a Veterans Administration Medical Center was evaluated using PFGE analysis *(143)*. A large amount of strain variation was detected, and 40% of patients observed over time were colonized or infected with more than one strain of MRSA. This form of molecular typing was very useful in evaluating the epidemiology of MRSA in this setting.

PFGE has also been useful in studying the spread of GAS in an outbreak setting. Healthcare-associated transmission of GAS occurred from a single-source patient to 24 HCWs in a hospital *(144)*. PFGE analysis revealed that all of the isolates were identified to that of the source patient. The 24 HCWs developed symptoms of pharyngitis <4 days after exposure to the source patient. Rapid identification, early treatment, and adherence to infection control practices were able to control the outbreak.

Outbreaks from gram-negative bacilli have been successfully evaluated with PFGE. Multidrug-resistant *K. pneumoniae* caused an outbreak in a university hospital in Lisbon, Portugal *(145)*. PFGE identified an endemic strain that presented in different wards in the hospital. In another study, a healthcare-associated outbreak of *K. pneumoniae* producing extended-spectrum β-lactamase was shown by PFGE to be of the same clone *(146)*.

PFGE of chromosomal DNA was found to be a reliable method for epidemiologic typing of *S. odorifera (147)*. In this investigation, neither biotype nor antibiogram was useful in differentiating strains. Although no source for the microorganisms or mode of transmission was identified, the isolates from the two patients in a cardiothoracic surgery unit were identical by PFGE of chromosomal DNA, suggesting possible healthcare-associated transmission.

PFGE of genomic DNA combined with clinical epidemiologic analysis was successfully used to investigate an outbreak of *M. abscessus* pseudoinfection *(148)*. Fifteen patients had positive cultures for *M. abscessus* without evidence of infection following endoscopy. Environmental and case-patient isolates had identical large restriction fragment patterns of genomic DNA separated by PFGE. An automated endoscope washer was implicated as the source of the pseudoepidemic. A similar outbreak of pseudoinfection by *M. abscessus* was detected by molecular typing (random amplified [RA]-PCR in this instance) in which the use of in-house prepared distilled water was the source of a pseudo-outbreak *(149)*.

Phenotypic differences among strains of the same *Candida* species may not reflect true strain differences because *Candida* is able to switch phenotypes. Because different phenotypes can coexist at the same site of infection, genotyping techniques were developed *(150)*. REA with PFGE has shown that isolates of the same *Candida* strain share the same DNA profile, whereas epidemiologically unrelated isolates have patterns that are distinctly different *(150)*. RFLP has also been used to delineate specific strains of *Candida* species for epidemiologic studies *(150)*. By the use of DNA content as an epidemiologic marker of strain identity, studies have shown that transmission of *Candida albicans* probably occurs through indirect contact between patients by way of the hands of HCWs *(150)*. Vazquez et al. *(151)* found that REA patterns of chromosomal DNA from *C. albicans* isolates cultured from patients who were geographically and temporally associated were identical.

This study also suggested that healthcare-associated acquisition of *C. albicans* occurs by way of indirect contact between patients. More recently, Vazquez et al. *(152)* have found similar molecular epidemiologic evidence that indirect contact between patients is an important factor in healthcare-associated colonization by *C. glabrata*. Finally, *C. inconspicua* has been identified by similar molecular typing techniques as a healthcare-associated pathogen in patients with hematologic malignancies and appears to emanate from a common source within the hospital environment *(153)*.

Combining several isolate-typing methods may allow for surveying a large population consisting of many different microorganisms. Chetchotisakd et al. *(154)* used PPA (for *E. coli*, *K. pneumoniae*, and *E. cloacae*), REA of plasmid DNA (for *S. aureus*), and/or PFGE of chromosomal DNA (for *S. aureus*, enterococci, *P. aeruginosa*, and other bacteria) to demonstrate that endemic bacterial cross-transmission in ICUs is relatively infrequent. DNA typing of these isolates found cross-transmitted bacteria not to be common causes of endemic ICU-related healthcare-associated infections.

Using a combination of PFGE, ribosomal RNA (rRNA), and PCR analysis, Bonilla et al. *(155)* demonstrated an outbreak of linezolid-resistant *S. epidermidis* infection in two hospitals in two different cities and states, which was caused by the clonal spread of a *cfr* gene–containing strain. In another study, an extended-spectrum β-lactamase producing *E. coli* was responsible for causing a significant number of serious infections throughout the United States *(156)*. A combination of susceptibility testing, PCR, and PFGE was used to demonstrate clonal spread of the *E. coli*, with the latter methodology suggesting ongoing dissemination among locales.

Multidrug-resistant gram-negative bacteria (GNB) are causing a greater risk to public health than gram-positive bacteria (GPB) for a variety of reasons. Resistance develops much faster in GNB than GPB, and newer antibiotics with activity against GNB are scarcer than for GPB. Emergence of a new antibiotic resistance mechanism with readily transferable plasmids was demonstrated using a combination of technology. PPA, PFGE, and PCR demonstrated international spread of highly resistant *E. coli* and *Klebsiella* producing a carbapenemase between Pakistan, India, and the United Kingdom *(157)*.

Another multidrug-resistant GNB, *A. baumannii* is an emerging pathogen that causes life-threatening infections in ICU patients and has high levels of resistance to antibiotics. Healthcare-associated outbreaks of *Acinetobacter* have been reported with increasing frequency, and prompt initiation of isolation precautions is warranted. Morgan et al. *(158)* demonstrated gowns, gloves, and unwashed hands of HCWs were frequently contaminated with multidrug-resistant *Acinetobacter*. They also demonstrated that *Acinetobacter* was more easily transmitted than multidrug-resistant *P. aeruginosa* using PFGE.

DNA HYBRIDIZATION

Genetic probing or DNA hybridization involves denaturing double-stranded DNA into single-stranded DNA. The single strands from the isolate can be joined to the complementary single-stranded DNA probe that is labeled with a marker such as P_{32}. The hybrids formed are then measured. The primary requirement for a successful probe is that the sequence be both unique and conserved in the group of microbes to be identified *(93)*. For diagnostic tests, useful probes are prepared by cloning-specific DNA sequences from the microorganism to be probed (106). The stringent requirement for complementarity as a precondition for strand reassociation is the basis for the great specificity of the DNA hybridization probe test (106).

DNA probes can be used with the method of Southern hybridization for epidemiologic studies and have been used successfully to investigate the epidemiology of infections caused by *Vibrio cholera*, *Yersinia enterocolitica*, enteroadherent *E. coli*, enteroinvasive *E. coli*, *Salmonella* species, *P. aeruginosa*, and *Legionella pneumophila (93,105)*. The genes that encode *E. coli* enterotoxins have been cloned from toxigenic strains and used as probes to detect the presence of the target gene in a clinical isolate (106). These probes are important in differentiating pathogenic *E. coli* from nonpathogenic *E. coli* found in the stool of ill and healthy patients *(105)*.

Because small amounts of homologous DNA can be detected, DNA hybridization is useful when isolation of a pathogen is impossible, insensitive, or too time-consuming (106). See Table 95-4 for additional advantages of using the DNA hybridization technique.

Besides toxin production genes, antibiotic resistance genes have been analyzed with DNA probes. DNA hybridization determined the extent of homology between two plasmids that suggested transfer of antibiotic resistance among different species *(110)*. Through the use of DNA probes, *E. coli* plasmid DNA was shown to have a high degree of relatedness with plasmid DNA from tobramycin-resistant strains of *E. cloacae* and *K. pneumoniae* that had been isolated from burn patients *(159)*. This pattern sug-

TABLE 95-4

Advantages of DNA Hybridization

Does not require the pathogen to be propagated or be viable
Able to safely handle difficult-to-grow and highly pathogenic (hazardous) microorganisms
Reduces the number of bands for analysis with restriction endonuclease and highlights specific DNA restriction sites
Can distinguish individual strains of bacteria
Can detect pathogens (cytomegalovirus, rotavirus, papillomavirus, chlamydia, and mycoplasma) in clinical specimens that are abundant but difficult to cultivate
Can track transposon movement

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; Eisenstein BI. New molecular techniques for microbial epidemiology and the diagnosis of infectious diseases. *J Infect Dis* 1990;161:595–602; Stull TL, LiPuma JJ, Edlind TD. A broad-spectrum probe for molecular epidemiology of bacteria: ribosomal RNA. *J Infect Dis* 1988;157:280–286; and Maslow JN, Mulligan ME, Arbeit RD. Molecular epidemiology: application of contemporary techniques to the typing of microorganisms. *Clin Infect Dis* 1993;17:153–164.)

TABLE 95-5

Disadvantages of DNA Hybridization

Costly, slow to perform, and cumbersome
Often less sensitive than culture when done on an individual basis
Radioisotopes may be required for use

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; Eisenstein BI. New molecular techniques for microbial epidemiology and the diagnosis of infectious diseases. *J Infect Dis* 1990;161:595–602; Stull TL, LiPuma JJ, Edlind TD. A broad-spectrum probe for molecular epidemiology of bacteria: ribosomal RNA. *J Infect Dis* 1988;157:280–286; and Maslow JN, Mulligan ME, Arbeit RD. Molecular epidemiology: application of contemporary techniques to the typing of microorganisms. *Clin Infect Dis* 1993;17:153–164.)

gested that interbacterial transfer of the plasmid between different species had probably occurred on the burn ward. Interbacterial transfer of a plasmid-mediating gentamicin resistance was first described in 1981. In this report, separate outbreaks involving *P. aeruginosa* and *S. marcescens* followed by *K. pneumoniae* and *S. marcescens* were related by the presence of plasmids that contained a common transposable sequence. This suggested transfer of a transposon (translocatable DNA sequence) between plasmids as the mechanism for transmission of gentamicin resistance *(160)*. Recent work suggests that dissemination of resistant genes carried on transposable elements may be important in vancomycin-resistant enterococci *(161)*.

DNA probes have also been used to characterize other microorganisms than bacteria such as mycobacteria, viruses, and fungi. DNA hybridization has identified fingerprint patterns to help define the epidemiology of infections caused by *C. albicans (162)*. The DNA probe can be used for mycobacterial cultures but is not sufficiently sensitive to detect microorganisms directly from clinical specimens *(163)*. Identification of individual *Mycobacterium tuberculosis* (MTB) strains is now possible through DNA fingerprinting *(163)*. Because most MTB strains share common drug susceptibility patterns and bacteriophage types, it has been difficult to document transmission of specific strains from person to person *(163)*. However, DNA fingerprints of individual MTB strains remain relatively stable over time and permit delineation of patterns of tuberculosis transmission *(163)*. DNA probes are available not only for MTB but also for *M. avium-intracellulare*, *M. kansasii*, and *M. gordonae*; these probes used with the Bactec system can provide identification within 2 to 4 weeks *(164)*. Despite the many uses of DNA hybridization, a few drawbacks exist. DNA hybridization is costly, slow to perform, and cumbersome. It is often less sensitive than culture when done on an individual basis, and radioisotopes may be required for its use (Table 95-5) (89,*105*,*110*).

RIBOTYPING

rRNA represents highly conserved nucleotide sequences that are found in most microorganisms. Probes have been produced based on rRNA that are unique to species, genus, and groups like all gram-negative bacilli and the intracellular pathogen *Legionella (105)*. Fingerprinting of rRNA has been valuable for typing strains of *S. typhi*, *Campylobacter* species, *Pasteurella multocida*, and various *Staphylococcus* species *(84,105)*. REA of rRNA can be used to distinguish isolates of *Staphylococcus* species and strains of *H. influenzae*, *Providencia stuartii*, and *Candida* species *(165)*. rRNA gene restriction patterns were used to show that *H. influenzae* isolates cultured from the trachea and blood of an infant and from the mother's cervix were identical, indicating that the mode of transmission was from mother to child *(165)*.

Ribotyping was found to be a more reliable technique than biochemical typing when evaluating *S. marcescens* strains. Identical ribotypes of *S. marcescens* were found colonizing 12 children in five different hospital wards over a 20-day period *(166)*. Combining epidemiologic findings with the ribotype patterns suggested cross-contamination between the patients on four of the wards.

Epidemiologic studies of *E. cloacae* have relied primarily on the study of phenotypic traits such as biochemical profiles; antibiotic resistance; and serologic, bacteriocin, and phage typing *(167)*. Because of insufficient discrimination, poor reproducibility, or low typeability, these methods are unsatisfactory for analyzing *E. cloacae*. Using RFLP of total DNA and ribotyping, Lambert-Zechovsky et al. *(167)* were able to document endogenous bacteremia and meningitis resulting from *E. cloacae* that originated from colonization of the gastrointestinal tract in an infant. Each of the five isolates from the infant had identical ribotypes, whereas the comparison strains exhibited different unique ribotype patterns. This case study supports the use of RFLP analysis of total DNA and ribotyping to study the epidemiology of healthcare-associated infections resulting from *E. cloacae* strains.

Ribotyping and PFGE can be used to characterize multidrug-resistant gram-negative bacilli. The prevalence of carbapenem-resistant *A. baumannii* and *P. aeruginosa* in Brooklyn, New York, was determined by ribotyping and PFGE on 419 and 823 isolates, respectively *(168)*.

Ribotyping revealed a single clone accounted for 62% of the samples and was isolated from patients at all 15 hospitals in the area. Ribotyping revealed that three clones accounted for nearly half of the isolates and were shared by most hospitals.

In another study, ribotyping and PFGE were used to characterize a foodborne outbreak. Acute gastroenteritis developed in 21 nursing home patients with 2 deaths after consumption of minced beef heart contaminated with *C. perfringens (169)*. PFGE was not able to characterize a majority of the *C. perfringens* isolates. However, ribotyping successfully distinguished four different groups of *C. perfringens*. The same ribopattern was detected in a food sample, autopsy samples from the two deceased patients, and stool samples from six further patients who had fallen ill with diarrhea.

C. difficile has surpassed MRSA as the most common healthcare-associated pathogen in many hospitals. In addition to an increase in the incidence of *C. difficile*–associated colitis is an increase in the severity of illness. Risk factors that promote the spread of *C. difficile*–associated colitis include, overcrowding, understaffing, high levels of anti-

biotic use (particularly of fluoroquinolones), and an aging population. PCR ribotyping and PFGE have successfully characterized the emergence of a hypervirulent strain of *C. difficile* that causes more severe colitis and a higher mortality than other strains *(170)*. These hypervirulent isolates have a genetic mutation that causes hyperproduction of toxins A and B. In addition, they are resistant to fluoroquinolones. The spread of this strain from North America to Europe and other parts of the world are of growing concern *(170)*.

The spread of *C. difficile* within and between hospitals can also be better tracked using molecular-based epidemiologic techniques. PCR ribotyping was used to identify epidemic strains of *C. difficile* causing an outbreak at multiple hospitals *(171)*. Unlike other studies, Jump et al. *(171)* found that the use of fluoroquinolones with enhanced antianaerobic activity was not associated with increased infection rates (see also Chapter 37).

Besides outbreak investigations, rRNA has been very useful in phylogenetic analysis. The gene sequence in ribosomal DNA was pivotal in the discovery of the causative agents of bacillary angiomatosis, human ehrlichiosis, Whipple's disease, and Tyzzer's disease *(172)*.

POLYMERASE CHAIN REACTION

PCR is the repetitive cycling of three simple reactions in a semiautomated, self-contained system capable of amplifying a single strand of DNA or RNA with 50 to more than 2,000 base pairs more than a million-fold in only a few hours (173). More than 22 different microorganisms that grow slowly or not at all on routine culture media can now be detected using PCR *(172)*. With this tool, the healthcare epidemiologist can rapidly diagnose an otherwise difficult-to-detect pathogen and, thus, initiate specific infection control measures promptly *(174)*.

By virtue of its speed and high degree of sensitivity and specificity, rapid and reliable detection of microbes present in small numbers is now possible. For diagnosis, PCR goes beyond the detection of microorganism-specific immunoglobulin M or antibodies in serum, demonstration of seroconversion to a microorganism on testing acute and convalescent sera, or detection of microorganisms in clinical specimens using cultures or antigen assays *(175)*. Pathogens that are difficult to culture, are in the latent stage, or require an antibody response to be detected can potentially be detected with PCR *(176)*. PCR is useful when other tests provide ambiguous results or are subject to technical failures. See Table 95-6 for the benefits of PCR use in epidemiologic investigations. Like other detection systems, PCR has some limitations and pitfalls. The nucleic acid sequence of the pathogens to be detected must be known to develop the appropriate primer. If the sequence is known and the microorganism is detected, the significance of a positive test result still depends on the clinical situation. For example, cytomegalovirus viremia detected by PCR or by culture could indicate asymptomatic shedding versus active infection, making clinical correlation an essential part of the investigation.

Noroviruses cause major outbreaks of gastroenteritis worldwide and cause healthcare-associated outbreaks, especially in nursing homes, pediatric wards, and cancer centers. Because of their environmental stability, ability to use different transmission routes, and low infection doses, their source may be difficult to determine during an outbreak *(177)*. Verhoaf et al. *(177)* were able to distinguish between viral genotype profiles from human feces and sewer-contaminated food using genotype analysis and PCR technology. They found that one-quarter of the outbreaks reported as food handler associated were probably caused by source contamination of the food *(177)*.

PCR has been used in several outbreak investigations and sheds new light on the pathogenesis and spread of difficult-to-detect microorganisms. Enterotoxigenic *E. coli*, a very difficult microorganism to separate from nontoxigenic strains, was successfully detected and identified with the PCR technique *(178)*.

PCR along with other techniques can evaluate infection control surveillance systems. PPA combined with PFGE and PCR was used to study the utility of surveillance for multidrug-resistant *Enterobacteriaceae* in the absence of an outbreak in new organ transplant patients *(179)*. The authors conclude that this form of surveillance is costly and provides little or no benefit for infection control or predicting clinical infections in this population. However, surveillance of colonization may play a greater role in the event that a clonal outbreak is identified.

PCR can also verify the accuracy of other techniques such as PFGE used in outbreak investigations. An outbreak of vancomycin-resistant *E. faecium* was identified in a teaching hospital in Medellin, Columbia, by using PFGE.

TABLE 95-6

Benefits of PCR in an Epidemiologic Investigation

Direct typing for specific microorganisms
Detection of genes that code for toxins, virulence factors, and antimicrobial resistance
Rapid diagnosis
Detection of microorganisms in low numbers
Detection of microorganisms that are slow growing or do not grow at all *in vitro*
Does not require an antibody response to the infecting agent
Does not require active replication; latent stage is able to be detected
Able to study the reservoirs and modes of transmission of difficult-to-track pathogens
Detection of microorganisms in body fluids (cerebrospinal fluid, ocular fluid, fetal blood)

(Data from Soll DR, Pujol C, Lockhart S. Laboratory procedures for the epidemiological analysis of microorganisms. In: Murray PR, Baron EJ, Jorgensen JH, et al., eds. *Manual of clinical microbiology*. 9th ed. Washington, DC: American Society for Microbiology, 2007:129–151; Eisenstein BI. The polymerase chain reaction: a new method of using molecular genetics for medical diagnosis. *N Engl J Med* 1990;322:178–183; Templeton NS. The polymerase chain reaction: history, methods and applications. *Diag Molec Pathol* 1992;1: 58–72; Jungkind D. Automation of laboratory testing for infectious diseases using polymerase chain reaction: our past, our present, our future. *J Clin Virol* 2001;20:1–6; and Peter JB. The polymerase chain reaction: amplifying our options. *Rev Infect Dis* 1991;13:166–171.)

PCR identified all 23 isolates as identical, thus complimenting the use of PFGE *(180)*.

The reservoirs and modes of transmission of healthcare-associated *Legionella* infection have been further elucidated using newer molecular techniques such as PCR methodology *(181–183)*. An indoor hot tub at a resort condominium complex was implicated as the source of an outbreak of Pontiac fever by using PCR *(184)*. Although cultures of water for *Legionella* were negative, direct fluorescent antibody and PCR were positive, thus incriminating nonviable and nonculturable *L. pneumophila*.

PCR was used to study two outbreaks of infection with a hypervirulent strain of hepatitis B virus (HBV) that was associated with a high mortality *(185,186)*. Mutations in the HBV genome were detected from the index patients and their contacts but absent from unrelated infectious patients, thus implicating the virulent strain as the cause of the outbreaks. The most notable outbreak investigation using PCR involved HIV transmission from a dentist to five of his patients in a healthcare setting *(187)*.

With the recent surge in the incidence of tuberculosis, rapid and accurate diagnosis is becoming increasingly important. As few as one or two microorganisms in a given *Mycobacterium* species can be detected with the PCR method *(127)*. This method can diagnose pulmonary tuberculosis when acid-fast bacilli (AFB) smears and cultures are negative *(127)*. Eisenach et al. *(188)* reported a sensitivity of 100% and a specificity of 99% when using PCR techniques to analyze sputum from patients with and without tuberculosis. Kirschner et al. *(189)* over a longer 18-month period noted a sensitivity of only 84.5% and a specificity of 99.5%.

In addition to REA with PFGE and RFLP, PCR has also been used to type *Candida* species. van Belkum et al. *(190)* successfully typed *C. albicans* strains with PCR amplification of variable DNA domains. They suggest that all colonies of *C. albicans* isolated from clinical specimens can be typed by PCR both prospectively and longitudinally. With this technique, suspected outbreaks resulting from *Candida* species can be investigated more thoroughly to clarify the role of exogenous transmission versus endogenous colonization leading to infection.

A novel variant of conventional PCR, AP-PCR, or random amplified polymorphic DNA, has been used successfully in several outbreak investigations. With this new technique, arbitrarily selected primer DNA is annealed to the template DNA under low-stringency conditions for the initial cycles of DNA replication *(191)*. This step requires no prior knowledge of the sequences to be amplified. The products of the initial cycles of low-stringency polymerization are amplified under high-stringency conditions, as in conventional PCR, and separated by gel electrophoresis *(191)*. The pattern generated is highly reproducible and specific for a given strain; furthermore, it can be used to distinguish different strains within a single species *(192)*.

Current typing schemes for meningococci include serogrouping of capsular polysaccharides or outer membrane proteins, multilocus enzyme electrophoresis of metabolic enzymes, and genomic restriction endonuclease digestion with or without PFGE *(193)*. An outbreak of meningococcal meningitis at a college campus was successfully investigated using AP-PCR *(193)*. All 3 disease isolates and 7 of 11 carrier isolates were identical, as found by using four different primers, and were easily distinguishable from unrelated isolates. AP-PCR further demonstrated the clonal nature of meningococcal disease outbreaks in which most disease isolates are of the same clone *(193)*.

Healthcare-associated transmission of multidrug-resistant gram-negative bacilli in intensive care settings has been elucidated with RA-PCR. A burn unit experienced an outbreak of multidrug-resistant *P. aeruginosa*. RA-PCR identified two predominant genotypes that were responsible for recurrent outbreaks *(194)*. One of the strains was endemic to the burn ward and developed multidrug resistance at the end of the study period. In another study, two outbreaks of multidrug-resistant *K. pneumoniae* in an ICU were analyzed by RA-PCR *(195)*. The first outbreak was caused by two different types of *K. pneumoniae*. RA-PCR identified yet a different strain that caused the second outbreak. The authors conclude that RA-PCR is easy to perform, highly reproducible, and had a high discriminatory power.

Typing of *C. difficile* to differentiate highly pathogenic from nonpathogenic strains has been accomplished with a number of techniques including bacteriophage, bacteriocin, toxinotyping, and REA of DNA *(119–121)*. Complex and difficult-to-interpret DNA patterns are sometimes produced with REA of DNA. Silva et al. *(196)* successfully used AP-PCR to genotype *C. difficile* isolates from various sources. Two strains isolated from patients on the same floor but different wards had the same DNA banding patterns, suggesting a common source of cross-infection through hospital contact. Others have found AP-PCR to be useful for genotyping *C. difficile (120)*.

The epidemiology of *Staphylococcus* species can be characterized using RA-PCR. Neonates are susceptible to infections caused by methicillin-resistant coagulase-negative *Staphylococcus*. Dissemination of one particular clone was identified using the RA-PCR technique among a group of neonates in a hospital ward *(197)*. In addition, persistence of the isolate and reinfection was effectively identified with this methodology. In another study, PFGE and PCR were used to characterize colonization of children and their guardians with *S. aureus (198)*. When both members of the child–guardian pair were colonized with *S. aureus*, transmission within the family was implicated because 67% of the colonizing isolates were the same strain.

An outbreak of MRSA in a burn unit was investigated with AP-PCR and restriction endonuclease analysis of plasmid (REAP) DNA *(192)*. Complementary evidence of a clonal relationship among isolates from patients and staff in the burn unit was established with these techniques. MRSA isolates from other hospital wards were clearly distinguishable from the epidemic isolates. The authors concluded that the combination of AP-PCR and REAP may be a useful means of tracking the healthcare-associated spread of microbial strains and their mobile genetic elements *(192)*. Conventional epidemiologic methods may be inadequate in some outbreak investigations, as this study suggests.

The ability of the healthcare epidemiologist or IP to identify patterns of MRSA spread is dependent on distinguishing the epidemic strain from unrelated MRSA strains *(199)*.

During the investigation of the MRSA outbreak in the burn unit mentioned previously, antimicrobial susceptibility patterns suggested a general grouping of MRSA strains, but definitive typing was not possible with this method. However, REAP analysis (plasmid fingerprinting) yielded useful information for strain typing but resulted in some ambiguities that were resolved by AP-PCR *(192)*.

Because of decreasing susceptibility of MRSA to vancomycin, newer antibiotics with MRSA activity, such as linezolid, are being used with increasing frequency, especially in severely ill patients in ICUs. With increasing use of an antibiotic, resistance quickly follows. Garcia et al. *(200)* reported the first clinical outbreak of linezolid-resistant *S. aureus* with demonstration of healthcare-associated spread. Genotype analysis with PCR and PFGE identified one predominant clone. Reduction of linezolid use and infection control measures terminated the outbreak.

Mycobacterium and *Candida* transmission has been documented with AP-PCR. An outbreak of *M. abscessus* from benzalkonium chloride antiseptic solution was investigated with RA-PCR and PFGE *(201)*. Joint and periarticular soft tissue infections developed after steroid injection from the same physician. Clinical and antiseptic solution strains of *M. abscessus* were indistinguishable by RA-PCR.

After the occurrence of two chronologically related cases of *C. tropicalis* fungemia in a neonatal ICU, a prospective study of fungal colonization and infection was initiated *(202)*. RFLP and RA-PCR identified fungemia more commonly in colonized than in noncolonized neonates, and no environmental source was found. The authors conclude that these molecular diagnostic tests can improve our understanding of the epidemiology of *Candida* infections, including the mode of transmission. It is likely that techniques for epidemiologic typing for application during outbreak investigations will continue to advance in the age of the evolving PCR technique.

SELECTIVE CULTURE MEDIA AND SPECIAL MICROBIOLOGIC TECHNIQUES

Selective Culture Media

Selective culture media, which inhibit microorganisms in the clinical sample that might obscure or inhibit the growth of the desired strain, may be used during outbreak investigations. For example, the ideal medium for stool specimens would inhibit the competing microorganisms from the normal flora and select out the pathogenic strain desired for analysis. *E. coli* O157:H7, the cause of severe bloody diarrhea and hemolytic uremic syndrome, was first linked to human illness in 1982. Modified MacConkey medium containing sorbitol allows for culture of stool specimens to diagnose *E. coli* O157:H7 infection *(203)*.

The laboratory diagnosis of antibiotic-associated colitis caused by *C. difficile* usually requires the detection of cytotoxin or enterotoxin in stool. However, investigations of *C. difficile*–induced outbreaks of colitis require the isolation of strains for comparison. Selective medium was developed for isolating *C. difficile* in the late 1970s, with cefoxitin-cycloserine fructose agar (CCFA) deemed most satisfactory *(204)*. Various modifications of the original formulation of CCFA now exist for selective culturing of *C. difficile* for use in epidemiologic studies *(205)*.

When investigating MRSA outbreaks, the ideal medium allows the growth of MRSA or clearly differentiates between MRSA and multiresistant coagulase-negative staphylococci *(206)*. Currently, the best discriminating medium to select for MRSA is mannitol salt agar (7.5% sodium chloride) or Mueller-Hinton medium supplemented with 4% sodium chloride, each containing methicillin, oxacillin, or both *(207)*.

A selective medium consisting of Mueller-Hinton agar with vancomycin (20 μg/mL), polymyxin (100 μg/mL), and streptomycin (100 μg/mL) was successfully used to culture for vancomycin-resistant *E. faecium* from rectal and environmental swabs during an outbreak investigation *(115)*.

Special Microbiologic Techniques

Susceptibility testing for penicillin-resistant pneumococci has rapidly evolved. Previously, this was done in most microbiology laboratories using the National Committee for Clinical Laboratory Standards (NCCLS) method with Mueller-Hinton agar containing added sheep blood and a 1-μg oxacillin disk to screen for penicillin resistance *(208)*. Today, disk diffusion and/or E-test methods are preferred *(209)*. In the future, PCR may become the standard *(210)*.

Traditionally, specimens for isolation of mycobacteria have been inoculated on Lowenstein-Jensen American Thoracic Society medium or Middlebrook 7H10 or 7H11 medium. Incubation for 4 to 6 weeks is required to detect growth with these methods. A more recent approach is to inoculate a thinly poured plate of Middlebrook 7H11 medium and examine with a conventional microscope *(127)*. This allows for slow-growing mycobacteria to be detected in as few as 3 days and identified in 7 to 10 days *(99)*. A biphasic broth culture system, the Roche Septi-Chek AFB system (Roche, Rockwell, MD), is comparable to the Bactec system *(127)*. Another newer method now available is the mycobacteria growth indicator tube (MGIT) (Baltimore Biological Laboratory). The MGIT system consists of a modified Middlebrook 7H9 broth and a sensor embedded in silicone on the bottom of a tube. The appearance of orange-colored fluorescence in the sensor when excited indicates the growth of mycobacteria *(211)*.

Antimicrobial susceptibilities for mycobacteria are generally determined by comparing the amount of growth in the media containing known drug concentrations with growth in the control media *(127)*. Traditionally, antimicrobial susceptibility results obtained by using Middlebrook 7H10 or 7H11 agar with the antituberculosis agents added at specific concentrations takes about 4 weeks of incubation. Currently, the Bactec radiometric system for mycobacterial susceptibility testing can provide results in a week or less *(127)*. The MGIT offers equal speed for mycobacterial susceptibility testing *(212)*.

CONCLUSIONS

The microbiology laboratory has become an integral part of a healthcare epidemiology and infection control program. The constantly changing spectrum of healthcare-associated

pathogens and their susceptibilities and the availability of newer technologies require constant communication, cooperation, and collaboration between microbiology personnel and IPs. In the 21st century, this relationship is more critical than at any time in the past.

The key to effective healthcare epidemiology and infection control efforts in the 21st century will be the proper application of diverse phenotypic and genotypic methods for detection, identification, susceptibility testing, and typing of healthcare-associated pathogens. Phenotypic methods, although readily available, are frequently misleading and, therefore, have limited value in epidemiologic studies today. Genotyping has overcome almost all of the limitations of phenotyping and now provides very effective tools for the healthcare epidemiologist and IP to use in epidemiologic investigations. Important genotypic methods are briefly summarized.

One of the first genotypic methods, PPA, is well suited for the analysis of outbreaks that occur over a relatively short period. This technique is convenient for use in diagnostic laboratories and requires a minimum of equipment and expense. Because many bacterial species harbor plasmids infrequently and because plasmids can be gained or lost, PPA may not be satisfactory for long-term follow-up studies.

REA of plasmid or chromosomal DNA has been very useful for typing many microorganisms in epidemiologic studies. RFLP profiles produced by REA can detect different strains of the same species because of variation in their DNA sequences. The advantages of total DNA RFLP include universal applicability, high sensitivity, and ease of performance. Because some REA patterns were too large and indistinct when obtained with agarose gel electrophoresis, PFGE was developed to provide clearer patterns with better discriminatory power. PFGE appears to give the best results for investigating staphylococci, enterococci, and *P. aeruginosa*.

DNA hybridization with Southern blotting is another molecular method that uses a labeled DNA probe to reduce the number of visible fragments to a manageable number and, thus, produces a clearer fingerprint of the microorganism.

Ribotyping has taken advantage of highly conserved sequences that are found in most microorganisms to delineate the epidemiology of a number of outbreaks. Ribotyping with rDNA is the method of choice when evaluating *Enterobacteriaceae*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*; this method takes about 5 days.

Finally, the most sensitive of all molecular typing methods, PCR, has allowed the identification of new entities and discrimination of nearly identical appearing strains. AP-PCR is the most rapid method (1–2 days) and is also the least expensive method that soon may be applicable to all bacteria.

The rapid development and use of genotypic typing techniques has significantly expanded the understanding of the epidemiology of many healthcare-associated pathogens. The challenge for the microbiology laboratory in the 21st century is to make these techniques readily available (in-house or from a reference laboratory) and affordable. With such tools, the healthcare epidemiologist and the IP should be able to achieve more effective investigations of outbreaks and, thus, will be able to develop better prevention strategies.

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CHAPTER 96

Economic Analysis in Healthcare Epidemiology

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Economic analysis requires technical skill and clinical expertise with results that contribute to fiscal accountability, programmatic support, policies, legislation, and ongoing resource allocation. Medical and technical advances in healthcare have occurred in parallel with rising healthcare expenditures and improved methods for economic analysis worldwide. In the United States (US), mandates for public reporting of healthcare-associated infections (HAIs) exist along with federally authorized expenditure of US$1.1 billion to conduct comparative effectiveness research of healthcare under Title VIII of the American Recovery and Reinvestment Act of 2009 *(1)*. In the United Kingdom, the National Institute of Clinical Excellence has created several hundred guidance reports on clinical-effectiveness and cost-effectiveness in medical conditions and debate exists over how national targets contribute to improved infection control practice *(23)*. From a global perspective, the World Health Organization is engaged in the promotion of healthcare epidemiology and relevant issues of economic analysis (4).

Attention to providing healthcare that satisfies both clinical and economic criteria exist, with stakeholder input from consumers, academicians, collaborative groups, and representatives from government and from industry. Healthcare insurers readily assess the type and the extent of service coverage, with contractual arrangements based on a variety of clinical and economic indicators with pay for performance strategies, incentives, and fund-transfer agreements over time. Policymakers influence public expenditures via mechanisms of healthcare coverage, patient safety, and allowable payments *(5)*. Forecasts from the Office of the Actuary at the Centers for Medicare and Medicaid Services estimate healthcare expenditures of US$3,600 billion, almost 20% of the US gross domestic product, by year 2014. As federal oversight of affordable medical care continues to evolve in the United States, healthcare epidemiologists will have a key role in comparative effectiveness research and practice.

Healthcare epidemiology programs in infection control and occupational health have had unique sustainability challenges given that these programs do not generate direct revenue streams and have historically been challenged to prove their worth (6,7). Resources for the treatment and prevention of HAIs among patients and the provision of health and safety among healthcare personnel require careful revenue assessments that include averting untoward events and optimizing clinical and economic returns on investment (*8–11*,12). In recent years, the methods used to determine the costs of HAIs have been analyzed in detail, with particular emphasis focused on measures to estimate incremental costs (12). Most economic analyses in infection control have focused on hospital-based point of care and a paucity of data exists for infection control interventions across the continuum of care. Gaps in economic analysis of infection control and occupational health programs are especially evident in resource-limited settings *(13–15)*.

From a historical perspective, two broad recommendations from the 1993 Panel on Cost-Effectiveness in Health and Medicine were that the economic analysis of healthcare studies should focus on cost-effective analysis (CEA), rather than cost-benefit analysis (CBA), and that decision making for resource allocations should be society based using reference case analysis *(16)*. In traditional CBA, the effect is monetary rather than units of health outcome and the recommendation for the societal perspective aims for study investigators to incorporate all costs and health effects regardless of who incurs the costs and who obtains the effects. Integration of these broad recommendations into healthcare epidemiology research and practice is plausible as infection control and occupational health programs aim to provide a safe healthcare environment for patients, families, and employees. In the early 1970s, the Study on the Efficacy of Nosocomial Infection Control (SENIC) project confirmed that a 32% reduction in HAI among patients was associated with the presence of hospital-based infection control programs *(17)*. In subsequent decades, the SENIC goals expanded to improve outcomes across the continuum of healthcare. Over the past decade, the number of economic analyses in healthcare epidemiology has increased, with attention now directed toward standardized methods for conducting economic analysis, improving mathematical models, and training infection control providers in economic methodologies (12). Of relevance, the inclusion of applied economic theory into practice, reports, and policies remains a core component and mission of healthcare epidemiologists' education worldwide. This chapter provides an overview of economic analysis in healthcare epidemiology and is intended for healthcare epidemiologists,

professionals in infection control and occupational health, prevention specialists, and administrative staff. The goal is to describe how to incorporate economic methods into the design, execution, and evaluation of infection control and occupational health programs.

APPROACH TO ECONOMIC ANALYSIS IN INFECTION CONTROL AND OCCUPATONAL HEALTH PROGRAMS

The approach to considering an economic analysis in healthcare epidemiology can be structured into three broad categories: output and cost factors, principles of economic theory, and practical considerations.

1. *Outputs and costs:* In determining if and when to conduct an economic analysis, the comparative outputs (effects) and anticipated cost estimates need to be identified (6,7). The output, potential mediating factors, and costs of the existing (A) program can be compared to the output, mediating factors, and costs of one or more alternative (B) programs (Fig. 96-1). While the most effective program may also have the lowest cost (dominant scenario), it is not necessarily true that the lowest-cost option is the most cost-effective. Consideration must be given to the scenario whereby production of the most units of a given outcome may be impractical to implement, because it is so costly from a supply and demand perspective and it either diverts limited resources from other uses or requires more resources than are available. The cost estimate should include identification of cost factors, data entry methods, calculation of program costs, and determinants of cost saving. If the feasibility assessment of effects and costs are dominant for one program versus the other, it would be plausible to proceed with a simplified cost-minimization or cost-consequence analysis. If instead the feasibility assessment suggests differential effects and costs, the inclusion of an incremental CEA should be explored as an aid to the decision-making process. While the purpose of economic analysis in occupational health typically facilitates an investment in health and safety, the efficiency of this process means that the costs of doing a little more (the marginal cost) to enhance safety equal the benefits (18). Hence, the marginal returns in terms of health and welfare enhancements of the healthcare personnel result from risk reduction (18).
2. *Principles of economic theory:* Economic analysis within healthcare epidemiology is complex given the dynamic algorithms for resource allocation, revenue generation, expenditures, opportunity costs, and assessment of health outcomes in hospitals, alternative care sites, and home-based care. Economic analytical methods are based on a fundamental concept of efficient use of available resources which includes the economics of resource allocation and the efficiency in the use of these resources *(19)*. Analytical difficulties include the estimation of a market price for the resources and the decisions related to allocation of limited resources among seemingly unlimited demands *(19)*. Opportunity cost is relevant to economic evaluations in healthcare epidemiology and represents the value of the resource when it is dedicated in its next best use. Opportunity costs are expressed as the value of lost output if the resource is employed in an alternative productive process *(19)*. Opportunity cost analysis is an important component of business decisions but is not equivalent to a line-item cost in a financial statement. The benefits from the next-best use in resource allocation may be smaller than those of the current use, indicating that the current use is best, or the benefits may be greater, in which case the alternative would be considered preferable *(20)*. Opportunity costs are incorporated into the methodology of CEA.
3. *Practical considerations:* Three core questions have been identified as relevant for assessment of HAI (21): Why measure the cost? What outcome should be used to measure the cost? And what is the best method for making the selected cost measure? (21). First, the costs permit objective assessment of the allocated resources. Second, in hospital-based analysis, one cost measure is the number of bed-days saved valued in dollars (21). A health economist may further value bed-days saved as the next best alternative use or the economic opportunity value of the marginal healthcare resources released as a result of fewer HAI (21). Lastly, the selected cost measure is at risk for measurement bias that pertains

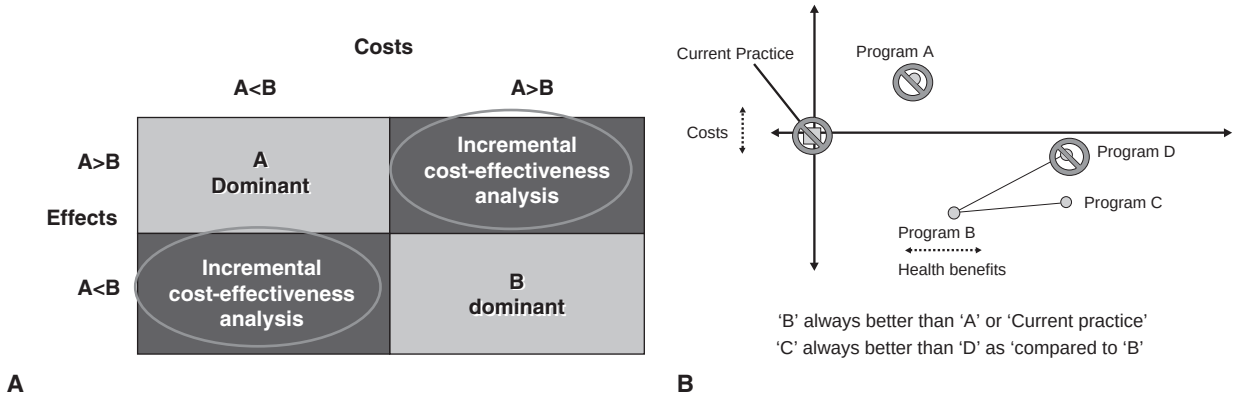

FIGURE 96-1 **A:** Determining when to conduct a cost-effectiveness analysis for program A versus program B. **B:** Is more infection control a smart investment?

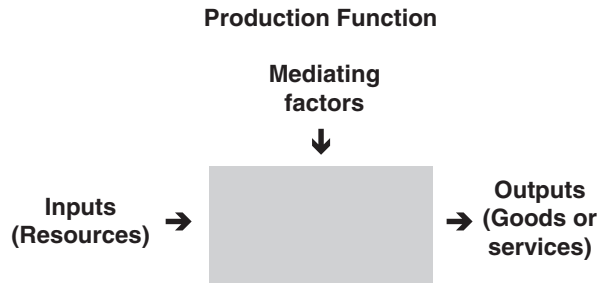

FIGURE 96-2 Production function. (Redrawn from Morris S, Devlin N, Parkin D. *Economic analysis in health care*. London, UK: John Wiley & Sons, 2007.)

to identification of the comparator group as well as time-dependent bias (21,22). After the decision to embark on a robust economic analysis has been made, the relationship between the resources involved in the output (outcome of interest) and the estimate of costs must be considered in more detail. The resources, or inputs, require a unit of measure such as health personnel hours or number of encounters, medical supplies, and diagnostic tests. Measuring this productive process in healthcare epidemiology is especially complicated because the patient is both an input and an output in the process *(19)*. The relationship between inputs and outputs can be extrapolated from an applied understanding of production function (22). A production function focuses on analysis of the relationship between quantities of the input and quantities of output in which the details are often a "black box" (Fig. 96-2). Three major components of the evaluative method are input or resources, mediating factors, and outputs that are goods, services, or outcomes. The mediating factors may influence the relationship between the inputs and outputs involved in the production of health. The cost estimates are typically categorized as direct costs, in dollar expenditures, and indirect or intangible costs, which influence the outcome of interest. Based on supply and demand economics, differentiators within the model are due to efficiency, product choice, and product distribution. Efficiency involves the obtainment of maximum output from productive inputs. Product choice includes determining what goods and services should be produced to meet the demands, and product distribution involves who gets the products produced *(19,23)*. For infection control and occupational health programs, different combinations of inputs can produce the same level of output. Hence, substitution analysis of inputs may identify cost saving and opportunity costs, and several analytical techniques exist for the economic analysis of healthcare programs and evidence-based medical care *(24,25)*.

Several specific issues should be clarified prior to the initiation of an economic analysis within an infection control and occupational health program, as detailed in the following:

1. *Type of institution:* As the site of an episode of healthcare becomes a continuum from the acute to alternative care settings, measurement of risks and resource allocations become more complicated for infection control or occupational health programs.
   a. *Acute care institution:* Resource allocations for healthcare epidemiology programs are often determined by hospital size (licensed bed number). In general, infection control budgets include supplies, overhead, and the salaries of staff such as a part-time physician, nurse, secretary, and data programmer. Based on a program budget, outcomes and economic analysis contribute to justification of the return on investment, if not break-even point, for a healthcare epidemiology program *(26,27)*.
   b. *Long-term care facilities:* Over 1.5 million persons annually reside in US long-term care facilities and the estimated number of infection preventionists per nursing home is fourfold lower than the estimate for infection preventionists in hospital-based care *(28)*. Guidelines exist for prevention and control of infections in long-term care, with endorsement to specifically reduce HAIs (29).
   c. *Home care and other alternative settings*: The role of infection control in home care is often collapsed into the general responsibilities and resources available to nurses within the individual home care organization. Identified unmet needs for infection control in home care settings are the development of valid definitions for home care–acquired infection and practical methods of surveillance *(30)*. Once established, estimates of incidence and risks can be determined in order to characterize effective interventions *(30)*.
2. *Endemic versus epidemic infection control strategies:* As the majority of healthcare epidemiology efforts are dedicated to the control of endemic infections, rather than epidemic infections, resource allocations should parallel this distribution of activity. In infection control programs, CEA needs to distinguish between endemic and epidemic infection control strategies and aim to identify estimates of economic burden incurred from the societal perspective. The Centers for Disease Control and Prevention (CDC) recommend four key components for infection control programs targeted to control the spread of multidrug-resistant pathogens: surveillance, applied research, prevention and control strategies, and development or expansion of infrastructure *(31)*. Infection control programs that target prevention and control of spread of multidrug-resistant pathogens should ideally take these components into consideration for CEA.
   a. *Surveillance:* The degree of pathogen surveillance within a healthcare setting can range from none to that of intense specimen procurement, reporting, and evaluation during an epidemic. The surveillance plan may vary, contingent on the identified pathogen, intervention, and goals of the program. For healthcare systems dedicated to the prevention and control of the spread of multidrug-resistant microorganisms, the options for surveillance span from a threshold alert on clinical isolates to the use of a suppressed or routine passive surveillance system to the incorporation of more elaborate programs with formalized active surveillance.
   b. *Applied research:* To adequately assess the impact of infection control programs by CEA, resource

allocation is needed for integration of molecular epidemiology methods such as molecular diagnostics of clinical specimens, data programming, and analysis from one or more information systems.

c. *Prevention and control strategies:* The strategies employed in healthcare epidemiology and infection control programs are myriad. Such strategies may be categorized as environmental, educational, behavioral, and pharmacologic.

d. *Development or expansion of existing infrastructure:* Secure, dynamic infrastructure is crucial for an effective healthcare epidemiology or infection control program. The infection control specialists in large and small programs need access to administrative leadership, database management support, performance monitoring systems, and ongoing educational programs. As a program or hospital department, infection control programs are accountable for patients, healthcare workers, and the public health components of assigned environments. During times of accreditation, healthcare personnel are expected to report on performance and update policies and procedures for the Joint Commission, Health Care Financing Administration, and other federal and state regulatory agencies.

3. *Interventions:* Infection control interventions that are best as candidates for widespread implementation are those that are readily modifiable and feasible. Primary prevention interventions involve strategies to reduce risk factors or prevent exposure. Interventions in secondary prevention reduce the effects of the risk or exposure. Treatment interventions treat the insult resulting from the risk or exposure. In occupational health programs for healthcare personnel, the worksite provides an opportunity to promote and sustain healthy behaviors related to diet and exercise *(32)*. Uptake of immunizations by intensive care unit personnel was associated with education and a committed occupational health team in at least one resource-limited setting *(33)*.

COMMON ECONOMIC ANALYTICAL METHODS

Economic analysis may be simple or complex. A simple analysis includes measure of the costs of an output (such as an infection) without a comparison group, similar to accounting (12). Five types of economic evaluations are commonly used in healthcare: analysis of cost minimization, cost consequence, cost-benefit, cost-effectiveness, and cost utility (18). In each of these analyses, there is the valuation of inputs (costs) and the distinctions are in how the effects (outcomes) are measured (Table 96-1). The first method is a partial economic analysis as it focuses solely on costs, while the latter four methods focus on costs, outcomes, and the incremental or additional costs or benefits of the intervention or program.

1. *Cost-minimization analysis:* A cost-minimization analysis includes the incremental costs of alternatives that achieve the same outcome. Competing interventions are the same, the only input is cost, and the aim is to decide the least costly way of achieving the same outcome. This simple cost analysis method entails a balance of risk and costs to optimize clinical operations *(34)*.
2. *Cost-consequence analysis:* A cost-consequence analysis considers the incremental costs and effects that achieve the same outcome, without an attempt to aggregate the costs and effects *(35)*.
3. *Cost-benefit analysis:* As an analytical tool, CBA estimates the net societal benefit of a program or intervention and is measured as the incremental benefit of the program minus the incremental cost, with all benefits and costs measured in dollars *(16)*. The goals in using a CBA are to eliminate procedures when the cost outweighs the benefit and to facilitate or encourage implementation of the procedure when the benefit outweighs the cost *(36)*. The methods include the estimates of costs and benefits and there is a clear decision rule to undertake an intervention if the monetary value of its benefits exceed

TABLE 96-1

Five Types of Economic Analyses for Healthcare Interventions and Programs

	Measure(s)		
Analysis (Type)	***Cost***	***Outcome***	***Distinctions***
Cost-minimization analysis (partial)	Monetary	Monetary	Focus on conditional, objective cost reduction within acceptable risk
Cost-consequence analysis (comparative)	Monetary	Monetary	Alternative outcome for which the components of incremental costs and consequences are calculated without aggregation into a CER
Cost-benefit analysis (comparative)	Monetary	Monetary	Monetary value to benefits (outcome)
Cost-effectiveness analysis-(comparative)	Monetary	Health unit	Net costs per outcome; cost saving incorporated into net cost with CER
Cost-utility analysis (comparative)	Monetary	Outcome equilavent across interventions such as QALY or DALY	Special type of cost-effectiveness analysis; interventions with differential outcomes can be compared

CER, cost-effectiveness ratio; QALY, quality-adjusted life year; DALY, disability-adjusted life year.

its costs. The two major limitations of this method are determining the level at which the benefit is significant enough to implement the intervention and its lack of a societal perspective *(36,37)*.

a. *Estimations of cost:* Estimations of cost for HAI require that the incremental costs associated with diagnosing and treating the infection be distinguished from the costs attributable to diagnosis and management of the primary medical problem. Incremental costs of HAI include costs allocated for laboratory, pharmacy, procedures, and additional hospital days. Haley et al. *(38)* reported in 1981 that approximately half of the additional costs of treating such infections were accounted for by extra days of hospital stay. Several methods for estimating costs by estimating incremental excess length of stay resulting from HAI have been identified: unmatched group comparison, matched group comparison, implicit physician assessment, and an appropriateness evaluation protocol method *(39,40)*.
   i. *Unmatched group comparison:* In this comparative approach to HAI, the total number of hospital days attributable to HAI is determined by comparing patients with and without HAI. There are no adjustments for severity of illness, and hence this method consistently overestimates additional incremental costs of HAI *(41)*.
   ii. *Matched control comparison:* For assessment of HAI using this method, patients with HAI are matched to uninfected patients who have comparable age, severity of illness, and underlying disease *(42–46)*. Alternatively, sites of care can be matched as part of the study design and evaluation *(47)*. These studies are likely to give the most accurate assessment of the additional incremental costs of the HAI *(44,45)*.
   iii. *Implicit physician assessment:* In this method, a chart review by a designated person is conducted via an outlined protocol. This method is limited by subjectivity and, in comparison with other methods, consistently underestimates the true incremental costs of HAI *(48)*.
   iv. *Appropriateness evaluation protocol method:* This method distinguishes original causes of hospitalization from those related to the identified HAI *(40,49)*. Each day of hospital care is linked to one or both of these categories. Objective categorization protocols are designed for this labor-intensive approach.

b. *Estimations of benefits:* Benefits of infection control strategies include subjective and objective determinations of the decrease in the occurrence or effects of infections resulting from infection control interventions. Such benefits may include a decrease in the number of hospital days or a decrease in estimated HAI rates *(50)*.

4. *Cost-effectiveness analysis:* The core purpose of a CEA is to provide a relative value to different healthcare interventions and to relate the value of the impact of these interventions to the value of specific health outcomes. Costs and benefits are not reduced to a common denominator. Instead, the costs and effects of an intervention or program and at least one alternative approach are calculated and presented in a ratio of incremental cost to incremental effect, with the effect being a measurable health outcome. Opportunity costs are incorporated into the cost-effectiveness ratio—most commonly as dollars per year of life saved *(19,20)*. Notably, wide variation in cost-effectiveness ratios has been reported in medical and public heath disciplines. To put CEA for infection control into perspective with studies of cancer screening and athletic cardiac evaluations, some traditionally accepted healthcare interventions save money, whereas others cost more than US$1 million per year of life gained. An intervention to promote colorectal cancer screening among veterans at average risk of developing colorectal cancer had a cost-effectiveness ratio of US$978 per person screened (95% confidence intervals, US$767–US$3,213) *(51)*. The estimated cost of continued mammography screening to age 75 to 80 years was US$34,000 to US$88,000 per life-year gained, compared with discontinuation of screening at age 65 years *(52)*. The calculations in CEA include the following:

a. The cost-effectiveness ratio is a mathematical ratio in which the numerator includes all changes in resource utilization relative to at least one stated alternative and the denominator includes all the health effects of an intervention relative to the stated alternative(s). Ultimately, the CEA provides ratios that show the cost (in monetary terms) of achieving one unit of health outcome *(53)*.
   i. *Numerator:* Variables for the numerator should include the costs of healthcare services, patient time expended for the intervention, paid and unpaid caregiving services, costs associated with lost productivity or illness (e.g., travel, child care, missed employment), costs linked to the nonhealth impact of the intervention (e.g., the environment), and time spent seeking an intervention.
   ii. *Denominator:* Variables for the denominator include those that are effects of the health intervention such as subsequent morbidity and length of life.

b. *Costs:*
   i. Direct costs are the value of all resources, goods, and services consumed in the provision of an intervention or in dealing with the consequences of the intervention. These estimates include both medical and nonmedical costs.
   ii. Indirect costs pertain to productivity gains or losses related to illness or death.
   iii. Marginal costs are the extra amount of resource consumption incurred for providing a service as compared with the costs of not providing the same service.
   iv. Incremental costs are the costs of one alternative (comparator) minus the cost of another alternative. The incremental cost-effectiveness ratio is the difference in costs between two alternatives compared with the difference in effectiveness between the same two alternatives.

c. *Discounting:* Discounting is the process of converting future dollars and future health outcomes to a present value.

d. *Reference case analysis:* When a CEA will contribute to decisions that pertain to broad or societal allocation of resources, a reference case analysis is recommended *(16)*. A reference case analysis includes a baseline computation of the cost-effectiveness ratio along with a meaningful set of sensitivity analyses that allows for comparison of the results with other published studies. This reference case analysis should include validated measurement of health-related quality of life that can incorporate the effects of morbidity on productivity and leisure. In addition, the health intervention of interest should be compared with existing practice rather than an unattainable alternative.

5. *Cost-utility analysis:* The cost-utility analysis is a special type of CEA, in which quality of life is also considered as part of the outcome. The outcome or benefit is measured in quality-adjusted life years (QALYs) and expressed as utilities which comprise both length of life and subjective levels of well-being. The outcomes of the intervention are translated into a measure that includes dimensions of both morbidity and mortality. The effect of competing interventions is expressed in a calculation of costs per QALY. An intervention is deemed efficient, relative to an alternative, if it results in higher or equal benefits at lower cost. Advocates for a payer threshold for a cost per QALY, such as US$50,000 per QALY, cite that an arbitrary value is validated (54). Of relevance, the source of the often-cited $50,000 per QALY cost-utility threshold in US healthcare is uncertain, and debate continues for a set cost per QALY threshold in healthcare (55,*56*,*57*,58). A proposed alternative is for the cost per QALY to vary across payers, populations, interventions, and time, and hence the weight of evidence for and against the US$50,000 per QALY benchmark, or any unique cost per QALY threshold, will likely remain a topic of US healthcare debate for several years (55). From an international perspective, few countries other than the US have economic thresholds to ration or limit healthcare based on cost-effectiveness estimates. Exploratory efforts are under way to determine if willingness-to-pay and value-of-life estimates offer additional determinants for decisions related to increases in health benefits in exchange for incremental expenditures and for transferability of estimates and values across populations (59–62).

COMPONENTS OF AN ECONOMIC ANALYSIS

The outcomes evaluation process begins with the identification of one or more desired outcomes. The measures of health outcomes most commonly employed are the number of lives, life years, QALYs, and disability-adjusted life years. If an intervention varies in intensity or periodicity, incremental cost-effectiveness ratios are calculated that express the additional cost per each additional unit of outcome obtained. Most importantly, the perspective taken for the evaluation of costs provides the foundation of the economic analysis. Additional components include costs, output, structured and process measures, and utility.

1. *Cost perspective:* The perspective taken for the evaluation of cost provides the foundation of the economic analysis. The cost-effectiveness construct and the ultimate results obtained from it depend on the perspective taken from the population affected by the intervention. Efficiency in resource use, or "getting the most out of limited resources," is a goal of every healthcare organization regardless of one's cost perspective *(19)*. Four such cost perspectives include the patient, provider, payer, and society.
   a. *Patient perspective:* Costs to the patient include copayments, lost time from work, and lost value or even years of life if there is a health status change.
   b. Provider perspective: For providers, profit must be considered. Short-term decisions are measured as the difference between receipts and the variable cost of providing the service, whereas long-term decisions are measures that include fixed and variable costs.
   c. *Payer (insurer) perspective:* Payers are accountable for contracted rates for services that often depend more on the contract than on the actual services delivered.
   d. *Hospital perspective:* An economic evaluation from this perspective is restricted to the clinical and economic outcomes that occur within the hospital system. In these analyses, the costs (or savings) associated with outpatient healthcare services and time lost by patient or family are not considered (12).
   e. *Societal perspective:* If the nature of the problem is broad, the perspective of the CEA should be equally broad and reflect the societal perspective *(16)*. In such an analysis, everyone affected by the intervention and all significant health outcomes and costs that flow from the intervention must be included in the analysis. Society is interested in a balance that ensures that resources are allocated in such a way that each unit is put to its most productive use. This type of analysis is rarely reported, so on a more practical basis, society prefers options that produce more output for a given amount of resources. Although health outcomes are often represented by years of life gained in CEA using the societal perspective, the measure of outcomes should be defined more broadly. In application of the reference case analysis, economic evaluation may vary between countries and the societal perspective must be that of the country in which the intervention is performed.
2. *Outputs versus outcomes:* Outputs are the number of service units that a program delivers. Outcomes are the results of the specific intervention. In setting up a health outcome analysis, it is imperative that long-term outcomes be distinguished from intermediate and short-term outcomes to better characterize the study design.
3. *Structured and process measures:* Structured measures assess organizational or programmatic features that are perceived to influence performance. Process measures assess the ways in which the intervention occurs.
4. *QALYs:* Quality of life is a rather broad construct that attempts to comprise all valued aspects of an individual's existence (e.g., aspects of health, economics, environment, politics, culture, and spiritual values). In health outcome measurement, QALYs are assigned to each time

period of evaluation with a weight, ranging between 0 and 1, which corresponds to the health-related measure during that period *(16)*. In analysis, a weight of 1 corresponds to optimal health, whereas a weight of 0 corresponds to a health state judged equivalent to death *(16)*. The major assumption that must be addressed with this measure is that a QALY may not be of equal value to all who gain from it, and the gain may not be equal during all components of the life span *(38,63)*.

5. *Utility and patient preference:* In quality of life measurement, utility refers to the preference for a particular health outcome. Patient preference for a particular health outcome can be quantified with standardized metrics and expressed as utility functions or preferences for a particular outcome and incorporated into CEA. Common patient preference measures include standard gamble and time trade-off.
   a. *Standard gamble:* Standard gamble is a determination of patient preference, or utility, for a particular outcome. A comparison is made between the probability of a particular health state (e.g., assured perfect health) versus an alternative health state (e.g., chronic infection, bed-bound, or death). In measurement of the gamble, the probability p is varied until the preference for the assured health state is equal to the preference for the alternative $(1 - p)$.
   b. *Time trade-off:* In this patient preference metric, a patient is asked to trade off years of life in a state of less than perfect health for a shorter life span in a state of perfect health *(11)*. Although occasionally patients will not trade any years of life for less than perfect health, this time trade-off measurement is calculated as the ratio of the number of years in perfect health equivalent to the often longer span in less than perfect health.

ECONOMIC ANALYSES IN STUDIES OF INFECTION CONTROL AND OCCUPATIONAL HEALTH

Economic analysis and comparative effectiveness research will become more prominent in healthcare epidemiology over the next decade. In a systematic audit of economic evidence in studies that linked HAI and infection control interventions between years 1990 and 2000, most (85%) of the 55 identified studies were conducted in either North America or Europe and were of analyses that were from the hospital perspective (64). Higher associated costs were reported in the occupational health studies than most other infection control prevention interventions, few investigations discounted future costs, and only one study used an end outcome measure with QALY that met the criteria of reference case analysis (64,*65*). In a subsequent systematic review of published studies from 2001 through mid-2004, 70 studies were identified that had economic analyses for HAI and infection control interventions (12). Most studies (80%) were from the US or Europe, with wide variation noted in the cost estimates of HAI (12). An additional key feature of the review was inclusion of a quality measure to systematically audit economic evaluations *(66)*. The overall mean attributable costs and standard deviation (SD) of specific HAI for the subset of publications worldwide that reported the outcome cost per patient were US$25,546 (SD US$39,875) for surgical site infection, US$36,441 (SD US$37,078) for bloodstream infection, US$9,969 (SD US$2,920) for ventilator-associated pneumonia, and US $1,006 (SD US$503) for urinary tract infection *(67–87)*. Most notably in the two systematic reviews, the use of a reference case analysis with economic analyses was uncommon and such reference in healthcare epidemiology remains best exemplified by immunization programs (12,64,*88–97*). A survey of publications in 2003 on cost-effectiveness research targeting preventive interventions identified 232 publications with original economic evaluations, 31% of which focused on infectious diseases (98). In an exemplary approach to methods, the investigators converted all local currencies to euro currency values of the base years of the study, per the advice of the Organization for Economic Cooperation and Development, and recalculated the costs to 2008 values using the price index of Statistics Netherlands (98,*99*,*100*).

Recent economic analyses of infection control and occupational health vary in design, execution, analysis, and year(s) of study. The following summary provides some cost estimates and a framework for comparative economic analysis in infection control, occupational health, and efforts specific to resource-limited settings.

1. *Infection control programs:* The estimated US burden of hospital-acquired infection was US$1.7 million, or approximately 4.5 infections per 100 hospital admissions in data from 2002 (101). Such infections ranked sixth in leading causes of US deaths (101). In a network of 28 hospitals in 2004, the median annual cost for HAI was US$594,683 (interquartile range US$299,057–US$1,287,499) per hospital *(20)*. The weight-adjusted mean cost estimate for specific infections in this study was US$23,242 per healthcare-associated bloodstream infection, US$25,072 per episode of ventilator-associated pneumonia, US$10,443 per surgical site infection, and US$758 per catheter-associated urinary tract infection *(20)*. Central venous catheter dressing changes by ward nurses (case) versus an infusion team (control group) were associated with catheter-related bacteremia in 1.7% of cases and 1.4% of the control group *(102)*. There were no differences in catheter-site infection rates, and the estimated cost savings was in excess of US$90,000 per year by delegation of this dressing change to the ward nurses *(102)*. Estimates of HAI in Europe, as well as estimates of excess costs, approach numbers in the US *(103,104)*. A hospital-based program to avert transmission of influenza A/H1N1 2009 viral infection concluded that protection measures targeting only infected patients had an incremental cost of US$23,000 per death averted, and if expanded to a universally enforced hospital program, the estimate was US$2.5 million per death averted *(105)*.
2. *Occupational health:* The losses to society from work-related accidents and illnesses are very large and often underappreciated from a nonsocietal perspective. The costs associated with a case of ill health include medical treatment, furloughs, and administrative costs inclusive of recruitment and replacement (106,*107*). Exemplary of an analysis of cost savings in occupational health,

occupational sharps' injuries in Sweden were first estimated to cost €1.8 million, or €272 per reported injury, of which €1 million was for hollow-bore sharps injuries *(108)*. The introduction of safety devices was estimated to avert 3,125 injuries, with a corresponding cost offset at €850,000 from the Swedish healthcare perspective *(108)*.

3. *Healthcare epidemiology in resource-limited settings:* Estimates of risk for HAI are 2- to 20-fold higher in developing countries relative to developed nations, and challenges associated with feasible, efficacious infection control interventions in developing countries have been identified *(109–112)*. The execution and report of economic analysis for infection control and occupational health studies from resource-limited settings, with distinctions in perspectives for middle-income versus low-income countries, will contribute to robust understanding of resource allocations for health and wellness in the decades to come. The financing of health and wellness is particularly complex in low-income countries. Global health initiatives may mobilize substantial resources, but the major challenges involve the need for institutional capacity to manage harmonization and ensure durable programmatic support when global health initiates expire *(113)*. While capacitance building will continue to impact infection control and occupational health programs in resource-limited settings, clinical and economic benefits are evident with improved diagnostic tools, surveillance programs for select pathogens and infectious diseases, and population-based research targeting improvements in public health *(114–118)*.

STRENGTHS AND LIMITATIONS OF ECONOMIC ANALYSIS IN HEALTHCARE EPIDEMIOLOGY

Economic analysis is basically about resource use and, hence, is pertinent to healthcare decisions in infection control and occupational health programs. To leverage resources it is often necessary to present a business case to key leaders and stakeholders, using well-aligned clinical data and economic analysis. The information must be readily understandable by all users with flexibility for an oral presentation, written technical report, peer-reviewed publication, or web-based program.

The assumptions, potential bias, generalizability, and limitations of the analysis should be considered and made transparent. At the level of dissemination and uptake, reporting bias for CEA exists, with a predominance of studies that report favorable incremental cost-effectiveness ratios (119). In a review of published studies between 1976 and 2000, studies categorized as those of higher methodological quality and those conducted in the United States and Europe, relative to elsewhere, were less likely to report incremental cost-effectiveness ratios below US$20,000 per QALY (119).

Economic analyses do vary in assigned monetary values, are limited by the validity of the assumptions incorporated into the evaluation, and at risk for overly simplistic results. In the assessment of the quality of the strengths and limitations of an economic analysis, there is a proposed list of 10 questions for reviewers to consider *(120)*. This list includes the following: (a) Is the analysis based on a hypothesis that tests a clearly defined question about a clinically relevant and economically important issue? (b) What viewpoint and cost perspective is considered for the defined costs and benefits? (c) Is the comparison of an intervention(s) effective? (d) Are the interventions practical within the recommended settings? (e) Which method of economic analysis is used, and is this appropriate? (f) How are the costs and benefits measured? (g) Are incremental, rather than absolute, benefits considered? (h) Is the here and now given precedence over the distant future? (i) Is a sensitivity analysis conducted? (j) Are "bottom line" aggregate scores overused?

FUTURE DIRECTIONS IN ECONOMIC ANALYSIS FOR HEALTHCARE EPIDEMIOLOGY

As the basics of economic analysis are incorporated into healthcare epidemiology educational programs, it is anticipated that more robust CEA will be conducted, reported, and published.

Published studies with economic analysis of infection control and occupational health, using a societal perspective, are uncommon, as are economic analyses of infection control in home-based settings and resource-limited settings. Studies comparing efficacy, safety, and cost-effectiveness of alternative ways to prevent and control HAI and promote safety will fill important information gaps facing clinicians, patients, and payers in the years to come and provide evidence to support appropriate allocation of limited resources.

SUGGESTED RESOURCES

- Infectioncontrol:*http://www.cdc.gov/ncidod/EID/vol10no4/02-0754_files/appendices.pdf*
- Occupational health: *http://www.ilo.org/safework_bookshelf/english?content&nd=857170233*

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CHAPTER 97

Legal Issues in Healthcare Epidemiology and Infection Control

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Infection control in hospitals is a major problem associated with significant personal and economic costs. There are about 2 million cases of hospital-acquired infection (HAI) each year, some by drug-resistant infectious agents, causing serious health consequences and nearly 100,000 deaths annually in the United States (*1–4*,5). Public health authorities, hospitals, physicians, and others use a number of strategies to reduce or eliminate the threat of infection. Efforts to reduce the risk of infection are medically appropriate; however, they also have serious legal implications. Hospitals thus necessarily consider legal rules and the need to limit liability as they design and implement infection control practices intended to preserve life and health.[1]

In many cases, of course, the two goals of preventing injury and limiting liability overlap. Thus, standard epidemiologic and infection control policies both protect health and serve to reduce or eliminate legal liability. The legal landscape is complicated. Legal obligations can be created at different levels of government (federal, state, and local) and promulgated in different ways (statutes, regulations, and court decisions). Some legal rules explicitly address infection control policies, while other rules (e.g., those governing medical confidentiality and discrimination against persons with disabilities) have an indirect but important impact on infection control regimens. Persons who work with healthcare epidemiology or infection control policies, therefore, must have an understanding of both the legal and the medical implications of their work.

The hospital setting creates risks for three different groups of persons: hospital patients, hospital workers, and persons who come into contact with either patients or workers. Hospital patients are most clearly at risk: surgical incisions can become infected, for example, or patients may suffer from infections transmitted by other patients or healthcare workers (*3,4*,5). Hospital workers, too, face risks in the healthcare environment. Workers may come into contact with patients suffering from a wide range of communicable diseases, of which tuberculosis (TB), viral hepatitis, and infection with human immunodeficiency virus (HIV) are currently among the most common examples *(6)*. The risk of infection is also present for others, such as family members or other hospital visitors *(7)*.

The legal system responds to the risk of infection in two major ways. First, state licensure standards, federal provider eligibility standards and reimbursement standards, and federal worker safety regulations each impose explicit or implicit duties on hospitals and hospital employees to reduce the risk of infection. Licensure standards can impose direct requirements to employ infection control practices. Payment schemes that deny hospital reimbursement for certain HAI indirectly establish a standard that these infections should be prevented. Regulations designed to protect hospital workers from the risk of workplace infections may impose specific duties on employers.

Second, the legal system allows persons injured by hospital-related infections to sue for damages. Courts throughout the country have been willing to hold hospitals liable for lapses in infection control procedures. These liability decisions, often called common law rules, indirectly define standards or duties for hospitals. A court's decision that holds a hospital liable for its failure to provide a piece of equipment, for example, implicitly suggests that other hospitals wishing to avoid liability should acquire the same equipment.

Statutory, regulatory, and common law duties are often interrelated: A jury might find, for example, that a hospital was negligent in its administration of an infection control plan, because the hospital failed to meet standards established in a state licensure statute. The legal rules can also appear to be in conflict, such as when a hospital has to implement its duty to prevent transmission of illness while meeting its legal obligations to protect the confidentiality of patients and the employment rights of its workers. Understanding the sources, scope, and limits of these legal rules is an important task.

THE HOSPITAL'S DUTY TO PROTECT PATIENTS AND VISITORS

Hospitals must comply with several types of legal rules designed to protect patients. These rules can be found in federal or state statutes and regulations, in the standards

[1]This chapter provides general information about some of the legal issues raised by epidemiology and infection control policies. A licensed attorney should always be consulted for specific legal advice.

of private accrediting organizations, and in the judgments of juries holding hospitals liable in tort cases. This complex regulatory structure can create an intricate and sometimes contradictory web of duties.

Hospital Regulation

There are several different types of hospital regulation. All hospitals in the United States are subject to state licensure requirements *(8)*. Hospitals seeking reimbursement from the Medicare and Medicaid programs must also meet standards established under federal and state laws *(8,9)*. Important standards also are established by public health authorities, such as the Centers for Disease Control and Prevention (CDC) and the CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) *(6,10)*, and by private accrediting groups, such as the Joint Commission (formerly the Joint Commission on the Accreditation of Healthcare Organizations) *(11,12)*.

Hospital licensure statutes are designed to protect patients. These statutes generally require that hospitals reduce the risks of infection to patients, staff, or others by maintaining appropriate equipment, employing persons with specialized training, and implementing mechanisms to reduce the risk of infection. The Florida statute provides, for example, that hospital regulators must adopt "reasonable and fair minimum standards for ensuring that hospitals implement "[i]nfection control, housekeeping, sanitary conditions, and medical record procedures that will adequately protect patient care and safety" (13).

The guidelines of public health entities such as the CDC and HICPAC are important even though they may not be incorporated into a specific statute or regulation, because they might be used, explicitly or implicitly, by licensing authorities or others *(10)*. The Joint Commission's hospital accreditation requirements are incorporated into many state licensure statutes *(14)* and the federal Medicare and Medicaid regulations *(15)*. The end result is that hospitals are subject to specific performance-based standards designed to ensure that they monitor and reduce the risk of infection. The CDC's National Healthcare Safety Network also creates the opportunity for studying the results of hospital infection control policies *(16)*.

These general infection control standards are supplemented by more specific requirements for some diseases. The special rules governing HIV and hepatitis B virus (HBV) are particularly important. Several states have enacted statutes designed to protect hospital patients from HIV or HBV infection *(17)*. Under federal law, states generally must implement the CDC's recommendations to reduce the risk of HIV or HBV transmission from healthcare workers to patients (18). The CDC's 1991 recommendations require healthcare workers who perform "exposure-prone procedures" to know their HIV and HBV status and to refrain from engaging in those procedures without the consent of an expert review panel (19). Depending on state law, hospitals may have a role in implementing these recommendations by defining which procedures are exposure-prone or through establishing expert review panels that can advise HIV- or HBV-infected practitioners (19,*20*). It has been difficult for hospitals to implement these regulations in the absence of consensus about either the degree of actual risk posed by HIV-infected healthcare workers or the identification of exposure-prone procedures (18,*21*).

A hospital's compliance with government regulations, public health guidelines, and private accreditation requirements can be very important in three respects. First, hospitals that fail to meet these requirements risk suspension of licensure, the imposition of civil fines, and the attendant bad publicity. Second, hospitals without effective infection control policies might lose eligibility for Medicare reimbursement, an important source of revenue. Third, a hospital's failure to comply with these public or private regulatory schemes increases the risk of tort liability. Injured patients will be able to claim that a hospital's violation of a particular statutory or regulatory requirement is evidence that the hospital was negligent in providing for the welfare of its patients.

The Deficit Reduction Act of 2005 resulted in significant changes to Medicare reimbursement policies with respect to HAI. The Act required the U.S. Secretary of Health and Human Services to identify certain HAIs that create higher Medicare costs and "could reasonably have been prevented by evidence-based guidelines" (22). Hospitals are denied Medicare reimbursement for care associated with these infections in many circumstances as of October 2008. The effort to use the financial incentive of nonpayment to encourage hospitals to act to reduce infections has its critics *(23–25)*. For example, critics argue that the rule places an undue burden on hospitals by refusing to pay for conditions that are not preventable *(24,25)*.

Hospital Tort Liability

Hospitals and healthcare professionals are increasingly concerned about tort liability. The charitable or governmental immunity doctrines that long protected hospitals from lawsuits have crumbled over the past 50 years *(26,27)*. The tort system requires a defendant to compensate a plaintiff when the plaintiff can show that the defendant's negligence caused the plaintiff's injury (28). *Negligence* is a legal term meaning that a defendant failed to exercise the degree of care owed to the plaintiff (28). Generally, individuals or institutions have the duty to exercise reasonable care (28). In the healthcare context, hospitals are often required to observe the standard of care that would reasonably be exercised by other hospitals under similar circumstances (28). Statutes, regulations, or accreditation requirements can be used to define a hospital's required standard of care (29).
There are several different types of hospital liability (28,30). Hospitals are generally held liable for the negligent acts of hospital employees under the doctrine of *respondeat superior* (28). Hospitals also are directly liable for institutional negligence, such as for failing to have equipment necessary to prevent HAI or for failing to establish policies or procedures designed to reduce the risk of infection. Matters are complicated somewhat by the fact that hospital patients are often treated by private physicians who are not hospital employees. A hospital generally will not be held liable for the negligence of a private physician so long as it is clear to patients that the physician is not a hospital employee (28). However, the hospital can be held liable if its employees knew or should have known of the risk of infection and failed to take appropriate action, even if the patient is also under the care of a private physician.[2]

There are four elements to a patient's tort claim against a healthcare professional or hospital. The plaintiff must show that the defendant owed her or him a duty to provide a particular standard of care, that the defendant failed to meet the required standard of care (negligence), that the breach of the standard of care caused the plaintiff's injury, and that the plaintiff's injury is of a type that deserves compensation (28). The plaintiff must prove these four elements by a preponderance of the evidence.

The first element has two parts: The hospital must have a duty to the plaintiff to provide a particular standard of care. In general, a hospital has a duty to protect persons who are foreseeably at risk for harm from the hospital's conduct. This is a relatively easy element for plaintiffs to prove. Patients are under the care and control of the hospital, and it is foreseeable that the hospital's failure to take care in the provision of its services could cause its patients harm. A hospital's duty to protect its patients from infection also arises from the statutes, regulations, and standards discussed previously. Hospitals clearly have a duty to protect patients from the risk of infection (29–31). Hospitals have an additional duty to protect nonpatients who are the foreseeable victims of hospital negligence. A hospital may in some circumstances be held liable, for example, for injuries sustained by the family members or visitors of infected patients who are foreseeably exposed to infection (30–32,*33*).

However, the issue of a hospital's duty is not always clear, particularly when family members and friends of a patient are involved. Courts sometimes hold, for example, that hospitals do not owe a duty of care to nonpatient family and friends who visit the patient or who provide care for the patient *(34–37)*.

The second part of the first element requires plaintiffs to establish the hospital's required standard of care. For hospitals, the standard of care is measured by what other hospitals would do under like or similar circumstances. Sometimes the standard of care can be determined by examining the relevant statutes or regulations. In *Ford v Saint Francis Hospital, Inc. (38)*, for example, a patient who contracted staphylococcal infection of his aortic valve while hospitalized for heart surgery alleged that the defendant hospital was negligent *per se*, because it was violating federal regulations governing infection control. The hospital was able to defend the action by showing that it had passed a state agency's surprise inspection shortly before the surgery took place.

Plaintiffs and defendants might also rely on the guidelines issued by public health authorities, such as the CDC and the HICPAC, to establish the standard of care. Both sides may also present testimony about the customary practices of other hospitals as a method of establishing the required standard of care (29). The testimony of medical experts generally is used to establish the standard of care against which the hospital's conduct will be measured (28,29). Newly emerging threats, such as the threat of bioterrorism, may complicate the situation because healthcare institutions and physicians must rapidly identify and implement a newly emerging standard of care (39).

The second element of the plaintiff's cause of action requires proof that the defendant breached the standard of care. This is often a difficult task for the plaintiff who may not be able to present evidence showing, for example, that a particular hospital employee failed to use the sterile technique required by the standard of care. Courts sometimes use the legal doctrine of *res ipsa loquitur* (the thing speaks for itself) to assist plaintiffs who cannot identify the specific act of negligence committed by the defendant (28). Under *res ipsa loquitur*, the jury might be permitted to presume the existence of a breach of the standard of care under some circumstances, such as where the patient's infection is rare and difficult to acquire in the absence of negligence (28). Courts have rejected the application of *res ipsa loquitur* and have required plaintiffs to prove a breach of the standard of care in cases alleging injury from some common types of infections because the inference that hospital negligence caused the infection is no longer justified *(40–43)*.

The first two elements of a negligence claim, therefore, require the plaintiff to prove that the defendant hospital breached a duty it owed to the plaintiff to provide a particular standard of care. There have been a number of cases analyzing a hospital's duty to protect its patients or visitors from infection; several examples can be used to illustrate how the first two legal elements apply in the typical hospital setting.

The first example involves the scope of a hospital's duty to exercise care in selecting and assigning staff. In *Taaje v St. Olaf Hospital* (44), the court held a hospital liable for an infant's death from TB based on a nursing supervisor's failure to "exercise due care to see that her nurses were free from communicable disease." Despite this decision, hospitals do not have an absolute continuing duty to screen all employees for all communicable diseases. The hospital's duty to screen—the standard of care governing screening—is established by medical knowledge and community practice at the time the patient received care. In one 1962 case, for example, the court refused to find a hospital liable for the transmission of *Staphylococcus aureus*, in part, because the standard of care did not require employee screening during the relevant time period *(41)*.

The debate about hospital duties to screen and select employees currently is focused on the risks presented by HIV- or HBV-infected healthcare workers. As noted previously, hospitals are required to follow the CDC's 1991 HIV- and HBV-infected healthcare worker guidelines (18,19). These guidelines impose the duty on healthcare workers to know their own HIV and HBV status rather than requiring hospitals to screen healthcare workers (19). Could a hospital avoid liability altogether by implementing even stricter restrictions on the continued practice of HIV- or HBV-infected healthcare workers? The answer is no. Healthcare workers infected with contagious diseases are considered persons with disabilities who are protected by federal and state laws prohibiting discrimination based on disability. Hospitals may only discriminate against an infected healthcare worker when the worker presents a significant risk to the health or safety of others, such as that identified in the CDC guidelines *(45)*. Workers who

[2]Individual healthcare professionals can be held personally liable for their negligent acts; however, the focus of this chapter is on institutional liability for errors in healthcare epidemiology and infection control.

present minute or insignificant risks are protected from discrimination (46).

The second example of litigation about the standard of care involves hospital decisions regarding the acquisition and maintenance of equipment and facilities. In *Bush v Board of Managers of Binghamton City Hospital* (47), the plaintiff claimed that his wife had died from diphtheria acquired in the course of her hospital stay. The court held that the hospital defendant could not be held liable for the woman's death, in part because the evidence indicated that its facilities were "suitable, adequate, and safe for the purposes in the manner used; that the means of sterilization and disinfecting employed were safe and adequate; and that the rooms were surgically clean" (47).

The third type of standard of care litigation involves disputes over the adequacy of hospital policies designed to identify and respond to the presence of infection. In *Helman v Sacred Heart Hospital* (48), the plaintiff claimed that he had acquired a staphylococcal infection from his hospital roommate. The plaintiff presented evidence on the required standard of care, including the existence of "hospital … rules … requiring isolation of all patients known to be infected with staphylococci and requiring all medical personnel to report open sores, boils and pimples, which emitted purulent drainage, among both patients and hospital personnel" (48). The plaintiff also presented evidence that hospital employees had breached this standard of care by failing to "observe the sterile techniques prescribed by the hospital in cases where infection is suspected; they [also] did not wash their hands or leave the room between administering to the patients, even after the plaintiff's roommate experienced a boil with purulent drainage" (48). The plaintiff, thus, presented evidence defining the required standard of care and demonstrated that the defendant had violated this standard of conduct.

In other cases, however, defendants have avoided liability by showing that hospital personnel followed standard practice in caring for a patient *(49)*. In *Roark v St. Paul Fire & Marine Ins. Co*. (31), the plaintiff claimed that he had acquired a staphylococcal infection because of the negligence of the Glenwood Hospital. The defendant was able to avoid liability because:

> *[e]vidence introduced at trial show[ed] [that the] plaintiff was given a shower with antiseptic soap, and that the surgical site was scrubbed with antiseptics prior to surgery. The standard procedures employed by the hospital to establish the sterility of the supplies, instruments, and environment were also detailed. The evidence show[ed] that the procedures employed me[t] or exceed[ed] national standards. (31)*

Similar results have been achieved in transfusion-related HIV transmission cases; most jurisdictions have shielded hospitals from liability so long as the hospital blood banking organization followed the standard of care in effect at the time the transfusion took place (*50*,51,52).

The degree of care required may vary with the type of patient. A hospital has a heightened duty to protect patients who it knows are particularly vulnerable to infection. In *Kapuschinsky v United States (53)*, for example, the hospital was held to a greater duty to exercise care because premature infants were particularly susceptible to infection. Hospitals generally have a heightened duty to protect immunocompromised patients.

The discussion of tort liability thus far has focused on the first two elements of the plaintiff's claim: establishing that the hospital has breached a required standard of care. The third element of a plaintiff's case is causation. The plaintiff must show that the defendant's negligence was the actual and legal cause of the plaintiff's injury (28). The causation requirement is another source of protection for hospital defendants and another source of problems for plaintiffs. Common infections, such as those resulting from staphylococci, present particular difficulties of proof for plaintiffs because there are multiple possible sources of infection *(54)*. Medical tests designed to determine the source of infection are extremely important. In the early 1990s, researchers relied on a genetic analysis of HIV in determining that dentist David Acer was the source of HIV infection for five of his patients *(55)*. Other techniques, such as contact tracing, historically have been used to identify possible sources of other HAIs *(56)*.

Causation can also be difficult to prove because of the lack of evidence linking the hospital's conduct to the plaintiff's injury *(57)*. In *Contreras v St. Luke's Hospital* (58), for example, Solomon Contreras brought suit against St. Luke's Hospital and his surgeon after he sustained a surgical site infection caused by enterococci. The court held that the evidence was insufficient to impose liability, because "there is no evidence that th[e] delay [in removing a bedpan] or understaffing had any connection with the infection. Similarly, there is nothing to indicate that the failure of the nurses to trim the plaintiff's ingrown toenail had anything to do with the infection" (58). Mere negligence and injury are not sufficient; the plaintiff must be able to show that the defendant's wrongful acts actually caused the injury *(59)*.

The fourth and final element of the plaintiff's tort claim is the requirement of a legally recognized injury. Often the plaintiff will seek compensation for the extra expenses associated with a lengthened hospital stay or for the additional pain and suffering accompanying the negligently inflicted infection. Occasionally, the patient dies from the infection, and the patient's estate and beneficiaries will bring survival and wrongful death claims. In *Jistarri v Nappi (60)*, for example, the decedent's estate sued the defendant doctors and hospital, claiming that a series of negligent acts during the decedent's treatment for a broken wrist had allowed staphylococci to enter the decedent's bloodstream, after which it weakened her heart and eventually caused her death.

Courts currently are struggling with whether to permit plaintiffs to recover damages for their fear of acquiring a disease when transmission does not actually occur. The cases largely arise in the context of HIV: Patients who might have been exposed to HIV in the healthcare environment argue that they should be compensated for experiencing fear about the risk of HIV transmission. Courts are divided on whether the fear of disease transmission is a legally compensable injury (61).

A small number of courts have adopted a liberal standard under which plaintiffs are permitted to recover for their fear of transmission so long as it is "reasonable." In *Faya v Almaraz* (62), for example, the plaintiffs learned from news

reports that their oncologic surgeon had HIV infection. They became afraid that the surgeon might have infected them with HIV during surgery. Both plaintiffs underwent HIV-antibody testing; both tested negative. They then sought compensation for their emotional distress from the physician's estate and from the hospital in which the physician had practiced. The Maryland Court of Appeals upheld the plaintiffs' complaint, noting that "we cannot say that [the plaintiffs'] alleged fear of acquired AIDS was initially unreasonable as a matter of law, even though the averments of the complaints did not identify any actual channel of transmission of the AIDS virus" (62). The court did restrict the plaintiffs to receiving compensation "for the period constituting their reasonable window of anxiety—the period between which they learned of Almaraz's illness and received their HIV-negative results" (62).

The New Jersey Supreme Court added a refinement to this approach. In *Williamson v Waldman (63)*, the court held that plaintiffs could recover for fear of HIV transmission even without proof of actual exposure to HIV so long as current medically accurate information about HIV would lead a reasonable person to experience substantial emotional distress about the risk of HIV transmission in a similar situation.

These cases represent the minority view. Most courts have placed serious restrictions on acquired immunodeficiency syndrome (AIDS) phobia claims. There are three major types of requirements: plaintiffs must show "actual exposure" to HIV-infected body fluids *(64,*65,*66–67)*, they must show that the alleged exposure followed a medically recognized channel of transmission *(68)*, and/or they must show a high probability that HIV transmission could have occurred (69).

The Minnesota Supreme Court's decision in *KAC v Benson* (65) illustrates the "actual exposure" principle. In this case, a plaintiff argued that she had suffered severe emotional injuries after learning that Dr. Benson had performed gynecologic procedures on her while he was infected with HIV. The plaintiff repeatedly tested negative for HIV antibodies. The court rejected the plaintiff's claims for damages associated with her fear of acquiring HIV, in part because she could not prove that the actual exposure to HIV had occurred during the medical procedures (65). Similarly, the Tennessee Supreme Court rejected a claim brought by a patient in an alcohol and drug treatment center who was not informed that his roommate had HIV infection. The plaintiff argued that he had used the room's toilet while suffering from an open sore and that he had shared his roommate's disposable razor. The court held that this did not constitute evidence of an actual exposure *(67)*.

Courts may also require the plaintiff to show a medically accepted "channel" for transmission of the virus. The Supreme Court of New Mexico applied this restriction in a suit brought by a woman whose hands with unhealed cuts were exposed to medical samples containing blood *(68)*. In this case, the court permitted the plaintiff's claims to go forward because she alleged a medically appropriate channel of potential transmission.

Finally, some courts require plaintiffs seeking compensation for the fear of a disease to prove that transmission of the disease is highly probable. In *Kerins v Hartley* (69), a patient of an HIV-infected surgeon sued for damages based on her fear that she had acquired HIV during surgery. The court rejected the claim, holding that the plaintiff was required to show that it was "more likely than not" that she would become HIV positive as a result of the surgery. This standard is clearly very difficult for plaintiffs to meet in HIV-exposure cases because the risk of transmission is usually very small. Some courts have held that "actual exposure" need not be proved where the plaintiff was exposed to a scientifically accepted means of transmission of HIV and the defendant unreasonably or intentionally interfered with information regarding the injured party's ability to prove the actual presence of HIV (70,*71,74*).

Some courts have explored whether and how to limit the time period for which the fear of HIV transmission will be compensable (*64*,70). Courts in several cases have held that the plaintiff's fear of developing AIDS was reasonable for 6 months after actual exposure, but became unreasonable after 6 months with repeated negative test results *(64)*. These decisions were rejected by a 2008 New York Court of Appeals decision, which held that a plaintiff should have been permitted to present evidence regarding emotional distress even after the 6-month HIV-testing period (70). The court held that judges and juries were capable of resolving these claims:

> *It also bears noting that defendants remain free to challenge AIDS phobia and other emotional distress evidence by presenting medical and scientific proof concerning the probability of a plaintiff contracting HIV after having tested negative at various points in time to ensure that the jury understands the risk a plaintiff actually faced and the future risk of a plaintiff testing positive. Likewise, defendants may question a plaintiff and any treating physicians to ascertain what information was available to the plaintiff concerning testing time frames and probabilities. A rational jury might conclude, based on evidence of this nature, that a particular plaintiff[']s fear of contracting HIV ceased to be reasonable at a certain point in time and, after that point, any residual anxiety was not sufficiently causally related to the underlying exposure incident to warrant recovery. Similarly, since a plaintiff "is not permitted to recover for damages that could have been avoided by using means which a reasonably prudent person would have used to … alleviate the pain" … a defendant who believes that a plaintiff has unreasonably failed to take steps to relieve emotional distress arising from an exposure incident can raise a failure to mitigate damages defense. (70)*

These cases involve plaintiffs who were tested using older HIV-antibody tests; courts will continue to grapple with whether and how to limit liability given the availability of quicker and more accurate, direct tests for HIV.

Most jurisdictions thus have severely restricted HIV/AIDS phobia claims. Hospitals and healthcare professionals should recognize, however, that the law remains in flux and that plaintiffs claiming HIV/AIDS phobia may be able to recover significant damage awards in some jurisdictions.

As noted previously, a hospital's tort liability for patient or visitor injuries rests on the plaintiff's ability to prove that a hospital had a duty to observe a particular standard of care, that the hospital breached that standard, and

that the breach caused the plaintiff's injuries. Injured plaintiffs have sought very significant damage claims in these cases. For example, the plaintiff in *Riggs v West Virginia University Hospitals* sought damages after allegedly becoming infected with serratia bacteria during anterior cruciate ligament (ACL) surgery *(72)*. The plaintiff endured complications and was required to undergo several subsequent operations before her infection was diagnosed. The jury awarded the plaintiff $10 million in noneconomic damages. The award was reduced to $1 million when the Supreme Court of West Virginia confirmed that the state's medical malpractice cap applied to the damages *(72)*.

Hospitals may offer some defenses to tort liability claims. For example, the hospital's liability might be reduced if the patient's own negligent conduct contributed to the injury (28). A patient may have failed to follow postoperative instructions, for example. However, it often will be difficult for hospitals to prove that a patient's own negligence contributed to her or his injury.

Healthcare workers and hospital administrators concerned with liability issues should understand these general tort rules. The best method for reducing the risk of liability is to reduce the risk of injury to patients and visitors. Hospitals should review their policies to ensure that they meet national standards of healthcare epidemiology and infection control as reflected in statutes, regulations, public health standards, national accreditation standards, and the practices of other hospitals. The special risks of infection for immunosuppressed persons should be considered. The development of appropriate policies is not sufficient, however. Hospitals must ensure that the policies are followed in practice and that appropriate records are maintained. A hospital's ability to prove that it met the standard of care and to present an appropriate defense ultimately will depend on whether appropriate documentation can be produced at trial.

THE DUTY TO PROTECT HEALTHCARE WORKERS

Hospitals also have a duty to protect their workers from harm. This duty is created under federal and state laws. Breach of the duty can lead to licensure suspension, civil penalties, and civil liability. The regulations designed to protect healthcare workers can be divided into roughly two types: those imposed to prevent injury and those designed to provide compensation to healthcare workers who are injured in the course of their employment.

Regulations Designed to Protect Healthcare Workers

The federal government regulates the safety of workplaces under the Occupational Safety and Health Act, which is enforced by the Occupational Safety and Health Administration (OSHA) (see also Chapters 74 and 79). All private hospitals are subject to OSHA regulation, and all federal hospitals are subject to equivalent standards *(73)*. State and local government hospitals are exempt from OSHA regulations, although many states have laws or regulations imposing safety and health standards similar to those imposed by OSHA *(74,75)*.

Under OSHA, an employer must provide a workplace that is "free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees" (76). In addition, employers must comply with all OSHA standards and regulations *(77)*. Therefore, hospitals must comply with specific standards issued to protect healthcare workers. Employees are also required to comply with OSHA regulations, but the statute does not impose penalties or other sanctions on noncompliant employees, only on noncompliant employers *(78)*.

OSHA has issued an extremely important regulation designed to reduce the risk of transmission of blood-borne pathogens in healthcare settings (79). Hospitals must comply with the blood-borne pathogen standard along with other standards governing the use of personal protective equipment *(80)*, the use of biohazard warning signs *(81)*, the proper implementation of sanitation and waste disposal *(82)*, and housekeeping *(83)*. OSHA was forced to withdraw a proposed rule designed to limit occupational exposure to TB *(84)*. The blood-borne pathogen standard explicitly requires that hospitals implement a variety of programs designed to reduce the risk of infection for employees. This standard can be divided into three major parts.

First, the regulation requires hospitals to analyze all employment positions to determine which employees have "reasonably anticipated" exposures to blood or other potentially infectious materials and to design an exposure control plan that specifies how employee exposures are to be eliminated or minimized *(85)*. Employees must be provided with adequate training to implement and update the exposure control plan *(86)*.

Second, the blood-borne pathogen standard directly requires the implementation of specified mechanisms to reduce the risk of infection for workers. Hospitals must implement Standard Precautions (formerly Universal Precautions) *(87)*. They must provide free and ready access to hand washing facilities and personal protective equipment such as gowns, masks, and gloves *(87)*. The standard specifies certain work practices that are forbidden, such as the recapping of used needles or the improper disposal of potentially infectious materials *(87)*. Employers must provide free and voluntary HBV vaccination to certain employees (see also Chapters 73, 74, and 79). All employees are to be offered voluntary and confidential postexposure incident evaluation and follow-up care *(88)*. After an exposure incident, the blood of the potential source of infection may be tested only if the source consents or if the consent is not required under state law *(88)*.

Third, hospitals are required to observe certain monitoring and record-keeping requirements *(89)*. Employers must keep records for each employee with an exposure incident for the duration of employment plus 30 years. The records are to be confidential and released to others only with the employee's consent *(89)*. The OSHA rules are consistent with the CDC's recommendations governing the management of occupational exposures to HBV, hepatitis C virus, and HIV (90).

OSHA can impose hefty penalties for violations *(91)*. Nonserious and serious violations can draw up to $7,000 in civil fines per incident; willful violations have a minimum penalty of $5,000 and can reach $70,000. A willful disregard of an OSHA standard that results in a death can be prosecuted criminally with convictions resulting in

imprisonment or fines. Hospitals seeking to limit OSHA liability should establish programs to comply with all OSHA requirements and, as importantly, should monitor employee compliance.

Injured Healthcare Workers and the Tort and Workers' Compensation Systems

Injured healthcare workers can bring claims under either workers' compensation or tort law. Most persons injured in the course of their employment are forced to seek compensation under the workers' compensation scheme established in each state or, for some types of employment, under the compensation system established under federal law *(92)*. The workers' compensation laws generally provide relatively quick access to preset levels of reimbursement for medical expenses and lost wages. Persons who are not covered by the workers' compensation scheme can pursue ordinary tort claims. The tort system generally provides higher levels of compensation to injured persons, but it is more difficult for injured workers to successfully pursue their claims because of the larger number of defenses available to defendants (93).

Generally, workers' compensation laws create a "no-fault" system in which injured workers do not have to prove that their employers were negligent to receive compensation and in which an employee's own negligence is not likely to bar recovery *(94)*. The workers' compensation rules also cover occupational diseases *(94)*. Employees usually have the most difficulty proving that the disease is "occupational." Coverage under the workers' compensation system is contingent on proving that the disease was acquired during the course of employment because of the particular risks created by that employment.

In many jurisdictions, it is not enough for an employee to show that she or he was exposed to an illness on the job; she or he must show that the employment creates some special risk of acquiring this illness. In *Paider v Park East Movers (95)*, for example, a truck driver sought workers' compensation benefits after acquiring TB from a coworker. The driver argued that he was exposed to TB, because his employment required that he be confined in the cab of the truck with his coworker. The New York Court of Appeals rejected this contention, holding that the claimant's disease resulted not from the ordinary and generally recognized hazards incident to a particular employment but rather from the general risks common to every individual regardless of the employment in which he is engaged. The claimant's illness, therefore, was not an occupational disease *(95)*. Fortunately for injured healthcare workers, certain types of illness, such as TB or hepatitis, are often covered under the workers' compensation laws as ordinary and generally recognized hazards of employment in hospitals *(95,96)*.

However, even where a particular illness is recognized as an occupational hazard, healthcare workers often must present proof that they actually acquired their illness on the job *(97)*. There is some disagreement about the nature of proof required. Sometimes courts have upheld workers' compensation awards based on evidence that the disease was an occupational hazard and that it was unlikely to be acquired in the employee's nonwork environment *(94,98)*. Other courts seem to require additional evidence of workplace exposure, such as evidence that the healthcare worker came into contact with a particular patient suffering from the disease or condition *(97,99)*.

The tort system provides compensation to injured healthcare workers who are not covered by state or federal workers' compensation schemes. Nonemployee physicians, for example, might be able to bring their claims under tort law rules (100). These healthcare workers must prove the four basic elements of a tort claim discussed previously (28). The worker must prove that the hospital had a duty to observe a particular standard of care, that the hospital breached its duty, that the breach caused harm, and that the harm was of a type recognized as deserving compensation (28). Hospitals can defend these claims by arguing that one or more of these four elements are absent; they can also reduce their liability by arguing that the injury was caused by the healthcare worker's own negligence.

It is clear that hospitals have a duty to protect their employees from foreseeable injuries such as occupationally acquired infectious diseases (28). The scope of this duty can be defined in the same way as the scope of the hospital's duty to its patients. The applicable standard of care can be derived from licensure codes, occupational safety and health regulations, accreditation standards, and the general practices of other hospitals (28,29).

The employee must prove that the defendant hospital breached the standard of care. In *John Doe v Kaiser* (100,*101*), for example, a surgeon sued the hospital in which he practiced, claiming that it "did not enforce Universal Precautions or provide its medical staff with materials or training on those precautions." In *Prego v City of New York* (102), an unpaid extern working at Kings County Hospital brought suit against the hospital, contending that it had breached its duty by providing "inadequate disposal facilities for contaminated needles."

The employee must prove that the defendant's breach of the standard of care actually caused the employee's injury. This may present problems for healthcare workers who cannot identify specific sources of infection. Thus, the surgeon in the *John Doe v Kaiser* case contended that the hospital's conduct caused his HIV infection. The hospital argued in response that there was no proof connecting the surgeon's HIV infection to his work at the hospital; it noted that "[d]uring the seven months that the surgeon worked at Kaiser before testing HIV positive, he did not report being exposed to body fluids or encountering lapses in Kaiser's Universal Precautions policies" *(101)*. In contrast, Veronica Prego had documented evidence of two different exposures to blood from HIV-infected patients (102). Healthcare workers should be attentive to the need to document potential exposures.

Healthcare workers must also meet the legal injury requirement. A healthcare worker who acquires TB, hepatitis, or HIV infection easily meets this requirement. This leaves claims by workers based on the fear of transmission alone. Court rulings here follow the general trends noted above. Some jurisdictions have adopted a liberal approach that permits disease phobia claims based on reasonable fears. Most jurisdictions have imposed some additional requirements, such as proof of actual exposure (62,*63–64,* 65,*66–68,*69,70,*71,72,103*).

Hospital defendants in tort suits brought by healthcare workers who are not covered by the workers' compensation system may reduce their liability by arguing that the

employee was contributorily negligent (28). The hospital must show that the employee's negligent conduct contributed to her or his injury. This claim is likely to be asserted whenever the healthcare worker has failed to observe a workplace policy. Healthcare workers who acquire hepatitis or HIV infection after failing to use universal precautions or attempting to recap a needle would be particularly vulnerable to this type of hospital defense. However, courts might excuse an employee's deviation from required practices, particularly where the employee is injured while responding to an emergency situation *(104)*.

Hospitals seeking to reduce liability to healthcare workers, either under the workers' compensation or tort systems, should implement healthcare epidemiology and infection control programs that meet all federal, state, and community standards. This should reduce the number of claims made under the workers' compensation system because it will reduce the total number of injuries. Appropriate implementation will additionally limit tort liability because the hospital will be able to demonstrate compliance with the required standard of care. Hospitals should devote resources to updating policies, as necessary, and to documenting the implementation of all policies.

CONFLICTS BETWEEN THE DUTY TO MAINTAIN CONFIDENTIALITY AND THE DUTY TO PREVENT INJURY

This discussion of the legal rules governing healthcare epidemiology and infection control has revealed a complex regulatory framework that places many demands on healthcare institutions. These legal obligations can come into apparent conflict. The most difficult problems are raised by the hospital's ability, or even its legal duty, to prevent injury by warning third parties of the risk of infection. Conflicts between confidentiality and risk reduction can arise in the relationship between the hospital and its patients or in the relationship between the hospital and its employees.

Historically, the duty to preserve the confidentiality of medical information was derived from constitutional law (for public entities) *(105)*, common law *(106)*, or statute *(107)*. These traditional confidentiality rules were applied to hospitals and to individual healthcare providers such as physicians. Many states also enacted specific statutes protecting the confidentiality of certain types of information, such as HIV status *(17*,108,*109,110*). Although still important, these traditional approaches have been eclipsed by the federal government's Health Insurance Portability and Accountability Act (HIPAA) privacy rule (111). The HIPAA privacy rule restricts "covered entities" (including hospitals) from using or disclosing "protected health information" except as permitted by the regulation *(112,113)*. By way of example, the statute provides that a physician may only disclose confidential information without written consent under limited conditions such that even filing a lawsuit does not necessarily waive the confidentiality of health information *(114)*. The federal rules create a "floor" for protection—weaker state confidentiality protections will be preempted, but stronger state confidentiality rules can still be enforced. This "floor" for protection, however, has been suggested to be inadequate, causing some to advocate for additional reforms *(115)*.

Despite its wide and deep legal underpinnings, the duty to maintain confidentiality is not absolute. What happens when this right to confidentiality is pitted against the hospital's duty to protect others from the risk of infection? There are two different paradigmatic examples of this conflict: In the first, the hospital is concerned with a patient's infectious condition; in the second, the hospital must respond to the medical condition of an employee.

In the first case, the hospital may wish to disclose the patient's contagious condition to employees or other third parties whom it knows might be put at risk of infection. Both federal and state rules permit the disclosure of otherwise confidential medical information to third parties where the goal is to prevent the transmission of disease. Under the HIPAA privacy rule, for example, a covered entity may disclose individual healthcare information "to carry out treatment, payment, or … operations" without securing patient consent *(116)*. Texas law provides an example of a common state law approach to the protection of healthcare providers. The statute permits physicians to disclose otherwise confidential medical information to "another physician or other personnel acting under the direction of the physician who participate in the diagnosis, evaluation, or treatment of the patient" (117). A hospital is also authorized to provide information to third parties. Under HIPAA, "[a] covered entity may disclose protected health information for the public health … to … a person who may have been exposed to a communicable disease or may otherwise be at risk of contracting or spreading a disease or condition, if the covered entity … is authorized by law to notify such person …" (118). Many states have similar rules derived from statutes or court decisions *(105–107)*.

There is a distinction between permitting and requiring disclosures. The fact that a hospital or healthcare provider is permitted to disclose healthcare information to protect third parties does not mean that it will be held liable for failing to make the disclosure. Courts have expressed concern about whether healthcare providers should owe a duty of care for nonpatients *(34–37,119)*. Even if there is a duty, it is not clear that the standard of care would require providers to breach confidentiality by disclosing information to a third party. The healthcare provider's duty may be discharged by counseling the patient about how to avoid transmission of the condition to others *(120)*.

Despite these caveats, healthcare workers infected by patients occasionally bring suit against hospitals for failing to disclose a patient's contagious condition *(121)*. Healthcare facilities tempted to permit disclosures of patient status to healthcare workers should monitor the process to restrict unwarranted disclosures of information *(122)* and to ensure that healthcare workers do not unlawfully discriminate against a patient based on that patient's disabling illnesses *(123,124)*.

Similar arguments apply to claims brought by nonpatients and nonemployees against healthcare providers for an allegedly negligent failure to disclose confidential information about a patient's contagious condition. In *Lemon v Stewart (125)*, for example, an HIV-infected patient's extended family sued a hospital for failing to disclose the patient's HIV status. The court rejected the claim, noting that there was no duty to disclose, despite the fact that the plaintiffs alleged that they had been exposed to the patient's

urine, feces, saliva, blood, and serum. Although there is no general rule resolving the conflict between the patient's right to confidentiality and the hospital's duty to protect others, the most straightforward solution is to secure the patient's consent to any proposed disclosure.

The second paradigmatic situation involves conflicts between the hospital's duty to protect patients and its obligations to protect the confidentiality of its employees and to refrain from discriminating against employees who have disabling illnesses. HIPAA excludes records held by the hospital in its role as an employer from the scope of "protected health information" *(112)*. Employees nonetheless have a right to confidentiality and a right to nondiscriminatory treatment that is protected by a variety of laws, including the OSHA blood-borne pathogen rule (79) and the Americans with Disabilities Act *(126)*.

Despite these protections, two courts have held that the need to protect patients can outweigh the healthcare worker's rights. In one case, the court upheld a trial court order authorizing the release of certain information about an HIV-positive surgeon to his colleagues and patients *(127)*. The court found that the hospital had demonstrated a compelling need for the disclosure because of the need to warn patients of the risk of HIV exposure *(127)*. Similarly, in *Estate of Behringer v The Medical Center at Princeton (122)*, the court upheld a hospital policy that required an HIV-infected surgeon to disclose his status to his patients before performing surgery. These cases may represent judicial and medical overreaction to the risks of HIV transmission by healthcare workers *(21)*, but they nonetheless indicate a trend toward diminished confidentiality protections for healthcare workers.

LEGAL ASPECTS OF EMERGING INFECTIOUS DISEASES AND THE RISK OF BIOTERRORISM

The recent emergence of health threats, such as SARS, West Nile virus, and H1N1, has created additional stresses for epidemiology and infection control. These diseases have spread across national borders and created diagnostic and treatment challenges. At the same time, the public and private healthcare systems are focusing on the need to prepare for possible bioterrorism events, such as the release of highly contagious and destructive agents, as well as novel infectious diseases and weather or climatic events that will strain the provision of healthcare *(128)*. These events have created three different sorts of legal issues.

First, it may be difficult for healthcare providers and patients to determine *ex ante* the standard of care for identifying and treating these newly dispersed diseases. The standard of care develops quite rapidly and may or may not be captured well by periodic updates in online journals, traditional medical journals, and the reports and guidelines issued by advisory groups and public health authorities. As one example that could give rise to legal claims, providers did not initially realize that the West Nile virus could be transmitted by blood transfusion *(128,129)*.

The second set of issues involves a reexamination of the relationship between public health law and public health policy. Recent pandemics and fears about bioterrorism have combined to make private and public health entities more conscious of the need to understand when and how individual liberties can be constrained to protect the public health. Would a renewed SARS epidemic or the threat of smallpox justify the imposition of mandatory medical examinations, vaccinations, treatment, or isolation and quarantine? Would private healthcare entities be required to seek a court order in these cases or would public health authorities intervene? Can public health authorities require healthcare providers to collect and to report on a wide range of health data to facilitate efforts to identify a public health threat? How will public and private entities interact in a public health emergency? Many public and private organizations are working on responses to these important questions *(130,131)*. A detailed review of the state of the law is beyond the scope of this chapter. In general terms, public health authorities are likely to be given whatever power is needed to address a serious health crisis, including the power to impose serious restrictions on individual liberty.

The third area of legal concern relates to the need to build an infrastructure of public and private healthcare facilities, which will be prepared to provide services in public health emergencies. The difficulties can be demonstrated with the small but significant example of the failure of a plan to use smallpox vaccinations to create a nationwide team of healthcare workers who would be able to provide immediate support in the event of an outbreak *(132)*. Legal concerns about compensation for vaccine-related injuries appeared to be at least one factor in the slow implementation of the project, although criticism of the risk-to-benefit calculations underlying the program undoubtedly played a larger role *(133)*.

CONCLUSIONS

No one can be sure what threats to public health will emerge in the coming years. The legal rules governing healthcare epidemiology and infection control policies are complicated and sometimes conflicting. Hospitals have a duty to protect patients and third parties from the risk of infection. A hospital's failure to meet this obligation can result in sanctions under licensing statutes and in civil liability. Hospitals also have a duty to protect their employees from the risks of infection. Breaches of this duty can also result in administrative sanctions and in civil liability. Hospitals seeking to meet their obligation to prevent transmission of disease also must be conscious of the need to safeguard confidentiality and to prevent discrimination against persons with disabling illnesses. Hospitals must also focus attention on documenting compliance with all relevant legal standards. Finally, the emergence of new public health threats has created new areas of legal concern for professionals engaged in epidemiology and infection control.

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SECTION XVI

Healthcare Epidemiology and Infection Control in Special Settings for Healthcare Delivery

CHAPTER 98

Epidemiology and Prevention of Infections in Residents of Long-Term Care Facilities

Jennie Johnstone and Mark Loeb

Infectious diseases pose an important threat to the health of residents of long-term care facilities (LTCFs) (1) who are at increased risk of infection due to advanced age and multiple comorbidities. Environmental factors such as close living conditions facilitate outbreaks of infection by increasing the likelihood of exposure among the often frail residents of LTCFs. Given demographic trends in aging, it is anticipated that this burden of infection will continue to increase. Infection prevention and control programs therefore play a paramount role in preserving the health and quality of life of residents of LTCFs. In this chapter, we outline the most common infections that place residents of LTCFs at risk and discuss both the reasons why the burden of disease is so high in this population and strategies that can be implemented for prevention. The role and structure of an LTCF infection control program are outlined, and the current scientific evidence for prevention of infectious disease in LTCFs is reviewed.

DEFINITION

Although LTCFs are often thought to be synonymous with nursing homes, the term in fact encompasses a heterogeneous group of institutions including nursing homes, psychiatric facilities, stroke rehabilitation facilities, facilities for the developmentally challenged, and group homes. The risk of infection in these facilities varies greatly but is highest in skilled nursing homes. Nursing homes, which may be freestanding or affiliated with acute care hospitals, are inpatient facilities for persons who require nursing care and related medical or psychosocial services. This chapter focuses primarily on infections that occur in the nursing home setting, because they account for the majority of LTCFs. The vast majority of LTCF studies about infection and its prevention are set in nursing homes. Wherever possible, this chapter includes observations and data from other types of LTCFs, but the description of infections in these other settings is unfortunately sparse.

As a prime example, an important recent infection control challenge comes from long-term acute care hospitals (LTACHs) *(2)*. These facilities combine the acuity of acute care with long-term placement. Patients often have severe respiratory and other medical problems that include need for chronic ventilation and reside in these facilities for a prolonged period of time *(2)*. Residents of LTACHs typically have had long lengths of stays at their acute care hospitals including stays in intensive care; hence, the burden of infection with antimicrobial-resistant microorganisms is high. Surveillance data from these facilities are relatively limited; however, one surveillance study performed in the Unites States found that 64% of patients were colonized or infected with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), or both *(3)*. Clearly, further defining the burden of infectious disease in LTACHs and its prevention requires further study and is an important area of future research *(2)*.

DEMOGRAPHICS

Demographic trends in the United States and Canada suggest that older adults are the fastest growing sector. In fact, it is estimated that in 2030, 30% of the population will be 65 years and older *(4)*. As a consequence, rates of admission to LTCFs are increasing. It has been estimated that the lifetime risk of a 65-year-old entering a nursing home is approximately 50% *(5)*. In terms of infection control, these figures raise challenges with respect to the burden of illness in this population.

INCIDENCE AND PREVALENCE OF INFECTION IN LONG-TERM CARE

The overall incidence of infection in various types of Canadian and US LTCFs is estimated to range from 1.8 to 9.4 infections per 1,000 resident care days. One well-designed inception cohort study estimated the incidence of infection to be 7.2 per 1,000 resident care days (6). This rate did not include cases of asymptomatic bacteriuria and used standardized definitions and involved intensive surveillance by a nurse practitioner who visited all residents 2 to 4 times per month. One limitation of the study is the fact that it was conducted prior to the development of LTCF surveillance definitions. Other study designs were limited by not including patients with upper respiratory tract infections or bronchitis, thereby underestimating the true frequency of infection *(7)*. Studies using the Centers for Disease Control and Prevention (CDC) definitions for healthcare-associated infection may have underestimated their rates, because some LTCFs lack routine access to laboratory and radiologic investigations.

A number of 1-day prevalence studies have been conducted in LTCFs in an attempt to capture the burden of illness due to infection in this population. Most have focused on nursing homes or other specific units for the elderly. The prevalence of infection on the day of study in all surveys ranged from 2.4% to 18.4%. This broad range likely reflects differing definition of infection *(8–13)*. For example, some studies counted asymptomatic bacteriuria, whereas others used CDC definitions of healthcare-associated infection that may have underestimated the prevalence of infection *(9,12,13)*.

WHY THE BURDEN OF INFECTION IN LTCFs IS HIGH

The reason for the high burden of infectious disease in LTCFs is multifactorial. Residents of LTCFs have multiple comorbidities and functional impairments and can be malnourished, all of which contribute to risk of infection. Furthermore, most residents of LTCFs are elderly and are at increased risk of infection due to immunosenescence, the waning of protective immunity with age. Outbreaks of infection in LTCFs are facilitated by environmental factors. Last, recognition of an outbreak may be missed due to unique challenges in diagnosis of infection in this population.

Comorbidities

Many residents of LTCFs have comorbidities. The most commonly reported diagnoses are circulatory system disease (26%), mental disorders including Alzheimer's disease (26%), and diseases of the respiratory system (11%) *(14)*. Diabetes mellitus is also common, affecting 20% to 30% of nursing home residents, and is known to affect immune dysfunction *(15)*. Underlying comorbidities predispose nursing home residents to infection including lower respiratory tract illness, skin and soft-tissue infection, and urinary tract infections through a variety of mechanisms.

At any point in time, nursing home residents are on an average of six to eight different medications *(16)*. Frequently prescribed drugs include sedatives, neuroleptics, and narcotic analgesics, which may depress the level of consciousness and increase the risk for lower respiratory tract infections *(17)*. Medication such as tricyclic antidepressants can precipitate urinary retention predisposing residents to subsequent urinary tract infections. Other commonly used medications in the long-term care setting include H_2 blockers and proton pump inhibitor therapy, which may increase the risk of lower respiratory tract infection *(18,19)*; corticosteroids, which reduce immune function; and antibiotics, which encourage colonization with resistant microorganisms.

Invasive medical devices such as urinary catheters, feeding tubes, tracheostomies, and intravenous catheters further increase risk of infection by breeching the already compromised host defenses of nursing home residents. Urinary catheters are particularly common and are used in 5% to 10% of nursing home residents (20).

Functional Impairment

Functional impairments such as immobility, incontinence, and dysphagia have been reported to increase the risk of infections (*21*,22). In one study, 95% of nursing home residents needed assistance with at least one self-care activity, and three quarters were dependent in three to five such activities *(14)*. Approximately 60% of all nursing home residents use a walker and almost half are incontinent of urine *(14)*. Decreased mobility and incontinence predispose residents to respiratory tract infections, skin and soft-tissue infections, and urinary tract infections.

Malnutrition

Protein calorie malnutrition is common in nursing home residents affecting between 52% and 85% of residents in one study *(23)*. Malnutrition is associated with impaired immune function manifested by a decrease in cell-mediated immunity. The consequences of malnutrition such as delayed wound healing, decreased level of consciousness, and decline in functional status all increase the risk of infection.

Effect of Aging on Immunity

There are a number of changes that occur to the immune system with age and are collectively called immunosenescence *(24)*. Although all components of the immune system appear affected by aging, changes in T-cell parameters are by far the most pronounced *(25)*. Changes include a reduction in the number of naive T cells and a corresponding

increase in memory T-cell subsets. Notably, aging is associated with accumulation of terminally differentiated memory T cells *(26)*. The lack of naive T cells is thought to impair the ability of the host to respond against novel pathogens *(24,27)*. The terminally differentiated memory T cells are considered to have poor functionality, resulting in impaired responses to recall antigens and is the mechanism thought to be responsible for increased risk of infection and poor response to vaccines seen in the elderly *(24)*.

Environmental Reasons

In addition to the risk factors for infection described above, residents of LTCFs are at increased risk of infection simply by living in an LTCF (28). Outbreaks of infectious diseases are extremely common due to environmental factors including sharing sources of air, water, the close proximity of residents to other residents, and shared medical care and caregivers (28).

Diagnosis of Infectious Disease in LTCFs

The diagnosis of infectious diseases in LTCFs can be a challenge as the classic presenting signs and symptoms of infection are often blunted, altered, or absent in elderly nursing home residents. Reasons for this include cognitive impairment or reluctance to complain *(29,30)*. In addition, comorbid conditions can mask the symptoms of infection or make them difficult to interpret. Declines in functional status in the frail elderly may be the chief herald of serious infection *(31)*. Thus, urinary tract infections may present with confusion rather than dysuria and pneumonia with a fall not a cough *(32)*. Compared with younger patients, older persons with bacteremia are less likely to develop chills, diaphoresis, altered mental state, physical complaints, or lymphopenia *(33)*. The signs of infection are often subtle and appreciated only by staff members who know the resident well.

In general, the principals and criteria used for the diagnosis of infection in LTCF residents are comparable to those used for healthcare-associated infections. It should be noted, however, that LTCFs often lack ready access to laboratory and radiologic services, and physicians may not be present to diagnose infections as they occur. McGeer et al. (34) offered a comprehensive set of definitions for surveillance in LTCFs that account for the unique circumstances of these institutions (Table 98-1).

LONG-TERM CARE AND INFECTION CONTROL: CURRENT CHALLENGES

The main infection control challenges in LTCFs include managing antimicrobial resistance (e.g., MRSA, VRE, and *Enterobacteriaceae*-producing extended spectrum beta-lactamases [ESBLs] among others); reducing the burden of endemic infections such as respiratory, urinary, skin, and soft-tissue infections; providing surveillance and early recognition of outbreaks; and recognizing emerging infectious diseases.

Antimicrobial Resistance

Nursing homes play an important role in the problem of antimicrobial resistance. The most common and worrisome resistant pathogens in LTCFs are MRSA, VRE, and ESBLs (*35–37*,38,*39–54*). Also concerning but less common antibiotic-resistant pathogens include aminoglycoside-resistant gram-negative bacilli (38,*47*), high-level aminoglycoside-resistant enterococci (38,*53*), multidrug-resistant pneumococci *(46,55,56)*, and fluoroquinolone-resistant gram-negative bacilli *(46,51,57)*.

The frequency of antimicrobial-resistant pathogens in LTCFs varies by location, stressing the importance of knowledge of local resistance patterns (*10,35,*38,*44,52–54*). For example, Scheckler and Peterson *(10)* found antimicrobial resistance to be rare in their survey of eight small rural nursing homes in Wisconsin. Likewise, Mylotte et al. *(54)* found antimicrobial-resistant pathogens uncommonly (in <20% of admissions) in residents of community nursing homes admitted to an inpatient geriatric service in Buffalo. In contrast, a number of large urban facilities have reported high frequencies of resistant pathogens. Trick et al. *(44)* found at least one antimicrobial-resistant bacterial isolate in 43% of 117 LTCF residents screened in one urban facility in Illinois. Of the 50 culture-positive residents, 24% harbored MRSA, 18% ESBL-producing *Klebsiella pneumoniae*, 15% ESBL-producing *Escherichia coli*, and 3.5% VRE.

Eradication of antibiotic resistance in LTCFs is particularly challenging due to high frequencies of antibiotic use and difficulties in eradication due to serious underlying disease, poor functional status, open wounds such as decubiti, presence of invasive devices, and prior antimicrobial therapy (*35,36,*38,*43,44,52,53*). As a result, residents of LTCFs can remain colonized for months to years. Resistant microorganisms can also be reintroduced from hospitals following a transfer for management of acute illnesses (*35,*38,*49,50*).

Endemic Infections

Common endemic infections in LTCFs include lower respiratory tract infections, symptomatic urinary tract infections, and skin and soft-tissue infections *(58)*.

Lower Respiratory Tract Infections Pneumonia in nursing home residents (nursing home–associated pneumonia [NHAP]) is associated with significant morbidity and mortality in this population *(59–61)*. NHAP occurs approximately once per 1,000 resident days of care, which is 10 times more frequent than in community dwelling elderly *(62,63)*. Residents are at increased risk of pneumonia due to decreased ability to clear the airways, altered oropharyngeal flora, poor functional status, and swallowing difficulties leading to aspiration (1). Although there are over 100 etiologies that can cause NHAP, *Streptococcus pneumoniae* is the most common *(64)*. Influenza is also an important cause of lower respiratory tract infection in residents of LTCFs and is discussed in the "Outbreak" section.

NHAP is the most frequent cause of death among nursing home residents *(65)* and has an estimated 30-day case–fatality rate of 10% to 50% *(59,62)*. The costs associated with NHAP are substantial (66) as one third of the patients who develop NHAP require transfer to hospital for management *(67)*. Hospitalization may be associated with a reduced quality of life and a decline in functional status *(68)*. A cluster randomized controlled trial evaluated a clinical pathway for the management of nursing home

TABLE 98-1

Definitions of Infection for Surveillance in Long-Term Care Facilities

I. Skin and soft-tissue infections
- A. Cellulitis/soft-tissue/wound infection—pus at a wound, skin, or soft-tissue site or four of the following: (a) fever (>38.0°C) or worsening mental/functional status and/or at the affected site, the presence of new or increasing (b) heat, (c) redness, (d) swelling, (e) tenderness or pain, (f) serous drainage
- B. Fungal skin infection—both a maculopapular rash and either physician diagnosis or laboratory confirmation
- C. Herpes simplex and herpes zoster infection—both vesicular rash and either physician diagnosis or laboratory confirmation
- D. Scabies—both a maculopapular and/or itching rash and either physician diagnosis or laboratory confirmation
- E. Conjunctivitis—pus appearing from one or both eyes for at least 24 h or new or increased conjunctival redness, with or without itching or pain, for at least 24 h

II. Respiratory tract infections
- A. Common cold syndromes/pharyngitis—two of the following new signs or symptoms: runny nose or sneezing; stuffy nose (congestion); sore throat, hoarseness, or difficulty swallowing; dry cough, swollen or tender glands in the neck
- B. Influenza-like illness—fever (>38.0°C) and three of the following during influenza season: chills, new headache or eye pain, myalgias, malaise or loss of appetite, sore throat, or new or increased dry cough
- C. Bronchitis or tracheobronchitis—a negative chest radiograph (or no chest radiograph was taken) and three of the following: new or increased cough; new or increased sputum production; fever (>38.0°C); pleuritic chest pain; new or increased findings on exam (rales, rhonchi, wheezes, bronchial breathing); and new or increased shortness of breath, respiratory rate >25 per min, worsening mental status, or worsening functional status
- D. Pneumonia—two of the signs listed under bronchitis or tracheobronchitis and a chest radiograph demonstrating pneumonia, probable pneumonia, or an infiltrate
- E. Ear infection—either a physician's diagnosis or drainage from one or both ears (ear pain or redness also required if drainage is not purulent)
- F. Sinusitis—physician diagnosis
- G. Mouth and perioral infection—physician or dentist diagnosis

III. Urinary tract infection
- A. The resident who does not have an indwelling urinary catheter must have three of the following: fever (>38.0°C) or chills; new or increased burning pain on urination, frequency, or urgency; new flank or suprapubic pain or tenderness; change in character of urine; worsening of mental or functional status (may be new or increased incontinence)
- B. The resident who has an indwelling catheter must have two of the following: fever (>38.0°C) or chills, new flank or suprapubic pain or tenderness, change in character of urine, worsening of mental or functional status

IV. Primary bloodstream infection—either two or more blood cultures positive for the same microorganism or a single positive culture with a microorganism not thought to be a contaminant and one of the following: fever (>38.0°C), new hypothermia (<34.5°C), a drop in systolic blood pressure >30 mm Hg from baseline, worsening mental or functional status

V. Gastroenteritis—one of the following: two or more loose or watery stools above what is normal within a 24-h period, two or more episodes of vomiting in a 24-h period, or a stool culture positive for *Salmonella*, *Shigella*, *E. coli* O157:H7, or *Campylobacter* or a toxin assay positive for *C. difficile* toxin and one symptom or sign of gastrointestinal infection (nausea, vomiting, abdominal pain or tenderness, or diarrhea)

VI. Unexplained febrile episode—fever (>38.0°C) on two or more occasions at least 12 h apart in any 3-d period with no known infectious or noninfectious cause.

(Adapted from McGeer A, Campbell B, Emori T, et al. Definitions of infection for surveillance in long-term care facilities. *Am J Infect Control* 1991;19:1–7, with permission.)

residents with pneumonia. In this trial, 680 residents aged 65 years and older in 22 nursing homes in Hamilton, ON, were randomized to either management according to a clinical pathway that included use of oral antimicrobials, portable chest x-rays, oxygen saturation monitors, rehydration, and close monitoring by a research nurse or usual care. Thirty-four (10%) of 327 residents in the clinical pathway group were hospitalized compared with 76 (22%) of 353 residents in the usual care group. After adjusting for clustering of residents in nursing homes, the weighted mean reduction in hospitalizations was 12% (95% CI 5–18%; $p = .001$). There was no significant difference in mortality, health-related quality of life, or functional status.

Tuberculosis is an important consideration in any resident of an LTCF presenting with a lower respiratory tract infection. The diagnosis of tuberculosis can be difficult in LTCFs as the clinical signs and symptoms are nonspecific (1). Sputum for acid fast bacilli should be obtained in any resident with an unresolving pneumonia or pneumonia with a characteristic radiograph (e.g., either cavitating disease or infiltrates in the upper lung fields). Healthcare workers should have a low threshold for suspecting tuberculosis in residents, and every institution should have standards for

control of tuberculosis that are summarized by the Society for Healthcare Epidemiology of America (SHEA)/Association for Professionals in Infection Control and Epidemiology (APIC) guidelines for infection prevention and control in the LTCF (1).

Urinary Tract Infections Although urinary tract infections are often cited as the most common infection affecting residents of LTCFs, most urinary "infections" actually represent asymptomatic bacteriuria (1). The prevalence of bacteriuria is high; thus, a positive urine culture in the absence of symptoms, even when pyuria is present, does not meet criteria for infection *(69)*. When careful clinical definitions of urinary tract infections are used, they are less frequent in residents of LTCFs than lower respiratory tract infection *(70)*. Antibiotics are generally indicated only when symptoms of infection are present, and bacteriuria in the absence of symptoms should not be treated. Symptoms of urinary tract infections can include frequency, urgency, dysuria, fever, or flank pain (in cases of pyelonephritis). Alternatively, urinary tract infections can also present as nonspecific functional decline or delirium. Because of the challenges in accurately diagnosing and treating urinary tract infections in nursing homes, a multifaceted intervention was tested in a cluster randomized controlled trial (71). The diagnosis of urinary tract infection was outlined in an algorithm (Fig. 98-1).

Skin and Soft-Tissue Infections Residents of LTCFs suffer from a number of skin and soft-tissue infections including decubitus ulcers, cellulitis, and scabies. Decubitus ulcers are exceedingly common, occurring in 20% of all residents, and are associated with increased risk of mortality (1,*72–74*). Decubiti are at high risk of becoming secondarily infected leading to deep soft-tissue infection and osteomyelitis. Once infected, they are difficult to treat and require complex medical and surgical intervention and are best treated by an interdisciplinary team. Prevention of pressure sores is the best approach. LTCFs should focus on turning, positioning, removing focal pressure, limiting shear forces, and keeping skin dry in residents at risk (1).

Cellulitis is typically due to group A streptococci and *S. aureus*. Areas of skin breakdown increase the risk of cellulitis; however, cellulitis can occur in the absence of open wounds (1). Cellulitis should be promptly treated to limit its spread and prevent complications such as bacteremia.

Scabies is a mite capable of causing skin infection and can be problematic in LTCFs. Scabies is characterized by extremely pruritic, small, burrow-like lesions associated with erythema, classically in interdigital spaces of the hands, but can also occur in the axilla, waist, buttocks, and perineal area. Scabies is very contagious, and the presence of a case should prompt an investigation by infection control for secondary cases (1). The mite can be transmitted by linen, clothing, and

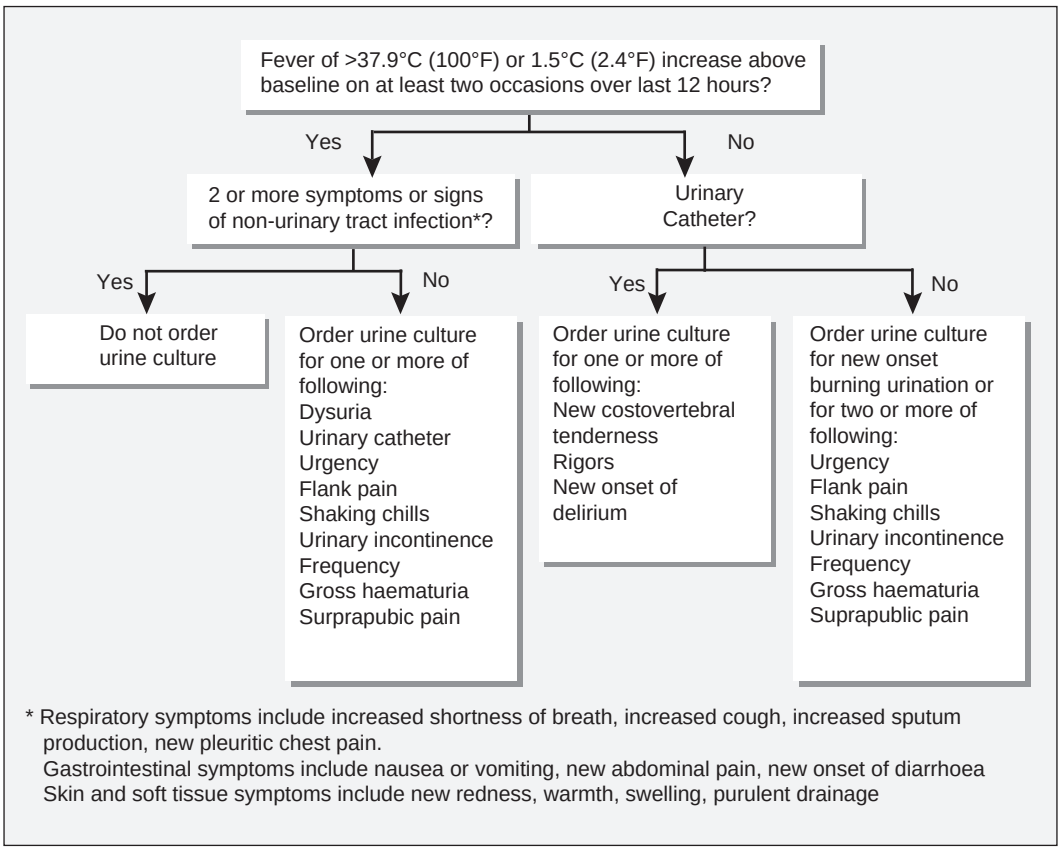

FIGURE 98-1 Algorithm for diagnosing urinary tract infections in long-term facilities. (From Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomized controlled trial. *BMJ* 2005;331:669–673.)

carpets; thus, all washable items should be washed using a hot cycle, and carpets should be thoroughly cleaned.

Other Infections There are a myriad of additional infections found in LTCFs, and the infections described above are by no means exhaustive. Other examples of common infections include gastrointestinal illness due to viruses (e.g., rotavirus, enterovirus, and norovirus) as well as bacterial infections including *Clostridium difficile*. Other endemic infections include bacteremia (either primary or secondary), herpes simplex, and herpes zoster. The wide spectrum of infections seen in residents of LTCFs illustrates the predisposition of residents of LTCFs to acquire infection.

Outbreaks

It is estimated that several thousand outbreaks occur at LTCFs in the United States each year (1). In a systematic review examining outbreaks in LTCFs, the largest number of reported outbreaks by a single pathogen was influenza virus followed by norovirus, group A *Streptococcus*, and *Salmonella* species *(75)*. The respiratory tract accounted for 45% of all outbreaks, and the gastrointestinal tract accounted for 36% *(75)*, consistent with previous studies *(58)*. Outbreaks in LTCFs affect both residents of the facility and healthcare workers, although the attack rates are generally higher in the residents *(75)*.

Influenza is an important threat to the health of residents of LTCFs. Influenza is highly contagious, with attack rates ranging from 25% to 75% and case–fatality rates >10% (1). Epidemics of influenza typically occur annually between November and April in the Northern hemisphere *(76)*. Fever and cough have been shown in a systematic review to be the best predictors of influenza in the general population; however, these findings may be more subtle in residents of LTCFs *(76)*. Diagnostic testing therefore plays a critical role in identifying residents with influenza, and a nasopharyngeal swab should be performed in any resident suspected of having a respiratory illness when influenza is circulating in the community as rapid diagnosis is key to preventing the spread. Polymerase chain reaction testing has emerged as the preferred gold standard approach for the detection of influenza infection because of the high sensitivity and specificity and because sample quality is less dependent on sample collection when compared to DFA and virus culture *(77)*. Once infected, transmission can occur 1 day prior to the onset of symptoms and can continue for at least 5 to 6 days. Infected residents are generally treated with antivirals and are isolated. Contacts can also receive prophylaxis. During an influenza outbreak, visitors and admissions are usually restricted, and infected staff should not work (1).

Norovirus accounts for the majority of acute gastroenteritis in LTCFs. A study evaluating the epidemiological and genetic characteristics of norovirus outbreaks in LTCFs in Oregon, between 2003 and 2006, showed that 8% of all facilities were affected each year *(78)*. Certain LTCFs experienced repeated outbreaks, sometimes with identical strains and sometimes with different strains. Between 2005 and 2006, the number of norovirus outbreaks more than doubled. It is hypothesized that this was secondary to the emergence of a GII, 4 strain of norovirus, a strain that appears to have emerged as the dominant strain in Europe as well *(78)*. The rising rate of norovirus infections in LTCFs emphasizes the need for more effective infection control strategies in LTCFs.

Outbreaks of hepatitis B and C virus infection (HBV and HCV) in LTCFs have been increasingly recognized *(79)*. Out of 33 nonhospital healthcare-associated HBV and HCV outbreaks identified in the United States between 1998 and 2008, 15 outbreaks occurred in LTCFs *(79)*. In total, 97 residents were identified as acquiring incident HBV infection. All 15 outbreaks were a result of lapses in infection control procedure. The patient-to-patient transmission of HBV infection was primarily through reuse of finger-stick devices meant for individual use on multiple persons or through other shared equipment such as blood glucose monitors *(79)*.

Emerging Infections

Emerging infectious diseases such as pandemic influenza and those due to multidrug-resistant bacteria have posed variable challenges in LTCFs.

Pandemic H1N1 influenza emerged as a novel pathogen in April 2009. Although pandemic H1N1 predominantly affected children and younger adults, outbreaks of pandemic H1N1 were still reported in LTCFs, stressing the importance of respiratory illness surveillance in all LTCFs *(80)*.

Recently, the multidrug-resistant bacterium *Acinetobacter baumannii* has become a challenge for LTCFs *(81)*. *A. baumannii* has the capacity to cause multisystem infection, including respiratory tract infection, bloodstream infection, soft-tissue infection, urinary tract infection, and central nervous system infection, and is associated with substantial morbidity and mortality *(81)*. A study performed in Michigan between 2003 and 2008 described the changing epidemiology of *A. baumannii* in community hospitals and LTCFs *(81)*. Over the study period, the prevalence increased by 25% and pan-resistant isolates increased from 0% in 2003 to 13.6% in 2008 ($p < .001$). Furthermore, resistance to antibiotics in the isolates obtained from residents of LTCFs increased from a mean of 4.5 antibiotic classes in 2003 to 5.7 in 2008 ($p < .01$).

INFECTION CONTROL PROGRAM ELEMENTS IN LTCFs

Prevention of infection is critically important as infections in LTCF residents are associated with mortality and frequently result in transfer to hospital (82,*83,84*). Infections are also associated with decline in functional status, which is also a risk factor for further infection as individuals with lower function are at greater risk for subsequent infection (22). Over the last two decades, the need for prevention of infections in LTCFs has gained increased recognition, and there has been increased adoption of LTCF infection control programs. The SHEA and APIC developed a guideline for infection prevention and control in the LTCF, which is summarized below (1).

The overall structure of an infection control program can be found in Table 98-2. Most infection control programs should include surveillance for infections, an epidemic control program, education of employees in infection control methods, policy and procedure formation and review, an employee health program, a resident health program, and monitoring of resident care practices (Table 98-3).

TABLE 98-2

Long-Term Care Facility Infection Control Program Structure

Leadership	*Expertise/Training*	*Role(s)*
Infection Control Committee/Oversight Committee		
Core members	Administration, nursing representative, medical director, IP	Identify areas of risk Establishes priorities
Ad hoc members	Food service, maintenance, housekeeping, laundry services, clinical services, resident activities, employee health	Plans strategies to achieve goals Implements plans Develops policies/procedures Allocates resources Assesses program efficacy at least annually
IP		
IP	Qualification via education, experience, certification	Surveillance Data collection and analysis Implementation of policies/procedures Education Reporting to oversight group/ICC Communication to public health Communication to other agencies Communication to other facilities

IP, infection preventionist; ICC, infection control committee.
(Adapted from Smith P, Bennet G, Bradley S, et al. SHEA/APIC Guidelines: infection prevention and control in the long-term care facility. *Am J Infect Control* 2008;36:504–535.)

The infection control program may also be involved in quality improvement, patient safety, environmental review, antibiotic monitoring, product review and evaluation, litigation prevention, resident safety, preparedness planning, and reporting of diseases to public health authorities.

The Infection Preventionist

The infection preventionist is the core component of any successful infection control program as he or she is the staff member dedicated to coordinating infection control activities (1). In a survey of LTCFs in New England, the mean time spent on infection control activities by the infection preventionist was 11.8 hours (median 8 hours, range 1–40 hours). The majority of time was spent on surveillance, 24% on teaching, and 22% on other activities including meetings *(85)*. The number of LTCF beds justifying a full-time infection preventionist is unknown; however, typically an LTCF with more than 250 to 300 beds requires a full-time person.

The Infection Control Oversight Committee

Each LTCF should have a small infection control working group consisting of the infection preventionist, an administrator, medical director, and nursing home supervisor. This committee should meet regularly to review infection control data, review policies and monitor program goals.

Surveillance

Data about LTCF-associated infections are essential to plan control activities and educational programs and to prevent epidemics. Good surveillance requires well-defined criteria for infection and sensitive case finding methods (Table 98-1). It is recommended that surveillance be performed one or more times per week for case finding in conjunction with review of reports from nurses, charts, laboratory reports, and medication records. Data should be compiled and analyzed on a regular, usually monthly, basis. Data regarding infectious morbidity are optimally presented in terms of incidence rates (e.g., the number of infections per 1,000 resident care days). Distribution of this information to appropriate committees and personnel and storage of the records are also important.

Outbreak Control

Routine surveillance facilitates the recognition of outbreaks. Once an outbreak is suspected, the infection preventionist may need to gather additional data to confirm the existence of an outbreak, develop a case definition, analyze the pattern of disease occurrence, formulate hypotheses regarding transmission, design control measures, evaluate control measures, consult with an experienced epidemiologist, or prepare reports for local authorities and supervisors.

Isolation and Precautions

LTCFs need defined policies for identifying and containing the risks of disease transmission posed by infected residents, staff members, and visitors. Some facilities use one of the major systems developed for use in the hospital, whereas other facilities develop their own. The availability of private rooms for patients requiring Contact Precautions or respiratory isolation rooms to prevent transmission of airborne pathogens is an important consideration in developing local policies. Specific guidelines for dealing with antimicrobial-resistant pathogens in LTCFs have been published in two SHEA position papers (38,*86*).

TABLE 98-3

Long-Term Care Facility Infection Control Program Elements

Elements	*Examples*
Infection control activities	
Establish and implement routine infection control policies and procedures	Hand hygiene Standard Precautions Microorganism-specific isolation Employee education
Infection identification	Develop case definitions Establish endemic rates Establish outbreak thresholds
Identification, investigation, and control of outbreaks	
Microorganism-specific infection control policies and procedures	Influenza Tuberculosis Scabies Multidrug-resistant organisms
Disease reporting	Public health authorities Receiving institutions Long-term care facility staff
Antibiotic stewardship	Review of antimicrobial use
Monitoring of patient care practices	Aspiration precautions Decubitus ulcer prevention Invasive device care and use
Facility management issues	General maintenance (i.e., plumbing/ventilation) Food preparation/storage Laundry collection/cleaning Infectious waste collection/disposal Environment (i.e., housekeeping/cleaning, disinfecting/sanitation, and equipment cleaning)
Product evaluation	Single-use devices
Resident health evaluation	Tuberculosis screening Immunization
Employee health evaluation	Tuberculosis screening Immunization Occupational exposures
Other program elements	
Performance improvement	Serve on performance improvement committee
Resident safety	Study preventable adverse events
Preparedness planning	Develop pandemic influenza preparedness plan

(Adapted from Smith P, Bennet G, Bradley S, et al. SHEA/APIC Guidelines: infection prevention and control in the long-term care facility. *Am J Infect Control* 2008;36:504–535.)

Hand Hygiene

Hand hygiene is one of the most important infection control measure in LTCFs, but adherence remains low *(87)*. LTCFs should adhere to available hand hygiene guidelines, and hand hygiene compliance should be monitored by the facility (1).

Resident Health Program

Comprehensive resident health programs ensure administration of appropriate vaccines; secure admission, annual, and postexposure tuberculin skin tests; and address risk reduction in residents prone to aspiration, obstructive uropathy, decubiti, and other medical conditions that may be complicated by infection.

Employee Health Program

Employee health programs ensure that all employees are free of communicable diseases at the time of employment. They also ensure that tuberculin skin tests are administered annually and as indicated after exposure, that appropriate vaccines are offered, and that exposures to certain infections (e.g., tuberculosis or HIV infection) are managed properly.

Antibiotic Stewardship

Resistant pathogens, high levels of use, and inappropriate use are well-recognized problems associated with antimicrobial agents in nursing homes (38,*86*). For this reason, regular review of antimicrobial use and patterns of resistance is recommended. Presentation of this information to the medical staff can guide practice patterns and decrease the prevalence of resistant pathogens.

Policies and Procedures

As in the hospital, the development and regular updating of infection control procedures to cover such topics as hand hygiene, laundry, dietetic services, physical therapy, disinfectant and antiseptic use, medical devices, pets, visitors, and disposal of infectious wastes form an integral part of the infection control program. Pet-assisted therapy warrants specific policies in LTCFs that use this approach *(88)* (see also Chapter 94).

Disease Reporting

LTCFs, like other healthcare organizations, are obligated to notify public health authorities in a timely manner about the occurrence of reportable infections within the facility.

Performance Improvement/Resident Safety

Infection control is an important aspect of any quality management program within LTCFs. As in the hospital, the infection preventionist in LTCFs, by virtue of training, experience, and focus, can uniquely contribute to the facility's quality management program.

EVIDENCE-BASED PREVENTION AND CONTROL OF INFECTION IN LTCFs

Although infections in LTCFs are common, there are few evidence-based strategies to reduce infections in LTCFs. However, those for which there is evidence can make important impact and should be implemented by infection control programs. The following section will review existing evidence-based prevention strategies.

Strategies to Decrease Antimicrobial Resistance

LTCFs are an important reservoir for antimicrobial resistance, and MRSA in particular *(89,90)*. There have been few methodologically rigorous studies investigating ways to prevent spread of MRSA in LTCFs. Recently, a cluster randomized trial took place that evaluated the role of an infection control education and training intervention program on the prevalence of MRSA in residents and staff in the United Kingdom *(91)*. Prior to randomization, all participants ≥65 years and the nursing staff in 43 eligible LTCFs underwent testing for MRSA colonization. An infection control audit was carried out using an audit tool that measured compliance with infection control standards. LTCFs randomized to the intervention arm received detailed information on their baseline infection control scores including methods to improve practice and in-depth infection control training that consisted of a 2-hour training session delivered via PowerPoint and DVD presentations. These training sessions were repeated at 3 and 6 months after each infection control audit and feedback. The control arm consisted of usual practice, and no additional training or feedback was delivered to the staff. Sixteen matched pairs of LTCFs involving 793 residents and 338 staff were evaluated. The intervention had no effect on MRSA prevalence among residents or staff over the 12-month study period despite the intervention group having significantly higher infection control audit scores (47/244 [19%] vs. 44/234 [19%] in the intervention group; RR 0.99 [95% CI 0.69– 1.42]; $p = .95$). Further trials evaluating alternative interventions are needed to identify other measures to reduce MRSA prevalence in LTCFs.

Proper hand hygiene may be the most important strategy to reduce the spread of antimicrobial resistance in LTCFs; however, there have been few studies of hand hygiene practice in LTCFs. One cross-sectional study used direct observation methods to measure adherence to hand hygiene among healthcare workers in two LTCFs in Hamilton, ON *(87)*. A total of 459 hand hygiene opportunities were observed, and overall compliance with hand hygiene was 14.7%. The study concludes that there is significant room for improvement in hand hygiene in LTCFs, and techniques to improved hand hygiene adherence should be investigated further using randomized controlled trials.

Antimicrobial use is an important driver of antimicrobial resistance in nursing homes *(92,93)*. In addition, overuse of antibiotics is associated with adverse events, drug interactions, and increased costs. Thus, a consensus conference was held to establish minimum criteria that should be present before initiating antibiotics in LTCFs *(94)*. Minimum criteria were outlined for common infections in LTCFs such as skin and soft-tissue infections, respiratory infections, urinary tract infections, and fever where the focus of infection is unknown. Studies are needed to validate these criteria and to document their impact on antimicrobial resistance.

Strategies to Prevent Infection

A list of available vaccination and prophylaxis recommendations for LTCF can be found in Table 98-4. Most evidence-based prevention strategies in LTCFs have focused on prevention of lower respiratory tract illness including prevention of pneumococcal pneumonia, influenza infection, and aspiration pneumonia and are summarized below.

TABLE 98-4

Vaccination and Prophylaxis Recommendations for Long-Term Care Facilities

Vaccine/Prophylaxis	*Recommendations*
Influenza vaccine	Optimal time for nursing home vaccination is October to November. Immunization of unvaccinated residents should continue as long as vaccine is available Contraindication—anaphylactic hypersensitivity to eggs Consider immunization for any LTCF resident
Influenza antiviral medications	When influenza vaccination is contraindicated: administer throughout influenza season or during peak community influenza activity Adjunct to immunization: administer to LTCF residents who are vaccinated after a community outbreak of influenza has begun until immunity has developed (~2 wk) Institutional outbreaks: administer to all residents regardless of immunization status for at least 2 wk, continuing for 1 wk after the end of the outbreak and as an adjunct to immunization if influenza is noted in the community before vaccination
Pneumococcal polysaccharide vaccine	All residents 65 and older and anyone with a chronic condition that increases the risk of pneumococcal disease (i.e., chronic lung disease, heart disease, diabetes, renal failure, alcoholism) Revaccination—persons 65 or older first vaccinated before age 65 should be given a one-time revaccination 5 y after initial vaccination
Tetanus-diphtheria toxoid (Adult Td)	Unimmunized/history unknown administer full series All other residents, booster every 10 y Clean wounds—Td if >10 y since last vaccination Dirty wounds, puncture, frostbite—Td if fully immunized and >5 y since last booster dose; if unimmunized, inadequate primary series (<3 doses) or history unknown, tetanus immune globulin plus primary immunization series Contraindications—neurologic reaction or hypersensitivity to previous dose

LTCF, long-term care facility.

Guidelines recommend immunizing residents of LTCFs against *S. pneumoniae* with the 23-valent pneumococcal polysaccharide vaccine *(95)*. Although NHAP has over 100 etiological agents, the most common cause of pneumonia remains *S. pneumoniae (64)*. At least 12 outbreaks of serious pneumococcal disease have also been reported in LTCFs *(96)*. A Cochrane review of randomized controlled trials found that the 23-valent polysaccharide vaccine prevented invasive pneumococcal disease in the elderly *(97)*. Since this meta-analysis was published, the efficacy of the 23-valent pneumococcal vaccine in preventing pneumonia was studied in nursing home residents *(98)*. In this prospective, multicenter, double-blind randomized controlled trial of 1,006 nursing home residents in Japan, residents were allocated to either the 23-valent pneumococcal vaccine or placebo groups and the participants were followed for 3 years. Vaccination with the 23-valent pneumococcal vaccine was associated with a reduction in pneumococcal pneumonia (12/502 vs. 32/504 in the placebo group, $p = .0015$) and all-cause pneumonia (55/502 vs. 91/504 in the placebo group, $p = .0006$) but not nonpneumococcal pneumonia (43/502 vs. 59/504 in the placebo group, $p = .0805$). The trial was not powered to detect a difference in invasive pneumococcal disease. The generalizability of this study to other nursing homes could be questioned as <10% of the participants died during the 3-year follow-up period and not a single participant dropped out of the study, which is unusual *(99)*. Regardless, there is evidence that the 23-valent pneumococcal vaccine can prevent invasive pneumococcal disease, and the vaccine is well tolerated; thus, it makes sense to administer the vaccine to nursing home residents *(99)*. The question of whether to administer the new pneumococcal vaccine formulations including the pneumococcal conjugate vaccine versus the 23-valent polysaccharide vaccine will need to be addressed in this population in the future.

It appears as though the benefits of influenza vaccine effectiveness in the elderly have been substantially overestimated *(100)*. Studies that are able to better adjust for functional status or other measures of frailty demonstrate a nonsignificant benefit of vaccination in terms of hospitalization and mortality, strongly suggesting substantial residual confounding factors arising from observational studies of vaccine effectiveness *(100)*. However, vaccination of healthcare workers with the influenza vaccine has been shown to decrease the incidence of mortality among nursing home residents in randomized controlled trials and should be encouraged. Potter et al. *(101)* randomized 12 LTCFs either to offer healthcare workers vaccination or no vaccination. The authors noted that vaccination of healthcare workers was associated with a reduction in total patient mortality from 17% to 10% (OR 0.56; 95% CI 0.40–0.80) *(101)*. Carman et al. *(102)* conducted a randomized trial using cluster randomization in 20 geriatric care hospitals that compared mortality in hospitals where healthcare workers were vaccinated with mortality in hospitals where no vaccination was offered. Vaccination of healthcare workers significantly reduced mortality of elderly people over a period of 6 months in hospitals where influenza vaccine was offered, compared with hospitals where influenza vaccine was not offered (OR 0.58, 95% CI 0.40–0.84, $p = .014$) *(102)*.

Increased aspiration is an established risk factor for NHAP *(103)*. A systematic study reviewed randomized controlled trial interventions to prevent aspiration pneumonia in the elderly *(104)*. Eight studies met eligibility criteria: two dietary interventions (pureed food vs. nonaltered food and compensatory positioning during feeding), two pharmacological therapies (amantadine vs. no treatment and cilostazol vs. no active treatment), one trial that compared enhanced oral care with usual care, and three trials that looked at the use of feeding tubes in patients at risk of aspiration. When amantadine was compared to no treatment, amantadine was protective from pneumonia (5/83 in the amantadine group vs. 22/80 in the no treatment group, OR 0.17, 95% CI 0.05–0.50, $p < .001$). However, amantadine is associated with gastrointestinal, neurological side effects and drug–drug interactions precluding wide adoption of this strategy. Furthermore, amantadine has activity against influenza, which may explain its benefit *(104)*. Similarly, the antithrombotic agent cilostazol prevented aspiration pneumonia (12/152 in the cilostazol group vs. 35/145 in the no treatment group, OR = 0.33 [95% CI 0.15–0.71, $p < .001$]), but the 7% risk of bleeding in the cilostazol arm limits its use as a preventative strategy. None of the other interventions reduced the incidence of pneumonia. However, the effect of using enhanced oral hygiene was of borderline significance (OR 1.74 [95% CI 0.93–3.26]).

A subsequent systematic review built upon this finding of potential benefit from enhanced oral hygiene and reviewed all randomized and nonrandomized controlled trials investigating its preventative effect from pneumonia in the hospitalized elderly and nursing home elderly *(105)*. In total, 15 publications met inclusion criteria; 4 of these were unique randomized controlled trials. All four trials showed a reduction of pneumonia in the elderly (absolute risk reduction [ARR] ranging from 6.6% to 11.7%); however, all of the trials were small (sample size ranging from 40 to 184), which likely explained why the 95% CIs crossed 0 in two of the trials. A larger, adequately powered trial is now underway.

CONCLUSION

The burden of infections in LTCFs is high. Having a formal infection prevention and control program in LTCFs is essential for limiting spread of infection. Infection control programs should ensure that existing evidence-based infection prevention strategies are implemented. However, given the burden of infection in LTCFs, research into novel prevention strategies in LTCF is an urgent priority.

ACKNOWLEDGMENTS

We would like to acknowledge Dr. Larry Strausbaugh and Dr. Carol Joseph who contributed to an earlier version of this chapter. Dr. Johnstone receives salary support from the McMaster University Bayer Healthcare Infectious Disease Research Fellowship (2009–2010) and Canadian Thoracic Society (2010–2011).

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CHAPTER 99

Epidemiology and Prevention of Infections in Home Healthcare

Philip W. Smith and Angela L. Hewlett

BACKGROUND

The Home Healthcare Field

Home healthcare is the most rapidly growing segment of the healthcare delivery system; about as many persons in the United States receive healthcare in the home as in acute care settings *(1)*. More than 20,000 agencies deliver home care to 7.6 million individuals, generating about $40 billion in expenditures *(2)*. Medicare is the largest payer of home health services *(3)*. The most commonly used services are skilled nursing care, personal care, and physical therapy.

Home healthcare specialists provide many services traditionally given in the hospital or in a long-term care facility (LTCF). The number and types of patients who receive professional care in the home setting are increasing; major categories of home care services include infusion therapy, respiratory therapy, dialysis, diabetic monitoring, wound care, other skilled nursing care, physical therapy, nutritional therapy, occupational therapy, social services, and hospice care. Also included in these general categories are patients requiring special nursing support by virtue of medical needs (e.g., enteral nutrition) or disease complexity (e.g., acquired immunodeficiency syndrome). In total, about 950,000 persons are employed in the home healthcare industry, mostly home care aides and registered nurses *(2,3)*. Other professionals including respiratory therapists, physical therapists, social service workers, speech therapists, pharmacists, and durable medical equipment suppliers are also involved in providing home healthcare.

Infections and Risk Factors in Home Healthcare Patients

Patients cared for at home have conditions that predispose to infectious diseases such as advanced age, multiple underlying comorbidities, and immunosuppressive conditions (*2–4*,5,*6–9*). Many infections acquired in the home are related to devices or breaks in local defenses (Table 99-1). Invasive devices were noted in up to one third of patients in the home (*4*,5,*9*), most notably urethral or suprapubic catheters (12–21%), nasogastric tubes (11%), intravenous (IV) catheters (6–17%), gastrostomy tubes (7%), and tracheostomies (2%). Some infections in the home setting are hospital-acquired (attributable to a prior hospital stay), most commonly urinary tract infection (UTI) and skin/wound infection (*10*). Although comparative data are not available, home healthcare patients are presumably less immunosuppressed than typical hospital or LTCF patients but more at risk for infection than other community-dwelling individuals.

Home healthcare patients may have a variety of infectious diseases that require infection control in the home. Limited data suggest that the prevalence of infection in home healthcare patients is 16% to 20% *(4,9)*. One prevalence survey found an overall infection rate in the home of 16%, with 8% of these infections being home care acquired, 16% hospital acquired, 41% community acquired, and 35% unknown *(9)*. The most common infections involved the urinary tract (27%), respiratory tract (24%), skin and soft tissue (24%), surgical wounds (12%), and bloodstream (2%). Others (11) have noted a relatively low rate of device-associated infection in the home (0.22 central line–associated bloodstream infections [BSIs] per 1,000 device days, and 1.24 UTIs per 1,000 device days). The definitions of infection in the home care setting are discussed below in "Surveillance."

The occurrence of an infection in a patient in an acute care hospital or LTCF does not imply that the infection was caused by the facility, or necessarily preventable. Infections that occur in home healthcare patients are much more difficult to ascribe to the home health agency, which has contact with the patient usually only a few minutes per day compared with 24 hours for the hospital or LTCF. Exposure to microorganisms from family members, visitors, or the environment are usually beyond the control of the home health agency, as are factors such as home sanitation, compliance with basic hygiene, and exposure to contagious persons (12). In the case of intravascular catheters, multiple providers may have access to the device *(13)*. The incidence, origin, risk factors, and preventability of infections in the home healthcare setting still remain largely to be defined.

HOME INFUSION THERAPY

The home infusion industry has grown rapidly, greatly advanced by the development and widespread availability of devices to secure long-term venous access.

TABLE 99-1

Infections of Importance in Home Health

Infection	*Associated Condition or Device*
Bacteremia	Intravenous access device
Urinary tract infection	Bladder catheter
Pneumonia	Nasogastric tube, tracheostomy
Peritonitis	Peritoneal dialysis catheter
Wound infection	Recent surgery

Antibiotic therapy, parenteral nutrition, hydration therapy, chemotherapy, and pain medications account for most IV home medications.

Infections in Home Infusion Therapy

Most infections in home infusion therapy are related to vascular access devices. The measured incidence rate of central line–associated bacteremia varies widely in the literature, from 7 to 58 bacteremias per 10,000 catheter days (*14*,15,*16–18*). Noninfectious complications of venous access in the home environment include thrombosis, bleeding, and air embolism *(19)*.

Infections related to indwelling vascular access devices can present as sepsis or fever without localizing signs or symptoms. Alternately, one may see signs of exit-site infection (erythema, tenderness, or purulent discharge at the catheter exit site) or a tunnel infection (erythema, tenderness, and induration along the subcutaneous tract). Catheter-related sepsis and tunnel infections often require catheter removal *(14)*. The most common microorganisms associated with these infections are coagulase-negative staphylococci, *Staphylococcus aureus*, aerobic gram-negative bacilli (such as *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*), and *Candida* species. In one report, gram-negative microorganisms were responsible for a greater proportion of central line–related bacteremias in pediatric oncology patients receiving home care than in those in the hospital; the mean time between catheter insertion and bacteremia was 133 days *(17)*.

Risk factors for BSIs in patients receiving home infusion therapy include bone marrow transplantation, parenteral nutrition, and use of multilumen catheters (20). The importance of aseptic technique is suggested by the association of lower education and younger age with patient BSI (21). Proper infection control technique is likely an important component of preventing home infusion-related infectious complications *(22)*, although little research has been done in the home setting. One investigator found that routine replacement of peripheral catheters every 3 to 4 days was not associated with a lower rate of complications *(23)*.

Home Parenteral Nutrition

One special area of home infusion therapy is home parenteral nutrition (HPN). Most infections in HPN are related to the indwelling vascular catheter *(24)*. Catheter-related bacteremia in HPN patients occurs at a rate of approximately 20 infections per 10,000 HPN days *(16,18)*. The leading causative microorganisms are coagulase-negative staphylococci, *K. pneumoniae*, *Escherichia coli*, *S. aureus*, and *Candida* species.

Infusate-related bacteremia from contaminated parenteral nutrition fluids is relatively uncommon but remains a concern. A variety of microorganisms have been shown to proliferate in parenteral nutrition solutions, particularly gram-negative bacteria and *Candida* species *(25)*.

Preventive Measures

Infection control recommendations for home infusion therapy pertain mainly to the prevention of vascular access–associated infections. Guidelines for preventing catheter-related infections in the hospital have been published *(22)*. The guidelines address frequency of catheter and administration set change, aseptic technique during catheter insertion, and length of hang time for lipid-containing solutions. The home care agency is responsible for ensuring sterility of solutions prepared for IV infusion. Both the patient and the home healthcare provider need to be familiar with the signs and symptoms of infection, the side effects of infusion therapy, and the maintenance and care of vascular access devices. See Chapters 18 for more information on the infection control aspects of long-term vascular access.

HOME RESPIRATORY CARE

Technologic advances have had a great impact on home healthcare patients with chronic respiratory conditions. Home care of patients with tracheostomies has become an accepted practice. This raises questions regarding the most effective aseptic techniques when performing tracheostomy care and tracheal suctioning. Sophisticated respiratory care equipment is used in the home and requires meticulous maintenance to prevent bacterial contamination and respiratory tract infection by inhalation. Finally, chronic ventilatory support may be provided with in-home ventilators, requiring adaptation of standard acute care hospital respiratory care techniques to the home care setting.

Home respiratory care patients are at particular risk for respiratory tract infections because of underlying pulmonary diseases and devices such as tracheostomies that bypass upper airway defenses. Marrie and Huang (26) found that the overall rate of community-acquired pneumonia (CAP) requiring an emergency room visit for home care patients was 25 per 1,000 person years. Home care patients hospitalized for pneumonia had double the hospital mortality, likely due to their increased age and greater functional impairment. The CAP incidence in patients receiving home ventilation was 1.5 per 1,000 ventilator days *(27)*. The causative microorganisms were similar to those in hospitalized patients with ventilator-associated pneumonia, namely *S. aureus*, *Pseudomonas* species, and other aerobic gram-negative bacilli.

Infection Control Aspects of Home Respiratory Care

There are no controlled studies of the risk of infection or of infection control methods for respiratory patients in the home environment. Recommendations *(28,29)* are based on extrapolations from current hospital practices (see Chapter 22). Areas of concern are listed in Table 99-2.

TABLE 99-2

Infection Control Concerns in Home Respiratory Care

Tracheostomy care
Changing of inner cannula
Tracheostomy site care
Suctioning technique
Reuse of suction catheters
Disinfection of respiratory care equipment
Ventilator circuits
Ventilator apparatus
Humidifiers
Nebulization equipment
Oxygen delivery systems

For patients receiving mechanical ventilation in the home, cleaning of the ventilatory circuits is important. Several circuits should be provided, and the circuits (including tubing, manifold, and humidifier) not in use should be cleaned and dried before being stored. Adequate precleaning of equipment is an important part of the disinfection process.

Room humidifiers that produce a fine spray of water droplets are frequently used in the home and are often contaminated with bacteria. These humidifiers are difficult to clean and pose significant risk to immunocompromised patients. Drying between uses decreases bacterial contamination. Humidifiers that work by simple evaporation are safer than those that produce a fine mist spray.

Guidelines for prevention of healthcare-associated pneumonia *(29)* have relevance for home care, including immunization recommendations (pneumococcal vaccine, influenza vaccine), suctioning, ventilator care, aspiration prevention after enteral feeding, and humidifier care. The American Association of Respiratory Care provides clinical practice guidelines for home suctioning, home ventilation, postural drainage, and ventilator circuit changes *(28)*, as well as a discussion of frequency of ventilator tubing change and infection control aspects of humidification. The home suctioning guideline discusses cleaning and reuse of suction catheters *(30)*.

HOME DIALYSIS CARE

Technologic advances have resulted in the ability of many patients with chronic renal failure to receive dialysis at home. Both peritoneal dialysis and hemodialysis may be administered in the home setting. Most infections in dialysis patients are related to access devices.

Infections in Home Dialysis

One of the most serious problems associated with peritoneal dialysis is infection involving either the catheter exit site through the skin or the peritoneal cavity itself. The former infection, analogous to indwelling central IV access device infections, may involve either the exit site or the tunnel. The latter generally presents as peritonitis *(31)*. The incidence of infectious complications related to continuous ambulatory peritoneal dialysis (CAPD) is about 1.1 to1.3 episodes per patient year *(32)*. Recurrent peritonitis is a leading cause of CAPD failure.

Most bacteria causing CAPD-related peritonitis are gram-positive bacteria (specifically, coagulase-negative staphylococci and *S. aureus*), reflecting the important role of skin flora in catheter-related peritonitis *(31,32)*. Polymicrobial infections and the presence of gram-negative bacteria suggest a bowel perforation by the catheter. Nasal carriage of *S. aureus* may be a risk factor for catheter exit-site infections by this microorganism *(33)*.

Preventive Aspects

A key to minimizing the risk of peritonitis due to CAPD is appropriate care of the exit site and surrounding skin. Initial care after catheter placement has been described and consists of cleaning the exit site and surrounding skin with an antiseptic agent, drying the skin, covering the exit site with a sterile gauze dressing, and securing with surgical tape. The catheter should be protected from mechanical stress. After the exit site has healed, routine care includes frequent examination of the exit site and tunnel for signs of inflammation as well as cleaning of the exit site *(34–36)*. The potential for contamination of the peritoneal dialysis system exists when the system is opened to connect or disconnect bags of fluid. Hand washing and aseptic technique are important. Infections in peritoneal dialysis are discussed in greater depth in Chapter 64.

A guideline for preventing infection transmission in chronic hemodialysis patients discusses cleaning and disinfection of equipment *(37)*. Hemodialysis and related complications are discussed in Chapter 63. Patients should be educated in basic hygienic techniques and the signs of access-site infection and sepsis.

INFECTION CONTROL ASPECTS OF OTHER TYPES OF HOME HEALTHCARE

Urinary Catheterization in the Home

The home healthcare patient may require continuous or intermittent urinary catheterization *(38)*. One study found an infection rate of 4.5 symptomatic UTIs per 1,000 catheter days (15). A survey of home care patients with urinary catheters during a 6-month period found the mean duration of catheterization to be about 300 days *(39)*. One quarter had a UTI at the start of catheterization, and 43% of the remainder acquired infection during the study period. Frequent catheter change was an infection risk.

Intermittent catheterization is usually limited to individuals with neurogenic bladders who are able to actively participate in their own care. Clean rather than sterile technique is often used in the home setting *(40)*, but virtually no data are available to guide infection control in the home in this area.

Guidelines for prevention of UTI associated with indwelling catheters can be found in the literature *(41)* and in Chapter 20. They emphasize aseptic catheter insertion, maintenance of unobstructed flow, use of a closed drainage system, and minimization of drainage tube disconnections.

The ideal approach to leg bags and equipment reuse in the home setting is not yet defined.

Home Skin/Wound Care

A Michigan prevalence survey found that 36.3% of a large sample of home care patients had wounds present—most commonly surgical wounds, pressure ulcers, and vascular leg ulcers. Of patients with wounds, 41% had multiple wounds *(42)*. In another survey, 9% of home care patients had a stage II or deeper pressure ulcer, and one third had more than one ulcer (43).

Fresh surgical wounds are not frequently encountered in the home setting; thus, clean technique is adequate for most wound care. Proper wound care involves minimizing touching and glove use for clean wounds, the use of gloves for infected or draining wounds, and proper disposal of soiled dressings. The patient, the family, and the home healthcare provider need to be educated on the signs and symptoms of wound infection, such as fever, pain, swelling, induration, erythema, and warmth. Guidelines for pressure ulcer prevention are available *(44)* and discuss pressure ulcer staging, diagnosis, prevention, and treatment, as well as skin assessment and nutrition.

Enteral Feedings in the Home

Enteral feeding via nasogastric or another enteral feeding tube is often undertaken in the home setting. The risk of infection is primarily related to the potential for aspiration resulting from the presence of the nasogastric tube. The possibility of bacterial contamination of enteral feeding solutions must also be considered *(45)*. In general, clean technique is appropriate for preparing and administering enteral feedings. To minimize the risk of aspiration pneumonia, tube placement should be confirmed and the patient should be kept in the erect or semierect position *(29)*.

Multidrug-Resistant Microorganisms in the Home

Multidrug-resistant microorganisms (MDROs) have become prominent in healthcare in recent years. Although most of the concern has been focused on hospital and LTCF settings, methicillin-resistant *S. aureus* (MRSA) has become a major concern in the community and the home *(46)*. A Brazilian home health service found a prevalence of 15% of MRSA carriage in a home service; although most were positive on admission, there were eight instances of cross-transmission to home health employees *(47)*. Another study noted a prevalence of 12% of MRSA colonization in posthospital patients admitted to home care, and almost 20% of household contacts acquired MRSA from the index patient (48).

The environment of patients colonized with MRSA may be contaminated with the microorganism, especially sites touched by the hands such as faucet handles (49,*50*). In one study of patients with MRSA admitted to a hospital, home nursing care was an independent risk factor for MRSA acquisition in the community (51). One of the few cases of vancomycin-intermediate *S. aureus* occurred in a home health patient who had received vancomycin *(52)*. Isolation is discussed below, but standard precautions are important in view of the fact that many MDRO carriers are unknown to healthcare providers.

THE HOME HEALTH INFECTION CONTROL PROGRAM

There is a trend toward formalizing infection control efforts in home health (53). The functions of an infection control program in this setting are listed in Table 99-3. The basic elements of infection control for out-of-hospital settings are (a) managing data, (b) developing control efforts, (c) preventing infections, and (d) training *(54)*.

An administrative structure should identify a designated infection preventionist (IP) who is responsible for the program, and the program may have a formal infection control committee (*55*,*56*,57). Ideally, the IP should be available to conduct infection control activities from within the agency. An infectious disease physician with experience in infection control should be available on a consultative basis.

Communication with other healthcare organizations is important, especially because many home care patients have recently been in acute care hospitals or LTCFs. Exchange of microbiologic and clinical information is helpful for medical decision making by healthcare providers and for infection control planning. Communication includes disease reporting to health departments and healthcare-associated infection reporting to the patients' institutions of recent residence. This is one aspect of regulatory compliance. Surveillance data facilitate detection of epidemics and adverse events and are key to quality improvement efforts.

Employee protection begins with a basic employee health program, addressing such issues as tuberculosis skin testing, postexposure protocols, and immunizations. Policies and procedures for infection control measures are designed to minimize infection transmission; they deal with asepsis, disinfection, and hygiene, including hand washing and waste disposal. Barrier protection methods are also part of employee protection and may vary depending on the patient's infectious condition (e.g., colonization with antibiotic-resistant bacteria) and level of compliance. The IP plays an important role in prevention of cross-infection in the home by education of patients and families.

TABLE 99-3

Components of a Home Healthcare Infection Control Program

Administrative structure
Communication
Disease reporting
Regulatory compliance
Surveillance system
Quality improvement
Employee health
Policies and procedure
Asepsis, disinfection, and hygiene
Waste disposal
Isolation precautions
Education of patients and families
Preparedness

Most agencies have policies and procedures for standard precautions, hand hygiene, handling sharps and needles, and cleaning or disinfecting equipment. A Missouri survey found that 90% of 95 home care agencies had written infection control policies, and 95% had a system for reporting exposures, injuries, or infections in their personnel *(58)*. Seventy percent of the agencies conducted infection surveillance (most used standard definitions, used standard data collection forms, and calculated infection rates). Two-thirds had a routine process for checking the antimicrobial sensitivities of pathogens, but only about half had a designated IP.

Another key element of infection control is education. In view of the limited time the healthcare providers spend in the home, it is important that they teach the patient and family about hand hygiene and good infection control techniques. Inadequate education has been associated with infectious disease outbreaks *(59)*.

Surveillance

The first step in developing an infection control program is to create a surveillance system for infections acquired in home healthcare and for employee exposures. Surveillance for home care–associated infections is a difficult task. Unlike the hospital or LTCF patient, the home care patient has contact with healthcare providers for a very small amount of time (a few minutes per visit, with contact perhaps not occurring daily). Multiple home agencies may serve the same patient. It is, therefore, not always clear which infections occur as a result of normal daily life (community acquired) and which are related to care received in the home (home care associated).

Collecting infection incidence or prevalence data in the home setting may be problematic *(60)*, requiring sharing of data by hospitals and laboratories and collection of information by home care nurses in the field. Laboratory data are often difficult to obtain in the home setting. Device-related denominator data are not readily obtained if devices are inserted or removed at various facilities without notification of the home care nurses. Denominator data permitting calculation of rates per 1,000 device days (e.g., urinary catheter, central venous catheter) are preferable (15) but not always readily obtained.

Surveillance has been advanced by publication of definitions of infections for the home care setting *(61)*, although the definitions have not been validated. Of necessity, these definitions rely more heavily on clinical signs and symptoms and tests that can be performed at the bedside like urine dipstick testing. For instance, according to the Centers for Disease Control and Prevention definitions of infection for hospitalized patients *(62)*, the diagnosis of pneumonia requires an abnormal or changed chest radiograph. Healthcare-associated pneumonia in a home care patient may be diagnosed without chest radiograph if the patient has any three of the following signs or symptoms:

1. New *or* increased cough
2. New *or* increased sputum production
3. New *or* increased purulence of sputum
4. Fever
5. Pleuritic chest pain
6. New *or* increased physical finding on chest examination
   a. Rales
   b. Rhonchi
   c. Bronchial breathing
7. Change in status or breathing difficulty
   a. New *or* increased shortness of breath
   b. Respiratory rate >25 per minute
   c. Worsening mental or functional status

Surveillance data should be collected and reviewed by the IP. Both outcome (e.g., BSIs per 1,000 central line days) and process (e.g., compliance with hand hygiene) measures may be monitored. Data can be used to provide valuable information to healthcare providers about the patient's condition, such as detection of febrile episodes in home care patients with hematologic malignancies. Surveillance in the home is also useful for detection of home care–associated outbreaks such as BSIs *(63)*. This is the ideal setting for focused surveillance, including collecting data on a few select infections such as IV-related infections, wound infections, or UTIs. Tracking device-related infections such as BSIs in patients with central lines and UTIs in catheterized patients has the advantage of focusing on high-risk patients and enabling collection of meaningful denominator data (e.g., BSI per 1,000 central line days). Finally, surveillance data facilitate patient safety and quality of care assessment in the home.

Asepsis, Disinfection, and Hygiene

Perhaps the most important infection control measure in the home setting is hand hygiene. A recent guideline recommends a 15-second soap and water scrub or using an alcohol-based rub until dry *(64)*. Waterless agents are convenient since running water is not always available. Adherence to hand hygiene by healthcare providers should be monitored, likely with observation in the home setting.

Reusable objects that touch mucous membranes, such as suction catheters and glass thermometers, should be limited to use on one patient and may be disinfected between uses on the same patient. A discussion of disinfectants is available *(65)*; bleach, 70% alcohol, and 3% hydrogen peroxide are good disinfectants for the home setting. Some household disinfectants (e.g., bleach) have activity against virtually all agents tested, including polioviruses (66).

The home care provider should educate patients and families on the basics of hygiene and asepsis to minimize the risk of infection transmission. This risk was demonstrated by acquisition of hepatitis C by a hemophiliac child from his mother during infusion of clotting factor concentrate in the home *(67)*. One survey of hemophiliac patients found inadequate infection control practices in the home *(68)*; frequent needlestick injuries were noted (often during recapping) and gloves were often not used for cleaning up blood spills or during blood product infusions.

While there are infectious risks in the household, there is little information on rational approaches to control of those risks. Hand hygiene is felt to be the most important measure *(69)*, and a risk-based approach has been suggested (70). Thus, more stringent environmental cleaning

FIGURE 99-1 Home nursing bag. Contents relevant to infection control: nursing bag, biohazard transport bag, biohazard bag, sharps container, isolation gown, masks, N-95 mask, gloves, goggles, cardiopulmonary resuscitation mask, antimicrobial hand soap and paper towels, hand sanitizer, gauze sponges, germicidal wipes, thermometer, methicillin-resistant *S. aureus* kit. The latter contains a disposable stethoscope, red biohazard disposal bag, disposable adult blood pressure cuff and a clear bag. (Courtesy of Bridget Young, Visiting Nurse Association of the Midlands, Omaha, Nebraska.)

may be appropriate for highly immunosuppressed patients such as transplant recipients. One randomized study of households assigned to cleaning with or without cleaning products with antibacterial properties found no significant difference in viral infections in the households *(71)*.

The home nursing bag is an important piece of equipment for the home healthcare professional (Fig. 99-1). The inside of the bag should ideally be clean, although the outside of the bag is often contaminated *(72)*. Contaminated items that cannot be cleaned or discarded in the home should be placed in an impervious container in the nursing bag, and hands should be washed before handling equipment inside the bag. The bag should contain a spill kit to deal with large volume of blood or body fluid spills.

Isolation Issues

Isolation techniques used in the home should follow the general principles of standard precautions *(73)*. Basic protective measures are indicated for use with all patients. This includes wearing gloves for contact with blood and body fluids, wearing masks for contact with a patient who is coughing frequently or unable to control secretions, and using a cover gown or apron if soiling with blood or body fluids is likely. Goggles should be available to protect the eyes from splattering of blood or body fluids. Blood spills should be cleaned up, after donning gloves, with a 1:10 to 1:100 solution of fresh bleach, and good hand hygiene technique should be followed.

Transmission-based precautions are additional barriers needed for patients with certain contagious diseases. For example, masks are also necessary for contact with a patient who has a contagious disease such as tuberculosis, influenza, mumps, measles, chickenpox, or pertussis. The high prevalence of patients carrying unknown infectious diseases such as MDROs, HIV, and hepatitis C underscores the importance of barrier precautions. Items such as gloves, goggles, gowns, and masks should be in the home nursing bag (Fig. 99-1). See Chapter 90 for more information on isolation precautions for patients with communicable diseases.

Waste Disposal

State regulations for medical waste vary considerably and may require the healthcare provider to remove medical waste generated in the home *(74)*. Liquid wastes, such as urine, can be flushed down the toilet, with care being taken to avoid splashing during disposal. Used needles and other sharp objects should be placed in a puncture-resistant container such as a portable sharps container. Other contaminated materials can be placed in a plastic bag that is sealed and discarded in the routine trash disposal system. The Environmental Protection Agency provides information on waste disposal in the home care environment including recycling and disposal options *(75)*.

Employee Health Program

Employee health information for hospital employees is available in the medical literature and in many cases is applicable to the home healthcare professional *(76,77)*. The employee should have updated immunizations, including tetanus, diphtheria, pertussis, measles, mumps, rubella, influenza, and hepatitis B. The varicella immune status should be known. Baseline and periodic tuberculosis skin testing should be performed. Other issues to be addressed include a protocol for postexposure prophylaxis for exposures to blood or body fluids containing HIV and hepatitis B or C *(78)* and recommendations for work restrictions for ill employees (see Chapters 73–76).

Employee education in infection control is an important part of employee protection. A study of home healthcare workers found that most blood exposures could have been prevented by simple glove use *(79)*. Employees need to be educated in Standard Precautions, barrier precautions for specific contagious diseases, and reporting of exposures.

There are significant data on the frequency of percutaneous injuries in home health nurses. In one survey, 14% of registered nurses reported one or more percutaneous injuries in the prior 3 years (80), while several surveys found that only about half of the needlestick exposures were formally reported to their employers (80,*81*). Injuries correlated with lack of compliance with Standard Precautions and use of available personal protective equipment (PPE) such as gloves, masks and gowns *(82)*. The infection control program should monitor employee compliance with preventive measures (e.g., influenza vaccination) as well as employee exposures.

Quality Improvement/Patient Safety

Quality or performance improvement (PI) principles can be applied to home healthcare as well as to healthcare facilities. The Joint Commission has proposed standards for patient safety in home care *(83)* as part of its ORYX initiative. This is an error-reduction program in which data collected are incorporated into PI initiatives. Elements to be studied include infection control, surveillance, and disease reporting. Measurable outcome indicators should

be selected, such as immunization levels, compliance with infection control practices, employee exposures, medication errors *(84)*, or home care–associated infection incidence.

The Centers for Medicare and Medicaid Services (CMS) in collaboration with the Centers for Health Policy Research has developed the Outcome and Assessment Information Set (OASIS) to measure patient outcomes and improve quality in home care. In 2008, a new risk-adjustment model for publicly reporting quality measures was created for home health OASIS, which can be found on the CMS Web site (www.medicare.gov) under Home Health Agencies. The updated OASIS data sets were implemented in 2010, and the user manual is available online (*85*, and see Chapters 10–12). Although case mix adjustments have been included, there have been problems with both ORYX and OASIS data sets regarding standardization of definitions and completeness of data *(86)*.

CMS has used OASIS to collect performance-based quality information. The CMS quality domains are effectiveness, efficiency, equity, patient centeredness, safety, and timeliness *(85)*. Risk adjustment is critical in the process of quality assessment in the home setting *(87)*. PI studies in the home setting have been shown to be feasible (88). Examples of publically reported quality measures include outcome measures (such as improvement in status of surgical wounds and acute care hospitalization) as well as process measures (such as whether pressure ulcer risk assessment was conducted, whether influenza vaccine was administered annually, and whether pneumococcal vaccine was ever administered).

Disease Reporting and Regulatory Compliance

Proper reporting is an important issue to be considered by the home healthcare professional. Home care–associated infections may be initially detected by the visiting home health practitioners and should be reported to patients' physicians for consideration of therapy and to the appropriate hospital or LTCF (if they are institutionally acquired). Contagious diseases (e.g., hepatitis, tuberculosis, impetigo, pertussis, and scabies) are especially important to report, and certain diseases are reportable to the health department. A proper home healthcare medical record should be kept.

The IP needs to be aware of regulatory compliance issues including Medicare, the Joint Commission *(89)*, the Occupational Safety and Health Administration, and state and local regulations that affect home care.

Home Healthcare and Preparedness

The home healthcare industry would be significantly affected by a national or regional disaster. Disaster preparedness involves a number of areas (see Table 99-4), including an internal readiness assessment, development of a disaster plan, and exercising the plan (e.g., in a tabletop simulated disaster drill). Before a disaster occurs, the issues of command and control must be clearly delineated and roles well defined. Reimbursement will depend on concurrent documentation, and communication is vital (e.g., with other healthcare facilities, public health, suppliers).

In any major disaster, hospitals and LTCFs will rapidly exceed capacity; hence, ill patients who normally reside therein may be discharged earlier to home care *(90)*. At the same time, the agency workforce may be depleted due to personnel who are ill, injured, or unwilling to report to work (e.g., in a SARS or influenza pandemic). This may necessitate healthcare personnel performing tasks beyond their normal scope of practice. If the event is an infectious disease, personal protective equipment will need to be provided even if normal supplies are disrupted. Mental health support is also important for healthcare providers during a crisis. Individual home healthcare workers should do some advanced planning in the area of personal preparedness *(91)*.

Preparedness reflects the growth and diversity of the home healthcare role. Home healthcare represents a dynamic equilibrium between the community and healthcare facilities like hospitals and LTCFs.

TABLE 99-4

Points of Consideration for Home Healthcare Preparedness

Hazard vulnerability assessment
Disaster plan development
Plan exercising
Stockpiling supplies and equipment
Reimbursement
Command and control
Communication
Increased patient numbers and acuity
Workforce issues
Scope of practice
Infection control
Mental health support

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance of Elaine Litton, Ashley Christiansen, and Bridget Young, RN, BSN, MBA (Vice President of Operations, Visiting Nurse Association of the Midlands, Omaha, NE).

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CHAPTER 100

Infection Control in Countries with Limited Resources

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Infection control in developing countries that are relatively resource limited is a challenging topic. Rarely do we hear about "road construction in developing countries" or "airplane navigation in developing countries" as there are often basic universal standards that are adopted in all countries regardless of their wealth or affluence in the fields of building construction, road maintenance, and airport safety. Of course, the reality is that the implementation of these standards varies considerably as has been seen with tragic effect in the tremendous death and destruction that have followed natural disasters such as earthquakes in Haiti or Sichuan. These are in contrast with the relatively limited human impact of the higher magnitude earthquake in developed countries with strict building codes and enforcement of regulations. Similarly in the infection prevention and control field, there are those who argue that the standards for infection control for developing countries must be the same as they are for developed countries *(1)*.

While this would appear to be an ideal, the reality is obvious—the gulf in resources is often so great that it would be impossible to expect poor countries to have the same standards in healthcare or building or airports as rich countries. This has been the rationale in the past for avoiding "unattainable targets" and somewhat mirrors the huge debate that is going on in the United States on whether "zero" is an attainable goal for the prevention of healthcare-associated infections (HAIs) (2). Even the opponents of "unrealistic targets" would agree that such goals are ideal. Indeed, a review of process measures and outcomes in central line–associated bloodstream infections (CLABSIs) in US and non-US (including Middle Eastern and Latin American) hospitals showed no significant differences between US hospitals in terms of infection control infrastructure, practices, and CLABSI rates *(3)*. This suggests that given a commitment to improving standards and processes together with adequate resources, there is no reason why healthcare facilities in the "developing" world cannot achieve standards of infection control comparable to the United States. The key issue is thus to ensure that the capacity is built up locally so that these universal standards of infection control can be realistically implemented in stages, if necessary, beginning with the most fundamental.

Often the resources available for healthcare are simply not available at the onset. In many developing countries, healthcare is seen as a lower priority on the national agenda, and even within healthcare, preventing HAIs has a lower priority than preventing infant or maternal mortality, for example, and probably rightly so. In addition, "structural adjustment programs" instituted by international financial authorities have mandated "user fees" and other restrictions on spending on government subsidies for healthcare *(4)*. However, there is light at the end of the tunnel! The recent developments in international relations including the commitment of leading industrialized countries to the Millennium Development Goals, together with the involvements of foundations such as the Gates and Clinton Foundations and programs such as PEPFAR, have put global public health firmly near the top of the international agenda, especially in development circles. Again, while the majority of these goals relate to maternal and child health, it has been recognized that the gains in maternal and child health will be rapidly lost if insufficient attention is paid to the prevention of infections associated with delivery and provision of basic child health services.

Furthermore, the World Health Organization (WHO) has taken the lead in global patient safety with its successive and successful global patient safety challenges (5). The WHO was founded in 1945 together with a number of international bodies including the United Nations out of the embers of the Second World War. It was the successor to the Office International d'Hygiene Publique of the League of Nations that was established primarily to prevent the cross-border transmission of infectious diseases, most notably cholera and plague. The WHO has a distinguished track record, most notably for leading the efforts to eliminate the scourge of smallpox. That was a concerted global effort driven across international and ideological divides—as a result, a disease that once claimed the lives of millions was finally eliminated in 1978. To date, this is the only disease that has ever been eliminated from the face of the earth. It is striking that the last cases of smallpox in history were acquired through laboratory transmission at a university medical facility in Birmingham, United Kingdom *(6)*. This led to marked improvements in biosafety worldwide. In recent years, the WHO has been at the forefront of the battle against emerging infectious

diseases, most notably during the SARS crisis. This was an unprecedented international collaboration that resulted in the rapid identification of a novel emerging pathogen from East Asia and international efforts to prevent its spread *(7)*. Although several agencies were involved in controlling SARS, the WHO was limited by the fact that it was unable to work in Taiwan, one of the affected areas, because Taiwan had been denied representation at the WHO *(8)*. The WHO published guidelines, notably case definitions for epidemiological purposes and issued travel advisories as well as sent experts to the affected areas through its Global Alert and Outbreak Response Network. These all contributed significantly to what was essentially an infection control response to an emerging pathogen and also raised the credibility and status of the WHO.

One of the other legacies of the SARS response was the strengthening of the International Health Regulations (IHRs) in 2005. The amendments were made to the regulations because of the recognition that failure to recognize, document, and at least attempt to control an emerging infectious disease outbreak in one part of the globe would have international consequences. The revised IHRs were adopted at the World Health Assembly in 2005 to "prevent, protect against, control and provide a public health response to the international spread of disease." Details of the revised IHR are available online at http://www.who.int/ihr/en/.

The WHO published its core components for infection prevention, and control programs earlier this year (9). These are the critical elements that have to be incorporated into *all* countries' national and local healthcare authorities. This forms a practical framework by which infection prevention and control programs can be structured in developing and developed countries. A summary of the core components is given in Table 100-1. We believe that a stepwise approach to infection control in low-income countries beginning with the basic elements covered by the core components should be part of every country's national health program.

The rest of this chapter is organized according to the WHO core components.

FORMAL ORGANIZED STRUCTURE

At the national level, this should include a national authority with qualified staff, a budget, and defined functions. This authority should also be tasked with ensuring preparedness and coordination of infection control and prevention activities for communicable diseases. At the local hospital level, each hospital should have dedicated leadership and authority for infection and control programs.

The ministries of health of most countries are concerned with many issues including maternal and child health; regulation and provision of primary, secondary, and tertiary healthcare; and often the training of physicians, nurses, and allied healthcare professionals. Few countries in the developing world have national infection control bodies similar to the different agencies operating within the U.S. Centers for Diseases Control and Prevention (CDC), for example. However, with the advent of the IHR, all countries are required to have some system in place for monitoring, detection, and reporting of outbreaks of international health significance. Some countries such as Egypt have established an infection control program within the Ministry of Health and Population *(10)*.

The Egyptian experience is very instructive. The national infection control program was developed in response to widespread outbreaks of blood-borne pathogens that were widely reported in both scientific and lay media. These included some of the world's highest rates of hepatitis C as an indirect result of widespread campaigns for population-based eradication of schistosomiasis *(11)* and outbreaks of HIV infection associated with dialysis centers *(12,13)*. There was the recognition by national health authorities that something had to be done to control the spread of infections in both private and public healthcare institutions. In addition to these highly publicized outbreaks of blood-borne pathogens, there were scientific studies documenting a high prevalence of HAIs in Egypt *(14)*, as well as antibiotic-resistant infections, in particular, those caused by extended-spectrum beta-lactamase–producing gram-negative bacilli (15).

This led to the formation of a working group that included the U.S. Naval Medical Research Unit, the WHO, several Egyptian universities, medical schools, professional bodies, and nongovernmental organizations. This eventually led to the creation of a department within the Ministry of Health and Population and the publication of national guidelines, establishment of training programs, promotion of infection control advocacy, and institution of regulatory measures to ensure attention to critical supplies and occupational health (15).

With a number of variations, the same thing has happened in many other countries in Asia, Africa, and Central and South America. A crisis occurs—most memorably, the SARS and avian influenza outbreaks resulting in huge amounts of media attention, much of it critical. This has led to major changes in most of the affected countries both at the central and the local hospital level to prepare for emerging infectious diseases including healthcare-associated respiratory viral infections *(16)*. In many of these countries, the national health authorities have become much more sensitized to infection control, especially to novel emerging pathogens. This was played out during the recent influenza A H1N1 2009 pandemic when many of the SARS-affected countries reacted very strongly to the new influenza *(17)*.

While these highly publicized outbreaks followed by strong public health–driven responses can provide a boost for infection control efforts in a country, it is the follow-up after the initial burst of attention that is the most challenging. The situation in Egypt was aided by international collaborations as well as strong participation by local experts. This is likely to be a sustainable approach in many middle-income countries as well as those with strong international collaborations or with well-developed domestic medical expertise such as India or the Philippines. The challenge is greatest in the least developed countries where medical resources are extremely limited, especially in those countries that are currently beset by civil war where even the provision of basic healthcare is severely constrained. Paradoxically, those are the settings with the greatest needs for infection control.

TABLE 100-1

Essential Requirements for Infection Control for ALL Countries Based on the World Health Organization's Core Components

(a) Infection control infrastructure
- Ministry of Health section dedicated to infection control
- Each healthcare facility should have a designated infection control officer
- A multidisciplinary infection control team should be constituted in each healthcare facility and should be recognized for its work
- There should be integration between the local infection control team, infection control officer, and national and international agencies

(b) Technical guidelines
- National Infection Control Guidelines, which can be adapted from WHO regional office guidelines
- Written Hospital Infection Control Policy, which can be an adaptation of national guidelines

(c) Trained healthcare workers
- There should be access to training either locally or through international or regional agencies for infection prevention and control staff
- Healthcare worker protection needs to be a priority specifically addressing blood-borne pathogens and healthcare-associated respiratory infections including tuberculosis and respiratory viruses
- A concerted effort should be undertaken to reduce injections and ensure that sharps are safely disposed

(d) Surveillance
- There should be some kind of surveillance system in place for healthcare-associated infections. At its most rudimentary, this can be surveillance for in-hospital mortality or readmissions or returns to the operating room for infection
- Surveillance should make use of what technology is available including mobile phone technology
- Checklists should be implemented to reduce the incidence of surgical site infections
- Closed urinary catheter drainage should be used with improvisation, if necessary, to ensure closed drainage
- A system of reminders possibly nurse based should be used to reduce the utilization of devices including urinary catheters
- Sedation protocols and education on aseptic technique are important for all facilities that mechanically ventilate patients
- Oral rehydration should be encouraged as much as possible to reduce the use of vascular access devices including peripheral intravenous catheters
- Bundles should be considered in attempts to reduce the incidence of central line–associated bloodstream infection

(e) Microbiology laboratory
- All healthcare facilities should have access to a microbiology laboratory
- The laboratory should make use of software such as WHONET to generate local antibiograms
- These surveillance data should preferably be aggregated at a national level to monitor the emergence of novel and resistant pathogens
- External quality assurance whether national or international should be considered for all microbiology laboratories

(f) Environment
- Healthcare facilities should ensure clean and safe water for clinical use
- Adequate ventilation should be provided for healthcare facilities using natural cross-ventilation if appropriate
- Locally produced, alcohol-based handrubs can be used effectively even in settings without running water

(g) Monitoring and evaluation of programs
- Infection prevention and control programs should be monitored on a regular basis, both internally and externally

(h) Links with public health and other services
- Procedures have to be in place to ensure adequate linkages with ministries of health and agriculture and other appropriate agencies in preparation for pandemic or epidemic infections
- Adequate waste management procedures need to be in place including incineration of medical waste
- Sterilization and disinfection need to be adequately monitored

This need in the least developed countries is best illustrated by the cholera outbreak in Goma a decade ago. During the Rwandan genocide, thousands of refugees fled their homes and were assembled in refugee camps, most notably in Goma, eastern Zaire (now the Democratic Republic of the Congo). The camps in Goma were affected by a devastating outbreak of cholera that claimed more than 10,000 lives *(18)*. Case fatality rates were as high as 48% on a single day, while the pandemic cholera in the neighboring country of Burundi had a case fatality rate of 6% to 1% *(19)*. While the majority of the deaths in Goma were ascribed to problems with the clinical management of individual cases of cholera, it is quite likely that failures in infection control led to an exacerbation of an already difficult situation in the camps.

In "peacetime" as well as in disasters, in many of these countries with very limited resources, basic healthcare is often provided either by traditional healers or

by international aid organizations. In the absence of a well-functioning national health authority, it is critical therefore that the international organizations that provide disaster or emergency relief have well-established infection control guidelines and policies that can be transferred to the local situation and even perhaps transmitted to traditional healers. This has been well recognized for outbreaks of viral hemorrhagic fevers—Ebola and Marburg—but should perhaps be part of the standard operating practice for all international aid organizations providing emergency and disaster assistance. The renowned international aid organization Medicins Sans Frontiers (MSF) was involved in the response to the Marburg virus outbreak in Angola in 2005 *(20)*. When the first few cases were recognized by the doctors in Uige, Angola, in March 2005, an international response was coordinated by the Angolan Ministry of Health and the WHO. MSF helped to establish an isolation facility—a Marburg ward—to ensure the isolation of patients with viral hemorrhagic fever and to ensure that those patients received some care. The ward was eventually handed over to the local authorities in June 2005, and the outbreak officially ended in July 2005. In the process, 18 healthcare workers (HCWs) died from Marburg hemorrhagic fever. There were many challenges in the MSF response to that outbreak including attempting to alter existing protocols, providing psychological support and providing supportive care for patients infected with viral hemorrhagic fevers.

While traditional healers have been recruited for the control of sexually transmitted infections and HIV/AIDS *(21)* to our knowledge, there are limited efforts to engage traditional healers in the practice of infection control. There is evidence that many people in developing countries would seek traditional healers before "Western" medicine for symptoms that might be related to contagious respiratory illnesses such as tuberculosis (TB) *(22)*. It does make sense that national health authorities are trusted and consulted far more often than modern medical facilities in the overall infection control program. The specifics of how to go about doing this are a challenge and remain to be worked out.

In between these extremes of deadly viral hemorrhagic fevers in remote hospitals, and middle-income countries with the potential to develop mini-CDCs, the majority of limited healthcare resource facilities have the potential to develop a national infection control authority that can establish at least some kind of reporting system for hospital mortality, ensure that there is a national plan for preparedness for diseases of international health significance as defined by the WHO's IHR, and have trained individuals who can enforce these plans. International agencies that provide assistance to these countries have the opportunity to assist in the development of these national authorities by providing training and short attachments with their own national infection control agencies that can be invaluable to developing country leaders in infection control.

At the local hospital or healthcare facility level, each hospital needs at least an infection control officer or a senior clinician, a laboratorian, or an administrator who reports to the chief of the facility who has at least 50% of his or her time devoted to infection control and prevention. Although the WHO document does not specify the specific fraction of time that needs to be dedicated to infection control and prevention, there are data from the SENIC study that show that hospitals with a dedicated healthcare epidemiologist have a reduced risk of HAI *(23)*.

In reality, most hospitals in developing countries, and many hospitals in developed countries, especially in rural or inner city settings, do not have a full-time healthcare epidemiologist. In countries where regulatory requirements mandate the designation of a healthcare epidemiologist or "infection control doctor," often, the person so designated does not have the required training or expertise. In the best of cases, the hospital microbiologist is designated as the infection control officer. In hospitals without a full-time microbiologist, often some other clinician—an internist, an intensive care unit (ICU) doctor, or a senior nurse clinician—is assigned the responsibility.

This is an opportunity for international agencies and professional scientific societies to provide training to HCWs from developing countries who have an interest in infection control so that they can take on the role of the infection control officer and lead an infection control team (ICT) at their own local healthcare facility.

In Brazil *(24)*, the Brazilian Ministry of Health mandated the establishment of hospital infection control committees in 1983, but the impact was limited. Subsequently, two other decrees were issued that led to the introduction of hospital infection control services with mandated staffing levels and independence. Physicians assigned to infection control are to be paid for 4 hours daily, while nurses are paid for 6 hours daily. Over the years, the structure and organization of infection control have evolved in Brazil, so that in many centers, interventions have been practiced that have a marked impact on patient care *(25)*.

The minimum that every developing country should have in terms of infection control infrastructure are as follows:

a. In the absence of a national infection control authority, a designated section of the Ministry of Health responsible for infection prevention and control.
b. At the local hospital, each hospital should have a significantly senior physician or administrator designated as the infection control officer for the hospital, who is empowered to take action for infection prevention and control activities.
c. Each healthcare facility should have an ICT made up of nurses, physicians, laboratory staff, and those with the expertise required for effective infection control and prevention activities.
d. It would be good to integrate the activities of the ICTs and authorities with international bodies including aid agencies and local medical facilities including traditional healers.

TECHNICAL GUIDELINES

Technical guidelines should be developed and disseminated at the national level for prevention and control of infections.

As mentioned above, national infection control guidelines have been developed and published in many developing

countries such as Egypt (15) and Brazil *(24)*. While countries might not have their own local infection control guidelines, regional bodies, such as the regional offices of the WHO, have issued guidelines primarily aimed at novel influenza. For example, the Western Pacific and Southeast Asian regional offices (WIPRO and SEARO) have published guidelines that are freely available online at http://www.wpro.who.int/NR/rdonlyres/006EF250-6B11-42B4-BA17-C98D413BE8B8/0/practical_guidelines_infection_control.pdf.

These guidelines were written mainly in response to the SARS epidemic when it became apparent that many countries in the Southeast Asian and Western Pacific region did not have much of the essential infrastructure that has been taken for granted in many developed countries (26). These guidelines are appropriately entitled "Practical Guidelines for Infection Control in Healthcare Facilities" and cover the whole range of infection control activities ranging from establishing an infection control program, the recommended structure and accountability for the infection control program to practical issues such as Standard Precautions, transmission-based precautions, environmental management including air and water, waste management, reuse of devices, disinfection and sterilization, care of HCWs, and special situations such as SARS, multiresistant microorganisms, and viral hemorrhagic fevers. These guidelines bearing the imprimatur of the WHO are accessible to countries in the region and can form the basis for national infection control guidelines.

These guidelines were published in 2004 and did not cover avian or pandemic influenza. The avian influenza zoonotic pandemic began to cause a great deal of concern in 2005 to 2006, and as a result, new guidelines were published to cover infection control for avian influenza and pandemic influenza. These guidelines were updated and, interestingly enough, had differences with the US CDC guidelines that were published around the same time. The differences between the US CDC guideline and the WHO guideline probably reflect the limited resources available to most WHO member countries. In particular, the US CDC recommended N95 respirators for all patients with pandemic influenza, while the WHO guidelines, from the beginning, recommended surgical masks.

At the local hospital level, the WHO core components include a recommendation that each hospital or healthcare facility draw up its own infection control policy (9). Most of these can be devised by adapting the WHO practical infection control guidelines, but other guidelines are available from international organizations such as the International Federation for Infection Control (IFIC; available at http://www.theific.org/) and the Asia Pacific Society for Infection Control (APSIC), among others. Many developing countries in Asia have developed their own local guidelines, some of which are shown in Figure 100-1.

These infection control policies should be published locally in the form of infection control manuals. These manuals can be taken off templates using the WHO, IFIC, or APSIC guidelines and then adapted to local conditions with details such as the contact person for sharps injuries, specifics about waste disposal, and other details added in to make the manuals useful for staff in the local healthcare facility. An example of this is the Infection Control Manual

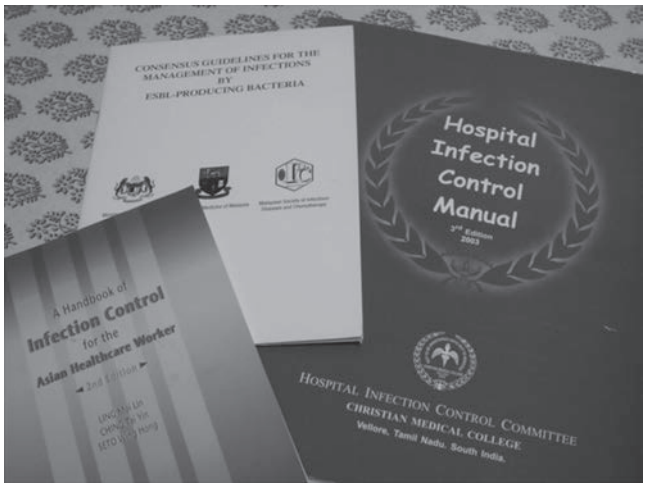

FIGURE 100-1 Infection control guidelines published at the local, national and regional level in Asia.

produced by the Christian Medical College in Vellore, India. This has been produced locally at a tertiary hospital in a rural setting in India and is widely disseminated in India through training programs conducted by faculty of the Christian Medical College, Vellore, in collaboration with international organizations such as the Society for Healthcare Epidemiology of America.

Many hospitals, especially in the middle-income countries in Asia, have sought accreditation from international bodies such as the Joint Commission International (JCI). The JCI has highlighted infection prevention and control as one of the key areas in its accreditation process. JCI-accredited hospitals can be found in Bangladesh, Brazil, Egypt, Indonesia, Jordan, the Kingdom of Saudi Arabia, Malaysia, Mexico, Thailand, Turkey, Vietnam, and Yemen, to name a few of the countries where healthcare facilities have met the criteria for JCI accreditation. This perhaps illustrates some of the issues with intracountry differences in the quality of healthcare delivery as some of these countries also have predominantly rural areas with very limited resources for healthcare and little in the way of infection control practices. At the same time, the presence of internationally accredited institutions in many developing countries provides a living demonstration of what can be achieved outside of Europe, Australasia, and North America. Many HCWs or their families will go to these facilities for their own healthcare. They experience the impact of international best practices without having to travel to some remote high-tech international location, but rather in their own country. The impact of JCI accreditation with improvements in medical technology in these hospitals will surely be felt over time. The diffusion of infection control standards thus could potentially be aided by good practices within centers of excellence, private or public in these developing countries.

Accreditation does not need to be done by an international agency. In the middle-income countries with established cores of well-trained individuals, accreditation by a credible government or non-governmental body can help to raise standards in infection control and

patient safety. This has been noted in the Lebanon *(27)*. In countries with even more limited resources, assistance from international aid agencies can be tapped to provide hospital accreditation standards to cover infection control practices in both urban and rural healthcare facilities. An example of this is in Uganda *(28)*, where assistance from USAID helped establish the Yellow Star hospital accreditation project in 2000. Although the project was not funded from 2005 onward, there remained a strong desire among leaders of local Ugandan healthcare facilities for an accreditation program for hospitals that encompassed infection control protocols, patient safety, and various infrastructure standards.

There is clearly a demand from the citizens of low-resourced countries for quality healthcare delivered locally at affordable prices. Governments and healthcare providers will need to respond to this demand, and accreditation of infection control programs will be a critical element in this drive.

At a minimum, each developing country should have the following:

a. National guidelines on infection control—these can be simple adaptations of the WHO practical guidelines for infection control.
b. Each healthcare facility should have its own infection control policy—these policies can be based on international guidelines from organizations such as the WHO, IFIC, and APSIC and need to be locally adapted. These policies need to be available to staff and disseminated as widely as possible.

HUMAN RESOURCES

At the national level, there should be standards for adequate staffing of infection preventionists and protocols or opportunities for training of HCWs in infection control.

International medical and nursing education has developed a great deal in recent years. There has been a proliferation of medical and nursing schools, and many of these in Asia, Africa, and Latin America have been established in collaboration with major teaching institutions from Europe, North America, and Australia. While the tertiary education sector is a major site for training of medical and nursing professionals in infection control, continuing education and outreach efforts into primary care settings are critical, because this is where the bulk of healthcare is delivered.

Countries need to establish national standards for training for infection preventionists. This has not been universally done in developed countries, but opportunities abound for developing countries, in particular middle-income developing countries that have partnerships and educational collaborations with developed countries.

Many countries do not have specialized training for infection control nurses or physicians. There are courses available, although these are primarily provided by professional societies such as the Society for Healthcare Epidemiology in America, the Hospital Infection Society, and the Association for Professionals in Infection Control and Epidemiology. Some universities provide postgraduate diplomas or degrees with a focus on infection control, but these are very limited. The experience of South Korea is instructive. Although Korea is not a limited-resource country, there are lessons to be learned from the experience there. In 1992, the Ministry of Health and Welfare in Korea mandated that every hospital with more than 80 beds needed to have an infection control committee. In 2003, a graduate specialist training program for nurses with a specialization in infection control was introduced *(29)*. This has raised the professionalism of infection preventionists and has raised the salaries and status of infection control nurse professionals.

In addition to training and providing the human resources to staff infection control programs, HCW safety is a critical issue in developing countries. HCWs in developing countries are exposed to infectious risks at least an order of magnitude higher than HCWs in developed countries.

Blood-Borne Pathogens

The rates of HIV, hepatitis B, and hepatitis C are much higher in many developing countries compared with developed countries. For example, the rates of hepatitis B in China can be as high as 7% to 9% *(30)*, and in West Africa, hospitalized patients have a hepatitis B seropositivity rate of 15% to 20% *(31)*. Many countries do not have national vaccination programs for hepatitis B vaccination *(32–34)*. This is critical. Hepatitis B vaccination has been shown to be highly effective in prevention of hepatitis and its complications. HCWs worldwide have a higher rate of death from hepatitis and its complications—this was noted in developed countries before the onset of Universal Precautions and hepatitis B vaccination. Efforts are under way to increase the hepatitis B vaccination rates for healthcare providers in developing countries. A recent study conducted in Uganda *(35)* found a hepatitis B vaccination rate of only 6%. Nearly half of all HCWs in that Ugandan tertiary hospital were still susceptible to hepatitis B. Volunteers or those who are going to provide healthcare in mission or relief efforts must be aware of the hepatitis risks and should make sure that they are up to date with hepatitis B vaccination.

HIV rates are very high in many developing countries, especially in sub-Saharan Africa. There is evidence that there are high levels of ongoing healthcare-associated transmission of HIV in healthcare facilities in these settings *(36)*. Postexposure prophylaxis for HCWs who sustain sharps injuries in these settings are not often routinely available. This has to be a high priority for any infection control program. Medical students and HCWs from developed countries who travel to areas with a high endemicity of HIV have been known to take along their own supply of postexposure prophylaxis for HIV *(37)*. This raises a number of ethical questions as the local staff are exposed obviously for far longer to greater risks. Other issues that have arisen are the high rates of resistance to antiretrovirals that have been documented in some developed country settings and, more alarmingly, the absence of resistance testing in the vast majority of resource poor settings. If an HCW sustains a sharps injury from a patient with a high viral load of HIV with a resistant virus, the postexposure prophylaxis regime is likely to be far more complicated than most protocols currently extant in developing countries.

It is also more likely to require salvage therapies that might not be available in that country.

Hepatitis C is also endemic in many developing countries. Paradoxically, a large part of this endemicity is due to unsafe injection practices in the first place. Often, this is the unintended consequence of well-intentioned public health programs such as the schistosomiasis eradication program in Egypt *(38)*. Testing for hepatitis C is not widely available although ELISA testing for blood safety has increased the prevalence of hepatitis C testing markedly in many resource poor settings. There may be limited facilities for follow-up of HCWs who sustain sharps injuries from patients who are hepatitis C positive. While hepatitis C treatment is now routine in most developed countries, many developing countries lack access to the expensive agents used to treat hepatitis C and the notion of preemptive therapy as recommended in some centers is thus even more remote.

Other blood-borne pathogens are even more lethal—most notably the viral hemorrhagic fevers—Ebola and Marburg, which have claimed the lives of large numbers of HCWs *(39)*. Other viruses that have had documented transmissions and are endemic in the tropics include dengue fever *(40)*.

Sharps injuries in the developed world have been markedly reduced by the use of safety devices including needleless access devices, blood-drawing equipment with retractable needles, and other safety devices *(41)*. Many of these devices are not available in resource poor settings and HCWs need to take extra precautions to ensure that they do not sustain these injuries. Some simple interventions that can reduce sharps injuries in developing countries include the provision of adequate lighting during procedures; the use of simple, safe sharps disposal containers (Fig. 100-2); destruction of sharps to prevent their reuse; use of containers to transfer sharps in the operating room rather than passing instruments; and training staff to ensure that at least one-handed recapping is done if the process of two-handed recapping cannot be eliminated altogether.

In addition to the issue of patient-to-provider transmission of infection, the other concern about provider-to-patient transmission becomes particularly acute in settings with a high endemicity of blood-borne pathogens. In some Asian countries, for example, students are barred from medical school if they are found to be hepatitis B surface antigen positive *(42)*. This potentially acts as a powerful disincentive for HCWs to disclose their status and poses potential risks to patients and the HCWs themselves as they might not be adequately treated for their own infections. There have been very few reports of provider-to-patient transmission of blood-borne pathogens from developing countries despite the much higher seroprevalence. This is most likely a result of lack of investigation or detection of these outbreaks. There have been a couple of tragic outbreaks of HIV disease that have led to litigation where HCWs have been blamed for transmission of HIV to patients in Libya *(43)* and Kazakhstan (44). None has been completely explained, but these cases have caused a considerable amount of distress among HCWs in general and may contribute to increased stigmatization among HCWs looking after patients with HIV/AIDS.

The risks of blood-borne pathogens are very real, and even if the estimates that have been reported are on the high side, there are potentially hundreds of HCWs who are infected with HIV in developing countries every year. In these settings with intense stigma and discrimination, the pressure on these HCWs can be tremendous. There is already an exodus of HCWs from developing countries to the North *(45)*, and the fear of blood-borne pathogens can only act as another push factor. Ganczak et al. *(46)* made use of the Haddon matrix to identify the risk factors for sharps injuries in the United Arab Emirates and observed pre-event factors including lack of training, event-related factors such as failure to use safety equipment, and post-event factors such as underreporting.

In developed countries, the incidence of healthcare-associated HIV transmission has declined significantly with the advent of safer devices and widespread training, education, and use of postexposure prophylaxis *(47,48)*. It is hoped that well-designed prevention programs can help to reduce the risk of transmission of blood-borne pathogens to HCWs and patients in developing countries. The basics of these programs include the following:

a. Reducing injections—where possible, oral rehydration and oral medications should be used instead of the ubiquitous injections that are routinely given in many healthcare facilities in developing countries.
b. Ensuring safe disposal of sharps—solid sharps boxes should be available wherever sharps are used. These boxes should be promptly incinerated to reduce the opportunity for recycling of needles.
c. Use disposable gloves wherever possible for procedures involving sharps.
d. Practice no-touch transfers in operating rooms—by using containers rather than passing instruments from staff to staff.
e. Ensure that multidose vials are not used for multiple patients or, if they must be used, that fresh needles are used for each patient.
f. Ensure adequate lighting and infrastructure so that sharps are used in a safe manner.
g. Ensure that all healthcare personnel, who are not immune, are vaccinated against hepatitis B.

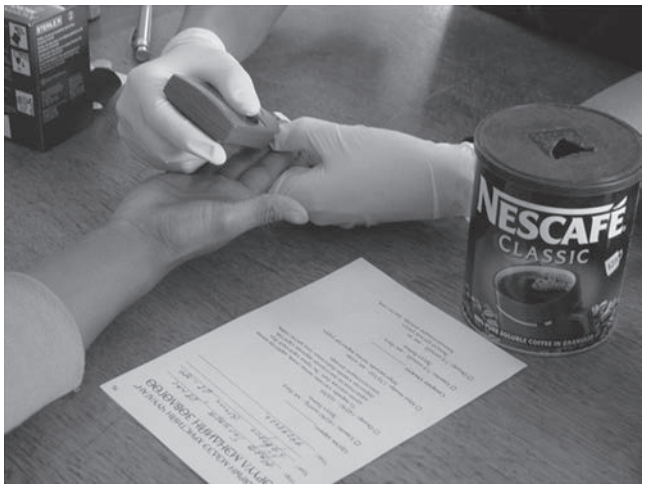

FIGURE 100-2 An improvised sharps box in East Asia.

Many of these recommendations are contained in the WHO document on reduction of blood-borne viral transmission in healthcare settings, which is available online at http://www.who.int/injection_safety/toolbox/docs/en/AM_HCW_Safety.pdf.

In addition to blood-borne pathogens, there are obvious concerns about respiratory pathogens. Here the literature is a little less clear. TB is the main disease that causes concern in Europe and North America, but there are also concerns about emerging respiratory viral pathogens. TB is endemic with very high rates of infection throughout the developing world. There have been documented healthcare-associated transmissions of TB with fatalities associated with drug-resistant TB *(49)*.

Interestingly, the majority of these outbreaks have occurred in the developed world—primarily in the United States. This is most certainly due to increased detection and recognition. There has been a recent review of extremely drug-resistant TB from South Africa, where 10 of 334 patients with extremely drug-resistant TB were found to be HCWs *(50)*. Eight of the ten were HIV-negative, and four of the ten died, despite treatment, probably because of delayed diagnosis. There are limited studies conducted in Malaysia *(51)* and documenting high rates of skin test conversion in HCWs in developing countries. Even in Singapore, which is not a developing country, interns working in public hospitals have an annual 5% conversion rate using interferon γ release assays to detect tuberculous infection *(52)*. On the other hand, there are data from Hong Kong that suggest HCWs have a lower TB rate than the general public (53). The argument made was that HCWs have a higher standard of living than the general public and that in turn might be associated with a lower rate of clinical TB.

In the United States, a hierarchy of controls including administrative controls, engineering controls, and personal protective equipment are used for protection against healthcare-associated transmission of TB to HCWs. Isolation in airborne isolation rooms with negative pressure is recommended *(54)*. These were almost nonexistent in most developing countries prior to the SARS and the avian influenza epidemics. With the emergence of these high-mortality infections with actual (SARS) and potential (avian influenza) healthcare-associated transmission, some facilities have been created in many developing countries (Fig. 100-3) *(55)*. While these facilities are unattainable in most low-resource countries, there are encouraging data that have come out showing that cross-ventilation especially in the older hospitals can be associated with higher air exchanges that can be achieved in many negative pressure rooms *(56)*. These air exchanges are also protective and using an animal model, the rates of TB transmission from patients with active cavitary disease are markedly lower in these rooms with good cross-ventilation, open windows, high ceilings, and ceiling fans. This was probably recognized a century ago in the design of older hospitals, many of which were situated on hills when TB was the major cause of death worldwide. It is reasonable to revive those ideas even as TB continues to plague many parts of the world and the specter of multidrug and extremely drug-resistant TB hangs over the world.

Disposable masks and N-95 respirators are not widely used in developing countries; however, cloth masks have been used for many years. These have been shown to be effective against pneumonic plague during the outbreaks of plague in Manchuria in the early part of the 20th century *(57)*. During the SARS crisis, in China, the 12-ply cloth mask was used primarily in most of the SARS wards and hospitals, and this successfully protected staff from contracting SARS *(58)*.

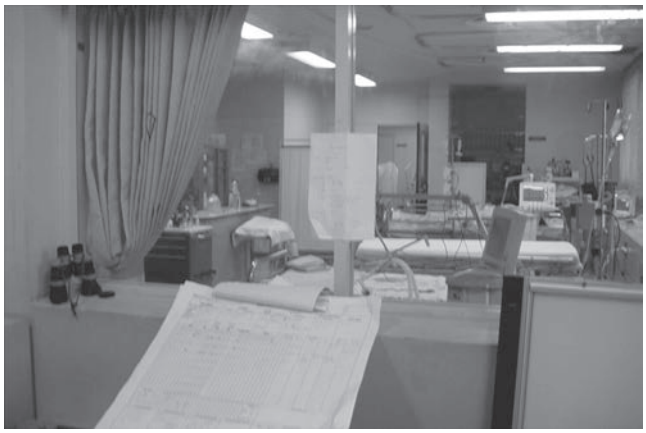

FIGURE 100-3 Negative pressure ICU in Southeast Asia.

In addition to TB, in recent years, there has been a much greater attention to influenza. Guidelines have been issued by both the WHO through its regional offices (WIPRO and SEARO) and many international governments in the developed and developing world. These are available online at http://www.searo.who.int/en/Section10/Section1027/Section1943.htm and http://www.who.int/csr/resources/publications/swineflu/en/.

While these guidelines focused mainly on pandemic and avian influenza, they have been carefully crafted to be applicable to all the member states of the WHO. These form a very useful base for infection control precautions both for endemic respiratory illnesses and for emerging and novel pathogens. The core elements of these are as follows:

a. Standard Precautions with an emphasis on hand hygiene and appropriate use of personal protective equipment and handling of samples, waste, and environmental surfaces.
b. Respiratory hygiene or cough etiquette.
c. Identification of potentially infectious cases. For novel pathogens, this would depend on broad clinical case criteria for the symptomatic and an even lower threshold for evaluation and observation for those who are contacts of confirmed or probable cases.
d. Patients who have confirmed or probable novel or avian influenza should be in well-ventilated single rooms or cohorted.
e. HCWs in developing countries should be at high priority for influenza vaccination when it becomes available, especially in situations with novel or pandemic viruses.

In summary, all developing countries need to have trained individuals who can conduct infection prevention and control programs. In addition, they need to ensure protection for staff from the following:

a. Blood-borne viruses: using vaccination for hepatitis B, reduced use and safe handling of sharps, and procedures for injury reporting, postexposure prophylaxis, and follow-up

b. Respiratory diseases: using adequate ventilation, administrative controls, appropriate personal protective equipment, and ventilation.

SURVEILLANCE

Surveillance should be standardized at the national level as far as possible with standardized case definitions and surveillance methods. At the local level, surveillance should include assessment of the local situation, selection of appropriate methods, and reporting.

Surveillance is an essential component of infection control programs worldwide. The objectives are to establish endemic baseline rates of HAI and to identify outbreaks and evaluate the effectiveness of IC prevention activities. Surveillance data can be used to identify preventable infections in high-risk areas, to help limited resources be more effectively targeted to high priority areas, for example, surgical site infections (SSIs) or ICU-acquired infections. Alert microorganism surveillance can be done if there is a good microbiology laboratory and support from the clinicians and senior management *(59)*. In developing countries with limited resources, the ICT can carry out basic surveillance to identify key issues and areas of concern. The simplest forms of surveillance that can be done at most hospitals and healthcare facilities in developing countries include mortality or readmission rates per surgical procedure or per ICU admission. Most healthcare facilities would at least track admissions and discharges for billing and state support purposes. These data can be mined to track trends in mortality, which act as a very crude measure of quality in institutions. This simple measure has not been widely practiced although a spike in hospital deaths is clearly something that administrators in developing countries would be very concerned about. If the ICT makes use of its expertise in healthcare epidemiology to conduct mortality surveillance for patients admitted to the ICUs, then this would be additional evidence of the value of an ICT to the healthcare facility in the developing country.

There have been a number of reports in both local and international media about deaths from complications of surgery in developing countries, and these have had a detrimental effect on allopathic healthcare in those countries. Similarly, there have been reports of SSIs in patients who travel to developing countries as medical tourists *(60,61)*. These highly publicized incidents involving medical tourists can only help to prompt the local authorities in developing countries to improve the safety of surgical procedures in their country.

Surgical site surveillance in developing countries can be done by a variety of methods as in developed countries. The sheer volume of workload handled by most surgical teams in these countries would probably preclude self-reporting by the surgical teams. In addition, even in many developing countries, the pressure on hospital beds has led to similar moves toward same-day surgery, which have occurred in the developed world. This has created problems in terms of postdischarge surveillance. These problems are even more acute as many individuals travel for long distances often over days to reach tertiary and secondary health facilities where they get their surgical procedures done. This makes it very difficult to track SSIs in patients from remote areas.

The WHO's second global patient safety challenge has been directed at safe surgery. This is a strategy aimed at all the WHO member states, the majority of which are low-resource countries. The key element in the strategy is the use of checklists. These incorporate elements including confirming the right site, right patient, equipment, and appropriate prophylactic antibiotics. This is freely available online at http://www.who.int/patientsafety/safesurgery/en/index.html. The WHO global patient safety challenge has been adopted by 300 institutions on five continents. Checklists have been shown in a variety of settings, including very resource limited ones to have a significant impact on clinical outcomes (62). This 19-point checklist, which was used in countries as diverse as India, Tanzania, England, Canada, and Jordan, was shown to significantly improve the timing of antimicrobial prophylaxis from 56% correct to 83% correct. The overall complication rate was reduced from 12% to 7% in the low-income sites and the mortality rate from surgical complications from 2.1% to 1% in those settings.

Periodic point prevalence surveillance can be used to monitor the effectiveness of infection control measures. These have been used previously in many countries using standardized methodologies that can be web based for ease of use.

In Iran, a series of point prevalence studies on bloodstream infections, urinary tract infections (UTIs), and SSIs were performed, revealing important data on the distribution of HAIs and providing a baseline for improvement programs *(63)*. Similar efforts have been undertaken in Saudi Arabia *(64)* and Malaysia *(65)*. The Malaysian study, in addition to detecting HAIs, also did an assessment of antimicrobial use.

In order for a point prevalence survey to be useful, it is critical that the staff members involved are trained and that the definitions and protocols are standardized. Many institutions use the US CDC's National Health and Safety Network (NHSN) definitions *(66)* as these are the most widely disseminated and are readily available. The concern is that on occasions, the interpretation and application of these definitions is not easy. For limited-resource countries that are planning on point prevalence surveys, it is critical to ensure that the surveyors are trained and tested. In addition, pilot surveys need to be conducted to validate the procedures and protocols. It would also be good for the results of the pilot surveys to be communicated to the clinical leaders in the relevant wards and facilities. This is very important as feedback can be provided to identify gaps that the surveyors might not be able to appreciate. The Internet can be used if hospitals and healthcare facilities across a country are conducting the point prevalence survey at the same time. This has been used successfully, for example, in the Pan EuroAsian Prevalence study of infections in urology *(67)*. A simple web-based data entry format is used for urology patients across the globe to assess community- and healthcare-associated UTIs. This global web-based effort in UTIs has continued to expand.

In many limited-resource settings, Internet access might be patchy and this might be a limitation for web-based surveillance systems. However, mobile phone networks have

a far greater penetration rate, and in many developing countries, mobile phones are used to communicate public health messages. It is possible that these might be used in the near future for surveillance of HAIs. In Sri Lanka *(68)*, field veterinarians used mobile phones to interact with central animal health surveillance authorities who received a marked increase in surveillance reports and detection of a possible outbreak in animals. In China, following the Sichuan earthquake, more than half of the infectious diseases reported to the local health authorities were reported by mobile phone *(69)*.

Mobile phone technology has probably even greater potential for national surveillance of HAI than for surveillance of HAIs in rural health as most healthcare facilities in developing countries are located in areas with reasonable mobile phone coverage.

In addition to doing surveillance for important outcomes such as SSI, length of stay, and mortality, it is also important that the ICT devote time to regular audits (process surveillance). Audits are usually simple to perform and are less resource intensive than outcome surveillance. They will help the ICT to identify inappropriate and unsafe infection control practices immediately. In addition, they will help the ICT to identify wasteful practices and help divert resources to implement evidence-based and cost-effective practices *(59)*.

There are surveillance protocols in existence in low-resource countries, most notably the International Nosocomial Infection Control Consortium (INICC). The INICC is the first multinational, collaborative HAI control program with a surveillance system based on that of the US NHSN, established to control HAIs in hospitals in limited-resource countries *(70)*. It was founded in Argentina in 1998, expanding to a network of 173 ICUs in 25 countries (*70*,71).

The INICC aims to create a global network of hospitals in the developing world that conducts surveillance of HAIs using standardized definitions and established methodologies; as a result, they hope to promote implementation of evidence-based infection control practices. The INICC also hopes to carry out applied infection control research; provide training and surveillance tools to individual hospitals that can allow them to conduct outcome and process surveillance of HAIs, measure their consequences, and assess the impact of infection control practices; and improve the safety and quality of healthcare worldwide through implementation of systematized programs to reduce rates of HAI, associated mortality, excess lengths of stay, excess costs, and bacterial resistance. The INICC published a surveillance study from 2003 through 2008 in 173 ICUs in Latin America, Asia, Africa, and Europe *(72)*. During the 6-year study, prospective data were collected from 155,358 patients hospitalized in the consortium's hospital ICUs for an aggregate of 923,624 days. Although device utilization in the developing countries' ICUs was remarkably similar to that reported from the United States in the CDC's NHSN; however, when standard definitions and accurate case finding were used, rates of device-associated HAIs were markedly higher in the ICUs of the INICC hospitals: the pooled rate of CLABSIs in the INICC ICUs, 7.6 per 1,000 central line days, is nearly threefold higher than the 2.0 per 1,000 central line days reported from comparable US ICUs, and the overall rate of ventilator-associated pneumonia (VAP) was also far higher: 13.6 versus 3.3 per 1,000 ventilator days, respectively, as was the rate of catheter-associated UTI (CAUTI), 6.3 versus 3.3 per 1,000 catheter days, respectively. The frequencies of resistance of *Staphylococcus aureus* isolates and Enterobacteriaceae were also far higher in the consortium's ICUs, and the crude unadjusted excess mortalities of device-related infections ranged from 23.6% (CLABSI) to 29.3% (VAP).

While the INICC is one model for surveillance of HAIs in developing countries, there are other potential models that can be tailored to the needs of the different regions. One of the strengths of the INICC model, however, is its focus on device utilization in addition to HAI rates.

There have been a number of success stories in developing countries in terms of reducing device utilization rates. This has been seen with CAUTIs.

CAUTIs are the most common HAIs worldwide in both developing and developed countries. The most important advance in the prevention of CAUTIs in developed countries has been the use of closed catheter drainage. In an early editorial by Beeson, significant bacteriuria rates of up to 95% of patients with indwelling urinary catheters were cited *(73)*. This high rate of catheter-associated bacteriuria in the era before modern closed drainage systems is likely to be comparable to rates in developing countries that are still using open drainage systems for urinary catheter drainage. When the urinary catheter system is open, there are multiple opportunities for pathogens to enter the catheterized urinary tract due to contamination of the drainage container or contamination of the drainage tube by individuals collecting urine from the end of the catheter.

Commercially available closed urinary drainage systems might not be within the reach of many healthcare facilities in developing countries. However, closed urinary catheter drainage can be achieved through modification of open drainage systems using improvised urine drainage containers.

More recently, efforts in both developed and developing countries have focused on reducing the incidence of urinary catheterization. In Thailand, a system of nurse-driven reminders as part of a multifaceted intervention can reduce the incidence of healthcare-associated CAUTIs *(74)*. This was a before and after study of an intervention that made use of nurse-generated reminders that began from the third day of catheterization. This resulted in a reduction of inappropriate catheterization from 20% to 11%, reduction in mean duration of catheterization from 11 to 3 days, and a significant reduction in CAUTIs from 21.5 to 5.2 per 1,000 patient days. The benefits of this intervention were most marked in the ICUs, and the nurse-generated reminders were accompanied by education programs to emphasize the importance of prevention of CAUTIs. The costs for patients in terms of antibiotics and overall hospital costs were reduced between 58% and 63%. This is clearly a simple, cost-effective intervention that can be applied in a number of developing countries.

The Thai experience replicated the experience of a group from Taiwan who also showed a significant reduction in CAUTI in ICUs by using nurse-generated reminders, which resulted in a 69% reduction in antibiotic costs due to a reduction in CAUTI from 11.5 to 8.3 per 1,000 catheter days with a reduction in duration of catheterization from 7 to 5.6 days *(75)*.

In Nigeria, a prospective randomized trial was conducted to assess the impact of early removal of the indwelling urinary catheter after caesarean section, and this showed no adverse impact and a nonsignificant reduction in CAUTI *(76)*. More recently, a group in Egypt successfully reduced the incidence of CAUTI post-cesarean section by simply not using indwelling urinary catheters *(77)*. This was not associated with an increase in urinary retention and in fact was better tolerated by the women compared to those who had indwelling urinary catheterization. These are two examples of initiatives from Africa that have shown that it is possible to reduce the use of urinary catheters and thus to decrease the incidence of CAUTI in healthcare facilities in developing countries.

VAP is another major problem in developing countries. In countries with access to ventilators, they can be lifesaving for endemic diseases such as tetanus in addition to other conditions seen more commonly in developed countries, including severe respiratory infections. VAP rates are high in developing countries due to a variety of factors, including sharing of suction catheters, solutions used for suctioning, reuse of ventilator tubing with inadequate sterilization, and possibly overuse of mechanical ventilation related to lack of availability of noninvasive ventilation means. Arabi and colleagues have recently performed a systematic review of VAP in developing countries *(78)*. They found 22 studies from the Middle East, Southeast Asia, and South America that made use of the US CDC's NHSN definitions for VAP. The most common pathogens associated with VAP were gram-negative bacilli, most commonly *Pseudomonas aeruginosa*, and the crude mortality associated with VAP ranged from 16% to 94%. There were eight studies that performed interventions, and outcome data were analyzed from before and after the intervention. The interventions that were effective in reducing VAP rates in developing countries included education campaigns to improve hand hygiene compliance, aseptic technique, and appropriate use of suctioning. Arabi's group also demonstrated that a sedation protocol and an educational program could reduce VAP rates from 28 to 11 per 100 ventilated patients.

Intravascular access device–associated bloodstream infections are a major problem in developing countries. This is particularly acute as in many developing countries, open infusion systems are still in use. These have been associated with higher rates of intravenous access device–associated bloodstream infections *(79)*. In addition, because of cost issues, many devices stay in place for far longer than is necessary, and there is often an incentive from either the patient or the provider to supply parenteral rehydration rather than oral rehydration.

Although use of large volumes of fluids in developing countries has been associated with better survival and improved outcomes *(80)*, there are considerable risks associated with intravenous therapy in low-resource settings. Furthermore, the efficacy of oral rehydration solutions has been established for more than 20 years in the treatment of severe dehydration due to endemic gastroenteritis in children *(81)*. Some of these problems were illustrated many years ago by Rhinehart and colleagues who investigated increases in mortality in children with dengue hemorrhagic fever that turned out to be due to HAIs (primarily bloodstream infections), in an ICU with limited hand hygiene and other resources. Through a skilful adaptation of the US CDC recommendations, these were brought under control *(82)*.

In recent years, the introduction of "bundles" to reduce the incidence of CLABSI has made a significant impact in many developing countries. A quasi-experimental study in Brazil demonstrated a reduction in CLABSI from 6.4 per 1,000 catheter days to 3.2 per 1,000 catheter days in an ICU *(83)*. Similar success stories have been recorded in Thailand *(84)*, where a sustained reduction of between 54% and 78% was sustained a year after the introduction of a CLABSI bundle together with a hand hygiene promotion campaign. It is important to note that in the Thai study, the baseline rate of CLABSI was high—14 cases per 1,000 catheter days—and the intervention was associated with a significant decrease in device utilization.

While the ability to implement these bundles will vary across the wide spectrum of healthcare facilities in developing countries, there is good evidence that educational interventions making use of locally produced guidelines can have a positive impact on CLABSI *(85)*.

SUMMARY

1. All developing countries need to have some form of surveillance for HAIs.
   a. This can take the form of a periodic point prevalence survey conducted across a range of healthcare facilities.
   b. Definitions need to be standardized to ensure that data can be meaningfully compared across institutions and can be used as a basis for quality-improvement programs.
   c. Countries should make use of whatever technology is available, including mobile phone applications to increase the accuracy and reliability of surveillance systems.
2. SSI surveillance is critical to safe surgery.
   a. SSI surveillance can be augmented by monitoring readmissions or returns to the operating room for infectious complications.
   b. Checklists, for example, the 19-item WHO surgical safety checklist, should be considered in all healthcare facilities. These can improve timing of perioperative antimicrobial prophylaxis and reduce SSIs together with other complications of surgery.
3. CAUTIs should be monitored together with urinary catheter use.
   a. Where possible, closed urinary catheter drainage should be used. Where this is not available routinely, it can be improvised.
   b. A simple nurse-based reminder system can be used to reduce the duration of catheterization and thus the rate of CAUTIs, antibiotic use, and costs.
   c. Strict attention to aseptic technique can reduce CAUTI and other device-associated infections.
4. VAP surveillance should also be done according to standardized definitions.
   a. Hand hygiene campaigns and attention to asepsis can reduce VAP rates in all hospitals.

   b. Sedation protocols should be used together with other evidence-based interventions to reduce VAP.
   c. Where possible, the duration of mechanical ventilation should be limited to as short a time as necessary.
5. CLABSIs should be monitored as with VAP and CAUTI using standardized definitions and with concomitant measures of device utilization. In addition:
   a. It is critical to increase the use of oral rehydration where possible to reduce the utilization of venous access devices.
   b. Educational programs should be put in place to ensure that all HCWs taking care of patients with venous access devices are trained in their use and care.
   c. The use of open intravenous fluid systems should be discouraged where possible. If they need to be used, strict attention needs to be paid to asepsis sterilization and disinfection.
   d. Elements of evidence-based CLABSI bundles should be introduced into all healthcare facilities.

MICROBIOLOGY LABORATORY

At the national level, there should be promotion of standardized laboratory techniques and defined biosafety standards. At the local hospital level, there should be access to laboratory services and protection of laboratory staff.

Historically, in many developing countries, the microbiology laboratory director has doubled up as the infection control officer. This has been inevitable because of the specialized expertise of the microbiologists and, in fact, the origins of many infection control programs to control the spread of resistant pathogens.

Developing countries have high rates of multiresistant pathogens. This is exemplified by the Asian guidelines on the management of healthcare-associated pneumonia, which list key pathogens causing healthcare-associated pneumonia as methicillin-resistant *S. aureus* (MRSA), multidrug resistant *Acinetobacter baumannii*, and multidrug resistant *P. aeruginosa*. The recommended second-line therapy for patients with healthcare-associated pneumonia is polymyxin *(86)*.

For some unclear reasons—perhaps climatic—multiresistant gram-negative pathogens appear to be more of a problem than gram-positive pathogens in tropical and subtropical countries, with the possible exception of MRSA *(87)*. Many protocols for identification of gram-negative pathogens are not as well standardized or as easily accessed in developing countries, and this is a further challenge. Resistance testing itself has to be done according to standardized protocols, and there are agencies with international arms that provide access to quality assurance programs that can be tapped to ensure some standards in resistance testing and reporting.

Microbiology laboratories associated with healthcare facilities need to have some form of external quality assurance to ensure that the data provided to clinicians are accurate and reliable. It has been recognized for some time that lack of reliable clinical microbiology laboratories is a barrier to the delivery of effective healthcare in Africa and other low-resource settings *(88)*. One potentially deadly consequence of the lack of reliable clinical microbiological resources has been the overdependence on syndromic management of patients (89). A recent review of community-acquired bloodstream infections in Africa *(90)* pointed out that multiple studies have demonstrated the importance of bacterial pathogens such as *Streptococcus pneumoniae*, *Salmonella typhi*, and non-typhoidal salmonellae in patients who present with undifferentiated fever to healthcare facilities in Africa. Many are inappropriately treated for malaria even in settings where the season or location is not typical. The authors point out that widespread use of simple appropriate blood cultures could ensure that appropriate treatment is provided to children and adults with community-acquired bacterial infections that are probably at least as common as malaria in many parts of the developing world. The alternative, which might appear tempting and is practiced in some parts of the world, is to add an empiric antibiotic to the antimalaria regime in the syndromic treatment of fever. The danger associated with this is the antibiotic pressure, which can only add to the antimicrobial resistance problem. As mentioned, antimicrobial resistance in healthcare-associated pathogens is a major problem, but this has also been noted in the community *(91)*. Blood cultures can be accurately performed in sub-Saharan African countries with proper training. Indeed, a study performed by Archibald and colleagues showed a lower rate of blood culture contamination in Tanzania and Malawi compared with a major US teaching hospital using the same protocol *(92)*. Blood cultures are fundamental as they can be performed by trained technicians, and they provide objective data to guide treatment and can provide useful parameters for surveillance. For example, the United Kingdom (again, most certainly not a low-resource country) has made MRSA bacteremia a notifiable infectious disease under public health law. This has arguably contributed to the lowering of MRSA infections throughout the United Kingdom. Many countries in Asia and Latin America have considered using bloodstream infection rates as national surveillance tools both to define healthcare epidemiology and to monitor infection control parameters. Thus, accurate and reliable blood cultures are critical in all settings.

The problem of drug resistance in the community is thought to be exacerbated by the easy access to antimicrobials bought over the counter. While many of us in developed countries would decry this practice, the reality is that with the shortage of healthcare manpower in developing countries—in particular doctors who can write prescriptions, rather than have a child die from an *Escherichia coli* urosepsis or pneumococcal pneumonia because the nearest physician is 200 miles away, it makes much more sense to go to the local market to pick up some potentially life-saving antibiotics. Perhaps the solution is to stop exacerbating the medical and nursing manpower shortage in developing countries by addressing the root causes of this issue (93). This has been recognized, but there are no obvious solutions readily available.

Antimicrobial drug resistance in hospitals in low-resource countries is an even bigger problem. This is due to a combination of factors including deficiencies in infection control practices and infrastructure as well as the pernicious practice by which physicians and hospitals

are compensated more for prescribing more expensive and broader-spectrum agents than for targeted antimicrobial therapy. This has led to severe distortions in antimicrobial prescribing and the situation that has led to the emergence of "untreatable" infections, for example. This is an issue that has to be addressed.

It is important to have longitudinal surveillance of resistance rates in hospitals. Okeke has pointed out that few sub-Saharan countries can reliably produce annual antibiograms that report resistance rates consistently *(91)*. The WHO has the freely available WHONET software that is widely used by a number of countries to collate and report antibiotic resistance rates. This can be used for benchmarking longitudinally in a healthcare facility, across the healthcare facilities in a region and internationally. In addition, over the years, there have been a number of antimicrobial resistance surveillance programs that have been sponsored primarily by industry. Although commercially driven, they have provided much useful information for practitioners in these countries and regions, so they have some idea of the epidemiology of resistant pathogens in their area.

One area of success in recent years has been the WHO's campaign to increase the laboratory detection and confirmation of TB and increase resistance testing. The WHO has set goals for the proportion of cases of TB, which are identified by smears as opposed to the traditional approach of syndromic treatment based on symptoms or on chest radiographs, which can be of variable quality. Other agencies such as the US CDC have also worked with developing countries to standardize microbiological diagnosis of TB and ensure quality control (94).

In addition, there have been a number of technological advances in the diagnosis of drug resistance in TB. Recently, a tabletop molecular diagnostic device that can rapidly, with minimal sample preparation time, generate accurate and reliable molecular evidence of the presence of *Mycobacterium tuberculosis* together with rifampicin resistance, which was found to be a sensitive marker for multidrug resistance in TB. This might be out of reach of most low-income countries, but there are alternatives including the innovative MODS approach to diagnosis of drug resistance in TB, which involves a series of wells and visual inspection *(95)*. This has been validated in Peru and potentially can be applied in a number of low-resource settings, but it will require training for the laboratory staff.

The recent 2009 H1N1 pandemic together with the H5N1 avian influenza outbreaks has greatly advanced the cause of molecular diagnosis of respiratory viral pathogens across the globe. Influenza polymerase chain reactions were performed in laboratories across Asia, Africa, and Latin America during the peak of the influenza pandemic, and the WHO and its partner agencies were able to provide timely epidemiological data that demonstrated the rapid spread of the 2009 H1N1 epidemic across international boundaries *(96)*. The capacity that has been built up for the molecular diagnosis of respiratory viral infections has the potential to be used for the molecular diagnosis of other pathogens such as TB or dengue virus, which are major problems in many low-income countries. In addition, there are efforts under way to use molecular methods to diagnose drug-resistant microorganisms or to rapidly identify bacterial pathogens in critically ill patients.

Another important element in microbiology laboratories is the ability to turn to a regional or international reference laboratory. There are a number of international laboratories run by the Wellcome Trust, Pasteur Institute, and the U.S. Military, which have served as reference laboratories for many low-income countries in the past. While there have been issues with ownership of specimens from developing countries and the enforcement of the biological diversity protocols (97), there is clearly a need for in-country expertise in the establishment of reference laboratories. For infection control, the ability to do molecular typing of isolates, which is often taken for granted in developed countries, can be a tremendous help when available in low-income countries. There is the possibility that diagnostic molecular laboratories that are now available in many countries in the developing world can perform molecular epidemiology studies with the appropriate protocols.

Summary

All countries need to have the following:

a. Adequately resourced clinical microbiology laboratories that can perform blood and other cultures and have access to external quality assurance programs that ensure that the results are reliable and accurate.
b. Antibiograms produced from each healthcare facility, which allow for the tracking of resistance patterns and epidemiology.
c. The ability to make use of software such as WHONET to report antibiotic resistance patterns longitudinally and across the country.
d. Laboratories that are integrated with ICTs so that alert microorganism surveillance can be put in place and appropriate isolation precautions can be enforced.

THE ROLE OF THE ENVIRONMENT MUST BE ASSESSED

Although a clean environment plays an important role in the prevention of HAIs, historically, many countries have placed an overemphasis on the role of the environment to the detriment of programs focusing on hand hygiene and isolation precautions. At the national level, there should be definition of the minimum standards for infection prevention and control purposes. At the local healthcare facility level, design and planning should ensure adequate safe water supply, ventilation, hand hygiene facilities, patient placement and isolation facilities, storage of sterile supplies, and rules and protocols for building and renovation as well as appropriate waste management facilities and practices.

All healthcare facilities should provide safe water for clinical use. There are low-cost means of doing this, and they should be put in place. Municipal tap water is a potential reservoir of healthcare-associated pathogens in many countries with limited resources. Tap water contaminated with gram-negative bacilli or nontuberculous mycobacteria has been associated with bacteremia, burn infections, and SSIs. This is particularly acute in developing countries where contaminated infusions or ventilator suction

using nonsterile water can lead to outbreaks *(98–100)*. In the developed world, Anaisie et al. *(101)* have described contaminated hospital water sources causing healthcare-associated outbreaks from many pathogens including mycobacteria, *Pseudomonas*, *Stenotrophomonas*, *Serratia*, *Acinetobacter*, *Aeromonas*, and molds such as *Fusarium* and *Aspergillus*. The ability of gram-negative bacteria to survive wet environments for long periods explains their common occurrence in multiple sites, especially in humid climates *(102)*. These microorganisms can potentially be spread to patients by HCWs whose hands become contaminated during hand washing *(98,99,102)*. In hospitals in countries with limited resources, infection control personnel must periodically do "sink" rounds to ensure proper functioning of sinks and adequate water chlorination. All water leaks and water damage should be repaired and remediated within 24 hours to prevent dissemination of pathogenic bacteria and moulds *(103)*. One of the best ways to ensure this is to have hospital engineering staff represented on infection control committees and/or have protocols in place so that a quick infection control risk assessment can be made when a leak occurs. Where safe water is not available, it is recommended to boil water to render it safe for utilization. Alternatively, water purification units may be used. Viable pathogens can grow in many sources of hospital water including drinking water, hand washing water, ice, dialysis water, shower water, water in storage tanks and distribution systems, ventilation ducts, and building materials that have become wet. Thus, it is important to ensure that the hospital environment is kept clean and dry and that staff exercise aseptic technique as carefully as possible.

Hand hygiene is the cornerstone of effective infection control programs worldwide. Hand hygiene facilities should be made available at the point of patient care. At the national level, governments must be committed to hand hygiene and allocate budgets, produce national guidelines on hand hygiene, produce posters and educational materials, and promote hand hygiene campaigns. The WHO's "Clean Care is Safer Care" campaign has succeeded in getting commitments from Ministers of Health of more than 100 countries worldwide (Fig. 100-4). Many countries have followed through on these commitments with national campaigns to improve hand hygiene. Although hand hygiene is a simple measure, the lack of compliance among HCWs is problematic worldwide, averaging <40% *(104)*. This is due to lack of time, inadequate facilities, or forgetfulness because of heavy workloads *(105,106)*. Moreover, hand washing facilities in some developing countries are primitive or scarce and inconveniently located. Supplies of soap and paper towels are often inadequate, and multiple-use cloth towels are commonly used; these towels become damp and can harbor gram-negative bacteria *(107)*. It is almost impossible to achieve 100% compliance with hand washing even in well-resourced developed countries *(108)*. To increase hand hygiene compliance worldwide, the WHO recommends making the use of alcohol-based handrubs preferable to hand washing in most clinical situations, unless hands are visibly dirty, when they have to be washed first (109). It is often easier to provide alcohol-based handrubs than sinks with running water and a functioning sewage system, where the overall sink-to-patient bed ratio should be of 1:10 *(110)*. Placement of hand hygiene products (soap and handrubs) should be aligned with promoting hand hygiene in accordance with the concept of the "My five moments for hand hygiene" (111). Pocket bottle handrubs are ideal for use at the point of care. However, if the commercial products are too costly for the local healthcare settings, WHO has

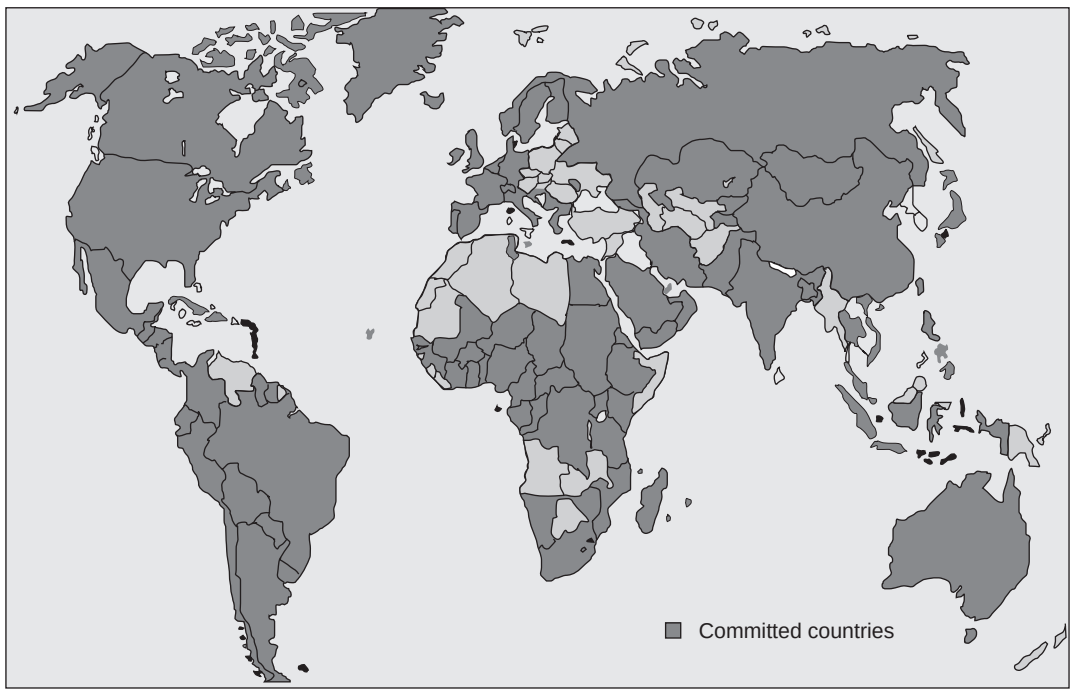

FIGURE 100-4 Countries committed to World Health Organization's hand hygiene campaign.

formulated much cheaper alcohol-based handrubs for local production with proven microbiological efficacy and a good safety profile. A *Guide to Local Production* has been published, which features simple instructions and illustrations detailing the process from procurement of raw ingredients to quality control and storage of the final product *(112)*. Allegranzi and colleagues recently reported their efforts in Bamako, Mali, a very low income country. A concerted effort with strong support from the local administrators involved the local production of a high-quality alcohol-based handrub that had a significant impact on hand hygiene compliance. There was strong support from the HCWs and preliminary evidence that this might have had an impact on HAIs *(113)*.

MONITORING AND EVALUATION

Monitoring and evaluation of infection prevention and control programs should be conducted periodically both at a national and a local or state level. This should be done in a nonpunitive manner that seeks to improve the quality of care rather than find fault with individuals.

Monitoring and evaluation of programs is critical to ensure the success of early efforts. This is self-evident, and there are a number of means by which this can be achieved. For infection control efforts that are funded by international agencies such as the World Bank, there are established protocols for monitoring and evaluation, and these should be put into place as soon as is practical (114).

For programs funded domestically, the international mechanisms for monitoring and evaluation should be adapted to local needs and situations. It is important to ensure a blame-free culture at the local level so that monitoring is not seen as a form of policing. In many countries, there is a lack of trust in systems; so it is important that individuals are not incentivized to "game" the system. International independent systems can be made use of, but there are risks inherent in trying to benchmark performance. The debates over "pay for performance" that have occurred in the developed world *(115)* have recurred in various forms in many developing countries. While flawed, there is a need for monitoring and evaluation of infection control programs to ensure that resources are not wasted and that patient safety is protected.

Summary

There have to be nonpunitive mechanisms for monitoring of infection control and prevention programs at both the local healthcare facility and national level.

LINK WITH PUBLIC HEALTH AUTHORITIES

At the national level, the regional offices of the WHO have links with national health authorities—these have to include infection prevention and control programs in addition to the classical internationally notifiable diseases such as cholera, yellow fever, and influenza.

At the local hospital level, hospitals have to have links with public health authorities for reporting of HAIs and to tap the resources of public healthcare professionals for outbreak investigation.

The SARS outbreak was a clear illustration of the need for infection control programs to have close links with public health agencies both in country and regionally and internationally. The countries that experienced the SARS outbreak were prepared for the 2009 H1N1 pandemic and rapidly implemented comprehensive pandemic plans *(17)*.

On a more mundane level, there needs to be close integration with municipal waste management providers. In low-income countries, there are many situations where medical waste is "recycled" unofficially by individuals who scavenge used syringes, wash them, and sell them to unsuspecting or impoverished patients who are unable to pay for new, sterile equipment. One way of preventing this is to ensure that all waste is segregated and that contaminated medical waste is promptly and securely dispatched to sites where it can be incinerated. A study of more than 100 primary healthcare centers in Iran found that while all used appropriate sharps disposal methods, there were some gaps that needed to be addressed in terms of training of staff and construction of septic tanks and disinfection systems for settings without access to functioning municipal sewerage systems *(116)*.

Sterilization and disinfection in low-resource countries is predominantly and most safely conducted through the use of steam sterilization and heat disinfection. Where disinfectants are used, their use must be carefully monitored to ensure that they are appropriately handled and stored and that there is no contamination. The issue of reuse of single use devices is particularly acute in low-income countries.

Links do not just need to be done locally within a country; ideally, low-resource countries could tap on neighboring middle-income countries to access some of the successful adaptations of international best practices to local situations. An example of this is shown in Figure 100-5, where a local nongovernmental organization funded the training of infection preventionists from a low-income Southeast Asian country in a middle-income neighboring country.

FIGURE 100-5 Training for infection preventionists in Malaysia.

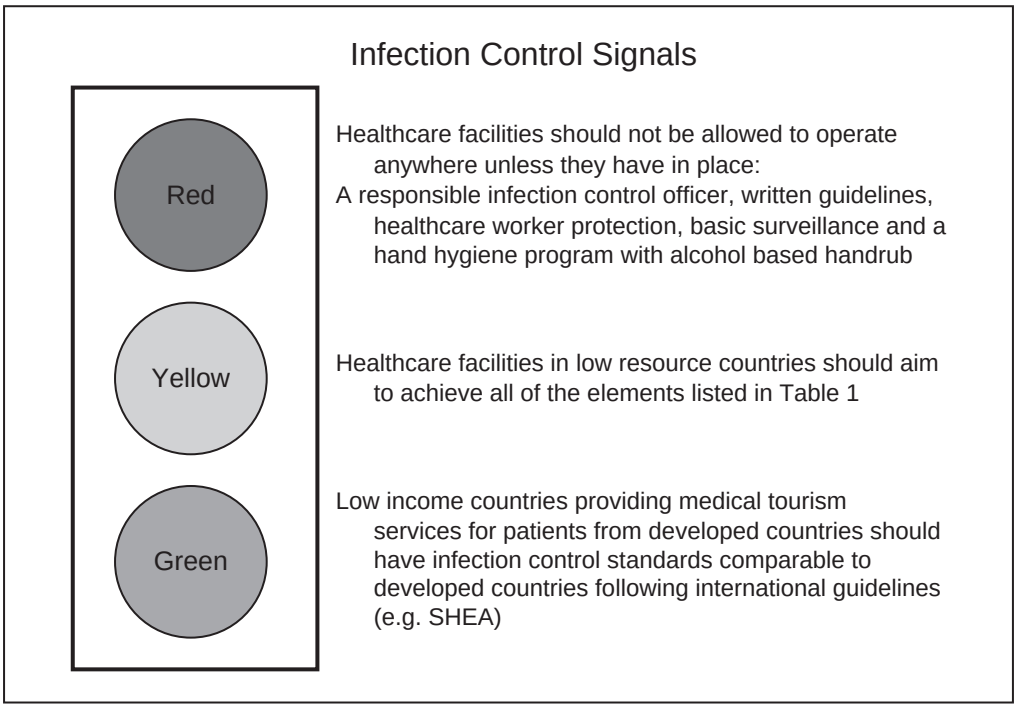

FIGURE 100-6 Proposed traffic signal system of infection control depicting, minimum standards for all healthcare facilities (red light), targets to aim for in low income countries (yellow light) and higher standards for those promoting healthcare to patients from developed nations (green light).

Summary

Links have to be established by infection control and prevention teams with local public health and other municipal authorities to integrate infection control programs with other activities directly related to the potential transmission of infections.

CONCLUSION

Infection control in low-resource countries is indeed a challenge. There is, however, a renewed commitment that has emerged in recent years to infection control. We have proposed a traffic signal system (Fig. 100-6). Even in the least-resourced countries, there are certain minimum standards that should be in place if a facility is to be allowed to conduct medical procedures. Absence of these would constitute a red light, suggesting that unsafe facilities should be shut down and resources channeled to transporting patients to safe facilities nearby. We believe that the recommendations in this chapter can be achieved over time in all developing countries. Importantly too, we recognize that many developing countries are marketing themselves as destinations for "medical tourists" from developed countries. It is vitally important for insurance companies and regulatory bodies in the developed countries to ensure that infection control standards in those facilities are comparable to those in the source country. Overall, low-resource countries themselves and their partners in the developed world need to work together in a stepwise fashion at whatever pace is appropriate to ensure that patients in healthcare facilities all over the world, in the words of Florence Nightingale, "do not suffer harm."

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SECTION XVII
Bioterrorism

CHAPTER 101

Biological Terrorism: An Overview

Margaret A. Hamburg* and C. J. Peters

Once considered a remote concern, the possibility that biological agents might be intentionally used to cause widespread panic, disruption, disease, and death is now widely recognized. Neither technical barriers nor moral repugnance can protect us from their use. Future attacks could occur again at any time from many potential sources and using many possible biological agents. Whether an unsophisticated delivery system with a limited number of infections, as we experienced with the anthrax letters, or a more technologically advanced and carefully orchestrated attack with mass casualties, the prospects are frightening. Further, we must recognize that this evolving threat presents the medical, public health, and scientific community with a set of difficult and pressing challenges. Before 9/11 and after 9/11 and the anthrax attacks of the next month, experts and commissions had predicted that biological attacks should be expected, and the drumbeat has continued and intensified in 2010. The type and extent of such an attack will depend on the balance between the technical expertise of the terrorists and the effectiveness of our defenses.

By its very nature, the biological weapons threat—with its close links to naturally occurring infectious agents and disease—requires a different paradigm than that for conventional terrorism, military strikes, or attacks caused by other weapons of mass destruction. A biological event could well unfold as a smallpox epidemic, or foci of less transmissible diseases spread out in time and place before authorities even realize that an attack has occurred. What is more, opportunities for access to dangerous pathogens here or overseas can be relatively routine in nature even with the increased regulations that are in place. Significant damage can be done even without large quantities of material or an elaborate delivery mechanism, and new possibilities for exploitation are embedded in the very science and technology advances that hold great promise for health.

There is an urgent need for systematic study and action concerning what is needed to control the development, proliferation, and use of biological weapons, as well as the crucial elements of response should an attack occur. Clearly, this will require new thinking about how to define and implement meaningful solutions and will require the full engagement of the biomedical community (1).

This chapter attempts to offer an overview of the threat of bioterrorism and some of the critical issues that need to be addressed as our nation prepares to deal with this disturbing and potentially catastrophic threat. Subsequent chapters will expand on the specific elements of preparedness and response at the national, state, and local levels, including discussion of the identification and management of many of the biological agents of particular concern.

WHAT IS BIOTERRORISM?

Terrorism can be most simply defined as "warfare deliberately waged against civilians with the purpose of destroying their will to support either leaders or policies" *(2)*; however, the term, as commonly used, includes the implicit connotations that some weaker group attempts to gain international support or tumble the government targeted in order to achieve their goals and that it often employs an element of fear in the targeted noncombatant population *(3)*.

*The author, Commissioner of the Food and Drug Administration, contributed this chapter in a personal capacity.

The use of these tactics is probably as old as organized governments and has been traced back as far as the 3rd century BCE tactics of Hannibal or the spectacular murders by the 11th century Assassin cult. In any case, this approach has continued to the present day and is evolving according to available technology. Today's terrorists use the Internet and cellular phones and incorporate the most modern destructive weapons. When we talk of bioterrorism, we refer to terrorism carried out using biological weapons. The international definition of biological weapons includes replicating microorganisms such as bacteria and viruses as well as toxins derived from microorganisms.

This definition includes a wide variety of attacks using any of a huge selection of microorganisms. Of course, many of these events would be of lesser impact and might be of little more consequence than a crime or assassination executed with firearms *(4,5)*. However, the element of terror is an important part of the impact. For example, the consequences of cyanide poisoning of analgesics or of imported grapes *(3)* had far-reaching consequences in the public mind and economy. Only 21 anthrax cases with 5 deaths in 2001 resulted in a great deal of fear in the involved areas, paralyzed mail communications, and handicapped government functioning. Even hoaxes can be highly disruptive and expensive.

There is a much more serious side to the threat of bioterrorism, and it is best understood through the history of biological warfare. Attempts at biological attacks date back far in history. For example, in the 1300s, the bodies of plague-infected victims were catapulted over the city walls during the Tatar siege of Kaffa. In the 1700s, during the French and Indian War, native American adversaries were given "gifts" of smallpox contaminated blankets by the British that decimated their numbers *(6)*.

The development of a more modern approach to biological weapons dates to the early decades of the 20th century. During the 1930s and 1940s, the Japanese conducted extensive experiments and large-scale field trials—primarily involving contaminated food and water supplies—on unwitting civilians and prisoner of wars (POWs) in occupied Manchuria. In fact, during World War II, every major combatant had a biological weapons program, although Japan is the only country that is generally agreed to have used biological weapons during the course of the conflict *(6,7)*.

We began our own bioweapons program in 1943, partially in response to the research programs established by the Japanese and the Germans as well. But in 1969, President Nixon renounced the use of biological weapons and ordered that our offensive program be ceased and all stockpiles destroyed *(8,9)*. This decision paved the way for negotiation of the Biological and Toxin Weapons Convention (BWC) treaty, which prohibits possession, or stockpiling, and transfer of bioweapons. The treaty was concluded in 1972 and subsequently ratified by more than 140 nations. The signing of the BWC represented a very important commitment to abandon pursuit of biological agents as weapons, but it did not—and still does not—contain explicit monitoring, inspection, or enforcement requirements *(10)*.

As the 20th century closed, several events gave bioweapons greater prominence on the national security agenda. The first strong indication came from the accident at a Soviet bioweapons factory in Sverdlovsk; a human error led to the accidental release of weaponized anthrax, with resulting cases in humans and cattle in the city. The source of the epidemic was suspected in the military and intelligence community but was denied by the Soviets and some American academics. Later investigations and Soviet admissions confirmed that it was, indeed, an epidemic of inhalation anthrax, practically pathognomonic of a biological weapon in the pattern observed *(9,11)*. As the Soviet Union broke up in the 1980s, there were startling revelations about the magnitude and scope of the bioweapons program in the former Soviet Union—which began in full force the same year as they signed on to the BWC. At the height of their program, they had more than 50 institutes, employed tens of thousands of workers (including an estimated 7,000 scientists deemed "security risks" on the basis of their knowledge and expertise; Ref. *12*), and made literally ton quantities of weaponized anthrax, smallpox, and other microorganisms. In addition they were developing resistant strains and new pathogen variants; and experimenting with innovative strategies to cause disease including recombinant microorganisms such as *Escherichia coli* expressing neuromodulators *(9,13)*.

Concerns were further heightened by the disclosure of an ambitious bioweapons' program mounted by Iraq *(14,15)* and the findings that Aum Shinrikyo, the Japanese group that released nerve gas in the Tokyo subway, had also experimented with botulism and anthrax, as well as sent teams to Zaire in an effort to obtain Ebola virus for use as a weapon *(16,17)*. Episodes here at home involving extremist groups or individuals who were able to obtain dangerous pathogens such as ricin, anthrax, and *Yersinia pestis* for dubious purposes added to the growing perception of risk *(18)*. Of course, the final breach of the barrier to use of biological agents for terrorism or weapons came with the anthrax attacks in October 2001.

WHAT IS THE REAL THREAT OF BIOTERRORISM?

Any consideration of bioterrorism must begin with a consideration of the scenario: who is executing the attack, why are they doing it, and what are their resources? This delineation will allow us to focus on the scope and sophistication we are concerned with and the possible modalities of the attack or defense. A lone person with little microbiological expertise poses a lower risk with microbes than with an automatic weapon. A state-sponsored program is the other end of the threat spectrum and could result in many thousands of deaths. It is possible that the terrorist's desired outcome is merely that the turnout for voting is diminished, as occurred with a sect in Oregon that contaminated salad bars with *Salmonella (19)*, or it may be more lethal such as Aum Shinrikyo's goals *(16,17)*.

Certainly, attacks on a limited scale have occurred and will occur again *(17,20)*. Terrorists or nation states will note the remarkable success of the 2001 anthrax attacks, and they will attempt to repeat them. In fact, anthrax is the most likely agent to be used in the future, because the microorganism is readily available in nature worldwide, the spores are stable on storage and in aerosol without special preparation, and *Bacillus anthracis* is easily grown

TABLE 101-1

Methods of Dissemination of a Bioterrorist Agent and Some of their Drawbacks

Injection—limited numbers
Water—purification plants, residual chlorine, and dilution
Arthropods, rodents—tricky biology
Food—access, synchronization, and wide coverage
Interhuman spread—will the agent really do it?
Aerosol—relatively few agents useful, technical difficulties in preparing for stable, efficient delivery

and purified. It is particularly worrisome that we do not understand who prepared the 2001 anthrax weapon or how it was prepared *(21)*.

However, most attention has been focused on attacks that carry the threat of very large numbers of casualties. It is easiest to analyze these according to how the agent would be disseminated (Table 101-1). Direct injection has been used *(22)* as an assassination tool with ricin, but is impractical in any large scale. Water is often mentioned and of course could be a risk on a small scale, but dilution and residual chlorine make it impractical on a large scale. Arthropods or rodents could be used with some agents such as tularemia or yellow fever and indeed plague-infected fleas were used by the Japanese in World War II *(7)*. However, the biology of such attacks can be difficult to predict or manage, as anyone who followed the arguments about the persistence of West Nile virus after its introduction into North America can attest. Food sources have been increasingly recognized as sources of multistate outbreaks and must be regarded as a vulnerable link, but we are also responding to them more effectively so that surveillance could give early warning and food lots could be recalled unless the dissemination occurred in a setting in which many consume the product synchronously. Clearly protection of the food supply at the source is an increasingly important consideration (23). The most efficient approach to infecting a large number of target humans would be to use an agent that would spread from person to person after the initial infections; only smallpox can actually do this. Influenza strains have been suggested, but they lack "directionality" toward an enemy and the immediacy required in most scenarios. That does not detract from the fact that influenza A is the greatest natural threat we face and that new strains could be responsible for millions of deaths worldwide *(18)*. Other infections such as plague and viral hemorrhagic fevers have a limited possibility for spread and will not cause secondary infections beyond possibly limited numbers of close personal contacts and a few in the medical setting.

This leaves aerosol dissemination on the list (Table 101-1); however, there are only a few agents that can be grown to high titer, are infectious by the aerosol route, and cause severe and fatal disease. The small particle aerosols are subject to ultraviolet inactivation in most cases, can be carried away by wind currents, and require special preparation and skill in dissemination. They have some advantages: they can be disseminated at night under inversion conditions and with attention to meteorological variables and be carried silently downwind to expose large numbers of people and/or animals. In fact, this approach was exactly that chosen by both the United States and the Soviet Union for their biological warfare programs and the testing suggested that it would be highly effective (24). The US program was tested in each step, ranging from indoor and outdoor tests of aerosols, actual determination of the minimal infectious dose in humans for selected agents, and extensive animal testing. They showed that aerosols of simulant microorganisms (microorganisms that resemble the one to be used as a weapon but of minimal virulence) or powders with similar aerosol properties could be disseminated over large areas and would have the potential to produce tens or hundreds of thousands of casualties *(25)*. Thus, each step of the use of such weapons was in place and there is no doubt that they would have been effective *(8,9,22)*.

There is considerable argument over exactly which microorganisms belong in this "rogues gallery" of aerosol infectious agents with lethal outcome. The Centers for Disease Control and Prevention (CDC) has proposed a grouping of categories A, B, and C, with category A being those of most concern (Table 101-2) (26). They were selected because of their catastrophic public health consequences with the expectation that, properly delivered, they would induce mass casualties that would overwhelm medical systems and carry with them a high mortality; no one would quarrel that these agents belong in the highest priority category. Smallpox has the additional threat that it would be contagious and spread among the unvaccinated populace. Botulism may have less potential as a mass casualty agent, but it certainly has a need for public health preparedness to manage the expected respiratory paralysis. This list has been the template for an enhanced defensive public health agenda. There are many arguments about what other microorganisms may be sufficiently dangerous to deserve consideration. Table 101-3 lists some of these, but there are differing opinions among different authorities.

If aerosol delivery of biological agents is so effective, why was it not used in warfare and why did the United

TABLE 101-2

Category A Bioterrorist Agents Defined by the CDC

Variola major (smallpox)
Bacillus anthracis (anthrax)
Y. pestis (plague)
Francisella tularensis (tularemia)
Botulinum toxin (botulism)
Viral hemorrhagic fevers
Filoviruses (Ebola and Marburg)
Arenaviruses (South American hemorrhagic fevers, Lassa fever)

Note: All are capable of efficient aerosol delivery. Only smallpox is highly transmissible from person to person.
(From Rotz LD, Khan AS, Lillibridge SC, et al. Public health assessment of potential biological terrorism agents. *Emerg Infect Dis* 2003;8:225–230.)

TABLE 101-3

Other Microorganisms of Concern in Bioterrorism Defense

Viruses
Other viral hemorrhagic fevers
Rift Valley fever
Tick-borne flaviviruses
Monkeypox virus
Alphaviruses Venezuelan equine encephalitis virus
Nipah virus
SARS coronavirus
Bacteria
Typhus and other critical rickettsiae
Glanders
Other
Crop agents
Veterinary pathogens
Bioengineered
Microorganisms

Note: The agents above are often mentioned in lists of formerly weaponized microorganisms or microorganisms suspected of having that potential.

States renounce its use? There are multiple considerations, but it is worthwhile to note that the Soviet program began in earnest around that time. The United States remained confident of the utility of nuclear weapons, and the Soviets were concerned about US superiority and therefore were seeking other weapons of mass destruction. Another powerful reason comes out of the analysis of why lethal chemical agents were not used by the major powers after World War I: support by the military establishment requires that they understand the capabilities of a weapon and have a systematic doctrine for its use *(27)*. This was not the case within the US military establishment, which has only begun to take biological warfare defense seriously after Desert Storm put them in the arena with an adversary that may have had effective biological weapons and was believed to be capable of using them if the situation demanded. The ability of biological weapons to strengthen the capability of an otherwise poorly armed Third World military with attainable financial and expertise requirements fits into the doctrine of "asymmetric warfare." Biological weapons are much cheaper and more easily produced than the equivalent nuclear capability, so they can provide weapons of mass destruction for nation-states that do not follow the nuclear route.

This discussion begs the question of how much expertise is needed for terrorists to mount such an attack should they not acquire weapons from a nation state. Obtaining many of the most dangerous agents from nature is not difficult for a determined person with the microbiological knowledge needed to produce a significant weapon. Their propagation in simple media or animals is straightforward for an experienced microbiologist and the equipment and supplies needed are readily available. However, a limiting step is to convert this slurry of potentially lethal microorganisms into a form that is stable and readily disseminated in aerosols. This is not an expertise that is readily available in the microbiological community. However, in other skill areas such as pharmaceuticals, cosmetics, and insecticides, there are extensive reservoirs of knowledge and ongoing research in both liquid and powder aerosols. For example, *Bacillus thuringiensis* spores, not pathogenic for humans unlike *B. anthracis* spores, disseminated as a liquid in approximately 120-μm aerosols aimed at settling and eliminating gypsy moths in a Canadian forest also gave measurable concentrations of approximately 7-μm particles near and inside houses (28). Under reasonable assumptions this dose of anthrax spores would result in a 14% to 17% fatality, and calibrating the spray apparatus to focus on smaller droplet size would only increase this *(29)*. Both practical and developmental studies are being carried out to define the conditions for liquid, spray-dried, and freeze-dried powders as success aerosols and published in the open literature (*30*,31).

However, basic expertise is needed to achieve success. One example of a nonstate attempt is provided by the failed efforts of the Japanese group, Aum Shinrikyo, to prepare lethal anthrax and botulinum toxin weapons. Adequate financing, equipment, and a locale were available, but the principal players had such a lack of microbiological expertise that a vaccine strain of *B. anthracis* was selected for their "weapon" *(16,17)*. We cannot depend on the ineptitude of terrorists for our protection.

Before the 9/11 attacks in 2001, several important commissions examined the vulnerability of the United States to terrorism and found the likelihood of a serious attack to be very high. The so-called Bremer (32), Hart-Rudman *(33)*, and Gilmore *(34)* commissions warned of catastrophic terrorist events including bioterrorist attacks, and indeed they were essentially correct in their assessments. Later reports from the Gilmore Commission *(20)* conclude that the post-9/11 status is still precarious. There are indications that Al Qaeda has interests in anthrax as a weapon *(35)*. Thus, the continuing escalation of terrorists dedicated to extreme lethal events and expert assessments suggest that the risks of biological attacks continue to be very real.

PREVENTION OF BIOTERRORISM

The fundamental approach would be to eliminate the seeds of terrorism, but this remedy does not seem to be forthcoming in the foreseeable future (36). The next step would be to design international arms control regimens that would stop the proliferation of biological weapons in state programs. Unlike nuclear and chemical threats, biological weapons do not emit radioactivity or have unique precursors or equipment for manufacture. The prospect of complete control by such a regimen is small; although it is an important and useful counterproliferation modality to have treaties such as the BWC in place and to be seeking improved ways to pursue enforcement and surveillance activities *(10)*.

Another approach has been to deny access of unauthorized persons to the microorganisms that might be used to produce weapons of mass destruction, and this has been pursued through establishing a list of "select agents" and stringently limiting access to these microorganisms. This clearly will have utility in preventing the use of

hard-to-obtain agents such as smallpox, Ebola, or Marburg viruses. It is ineffectual and expensive when applied to agents such as anthrax, plague, and tularemia, which are widely available from nature worldwide. In fact, it is counterproductive through enhancing unrealistic public attitudes, about the danger or research quantities of these agents limiting research, and discouraging scientists from working with these agents.

One might also attempt to protect the public by limiting effective processing of biothreat agents for aerosol dissemination, but much of the knowledge and equipment could be available through the pharmaceutical, cosmetic, agricultural, paint, and other manufacturing communities. Probably the single most dangerous persons are those from the Soviet biowarfare program. They have specific knowledge about processing, stabilization, and other manipulations for preparing infectious agents for aerosolization.

The strongest approach in the short term is to utilize the intelligence community in the United States and abroad to detect the next attack. Although this approach is likely to be successful in many instances, we cannot depend on it to always permit us to intercept a bioterrorist attack before its execution and a medical defense will be needed as well.

In the long run, we must recognize that those same advances in science and technology that hold enormous promise for improving health and combating bioterrorism also present many opportunities for misapplication or inadvertent harm. We need to ensure that the tools of modern genomic biology are not used to create new and more dangerous microorganisms. This is a complex challenge, for no one would want to impede the progress of legitimate and important science. However, we also have a responsibility to face up to the very real concern of the potential misuse of the biotechnological tools increasingly available to those who want to do harm.

With leadership from the scientific community, we must begin to examine the context and conduct of modern science, and what opportunities may exist to constructively reduce this emerging threat. A recent report from the National Research Council of the National Academies emphasizes "that biological scientists have an affirmative moral duty to avoid contributing to the advancement of biowarfare or bioterrorism." The report goes on to state that "scientists can and should take reasonable steps to minimize this possibility," indicating that it is "the responsibility of the research community, including scientific societies and organizations, to define what these reasonable steps entail and to provide scientists with the education, skills, and support they need to honor these steps" (32). On a policy level, such prevention efforts will require a global approach, including the development and implementation of international standards, norms or guidelines for biosecurity, and the practice of biomedical research.

MEDICAL DEFENSE AGAINST BIOLOGICAL THREATS

Because of the diversity of threats, one must settle on defined scenarios for response planning. Uses of biological agents to cause disease in small numbers of people are probably best dealt with by alert medical and public health communities that will recognize the possibility that such outbreaks are due to human intervention and respond accordingly *(4,5)*. At the current stage of national planning, most effort has gone into preparations for mass casualty situations. The scenario usually envisaged is not a "lights and sirens" kind of attack. Most likely there would be no announcement—no envelope saying "this is anthrax, take penicillin." Without a fortuitous discovery early on, there would be no discrete signal that an attack had occurred; no site you can cordon off while you take care of the casualties, search for clues, and eventually clean up and repair the damage. Instead, this type of event would probably unfold as a disease epidemic, spread out in time and place before authorities even recognize that an attack has occurred. We would know we had been attacked only when people began appearing in their doctor's office or emergency rooms with unusual symptoms or inexplicable disease. The "first responders" to a bioterrorism event would not be Hazmat teams but rather public health officials and health care workers. "Ground zero" would be hospitals, labs, and health care facilities. Unfortunately, in many scenarios, diagnosis of the problem may be delayed, because medical providers and laboratories are not equipped to recognize and deal with the diseases of greatest concern. What is more, effective medical interventions may be limited, and where they exist, the window of opportunity for successful intervention would be narrow.

The response to such events must involve above all a strong public health system, an element in the national infrastructure that has been severely neglected and in need of repair for bioterrorism response, protection from emerging infectious diseases, and even dealing with established quotidian disease threats *(18)*. Strengthening surveillance systems will be among the most important elements of the early warning systems. Many innovative ideas such as syndromic surveillance through a variety of electronic means are in urgent need of evaluation for sensitivity and specificity (37) (see also Chapter 103). Some of these approaches may prove more useful for reassurance about nonevents or assessing ongoing attacks than early detection. It is absolutely clear that effective surveillance will require a large investment in basic epidemiological investigation of case clusters, but it is by no means clear that the trained manpower and resources for this effort exist. In addition, improved communication—including computer connectivity—will be essential to quickly collect, analyze, and share information among public health and other officials at local, state, and federal levels as well as other essential partners.

One of the important elements of the response will be an enhanced laboratory response in the public health and the clinical arena. The importance of high volume testing was abundantly clear during the 2001 anthrax episodes, and the CDC's strengthening of the Laboratory Response Network was an important component of bringing existing resources online to respond. In the hospital laboratory there are two important considerations. First, the most dangerous bacterial bioterrorism agents are not necessarily optimally cultivated in the systems used and may even be discarded from considerations by some of the automated processing. Second, the distribution of infectious

diseases is generally log-normal and characterized by the median and the dispersion *(38)*. One consequence of this is that the number of cases is skewed toward the earlier times and so early recognition is important to give an increased therapeutic and prophylactic window. The only way we will be likely to achieve this is if point of care diagnostics are available for many of the threat agents, particularly plague.

It is worth noting that the front line for recognition of a bioterrorist attack will likely be the clinician. This was true in the 2001 anthrax attack, in which a Florida clinician used the classic tools of infectious disease diagnosis to recognize a case of inhalation anthrax with secondary meningitis (39); it is true in most emerging infectious disease outbreaks; and it will likely hold for the next bioterrorist attack. The implications for clinician education and awareness are obvious.

Once an outbreak is recognized, treatment and postexposure prophylaxis will of course be paramount. In the late 1990s, a National Pharmaceutical Stockpile was established to address this concern *(40)*. The response capability of a stockpile of vital medical supplies, including selected drugs, vaccines, antidotes, and medical equipment, was demonstrated in several recent tragedies, including the World Trade Center bombings and the anthrax attacks. Responsibility to maintain and oversee use of this stockpile, now called the National Strategic Stockpile (NSS), has just transferred from the CDC to the new Department of Homeland Security. The NSS is cached in selected locations across the country to be delivered within 12 hours to any place in the nation that requires assistance. Of course, the nature and quantities of materials maintained in the stockpile needs to be reviewed and extended.

OTHER CONSIDERATIONS

There are many rapidly changing fields that we cannot cover in this chapter. Many are discussed in the following chapters in this section. We will touch on some of the others.

1. Absence of surge capacity in acute care hospitals. With the improved efficiency in bed utilization in today's hospitals we have lost the ability to respond to the room and staff demands that would be expected from any significant bioterrorist attack. This is evident in the frequent diversion of ambulances and closure of emergency rooms in response to even a moderate increase in influenza A cases. The experience with SARS in several foreign cities has demonstrated how easily healthcare systems elsewhere can be overwhelmed, and how the breakdown of care and services can contribute to ongoing and international spread of disease.Absence of surge capacity in acute care hospitals. With the improved efficiency in bed utilization in today's hospitals we have lost the ability to respond to the room and staff demands that would be expected from any significant bioterrorist attack. This is evident in the frequent diversion of ambulances and closure of emergency rooms in response to even a moderate increase in influenza A cases. The experience with SARS in several foreign cities has demonstrated how easily healthcare systems elsewhere can be overwhelmed, and how the breakdown of care and services can contribute to ongoing and international spread of disease.
2. Some progress has been made in improving the legal underpinnings of quarantine and other emergency decisions that might be important in dealing with a bioterrorist situation, but this remains geographically spotty and generally untested.
3. Use of drugs and diagnostics that are unlicensed or perhaps licensed for other indications is a major concern. The FDA and others are working positively in this area (41), but we are far from resolving the issues that surround diseases that are not commonly seen in the United States and in some cases anywhere in the world.
4. Communications are always cited as a problem, but the scope of needed improvements in the biodefense field is phenomenal. Obvious basic concerns about sharing information among public health and medical personnel during evolving situations are complicated by the need to extend this to civil authorities, law enforcement, the public, and the media. Some of the issues are not merely solved by computers or phone lists; there are deep cultural divides among these compartments and issues of control. To deal with such an emergency, there will be no substitute for having an informed cadre of reporters who understand the issues and have some rapport with the public health authorities; this will facilitate dealing with the anxious, the incubating, and the sick with minimal public panic.
5. Although public education might be subsumed under the rubric of "communication," this aspect is so important that we mention it separately. An appreciation of the basic facts of infectious diseases and bioterrorism will be essential in obtaining an effective response to an attack and in engendering support for the counterterrorist agenda. We must begin now because there continue to be significant gaps in both media and public understanding of the situation and we remain unprepared.
6. We have not dealt with the issues of infectious agents directed against crops or domestic animals. Even without the loss of one human life, it is resoundingly clear that a terrorist could achieve their goals of producing mass panic, economic damage, and the undermining of public confidence in government by an attack on animals or crops. If the agent is one such as Rift Valley fever, which is an agricultural pathogen and which is also a human pathogen, the complications will be multiplied *(42)*.
7. The research agenda is enormous. It ranges from the psychological effects of bioterrorism through operations research to the most basic molecular biology. Most of the biothreat microorganisms are emerging infectious diseases and/or regional threats outside the United States. However, through global neglect of these agents, we have a poor understanding of their basic biology and treatment. We have not begun to think through some of the trade-offs in our attempts to medically protect the civilian population from bioterrorism. As one example, traditional infectious diseases control as well as protection of the military against biological warfare regards vaccines as the gold standard. However, in today's world with multiple threat agents and no certainty of

the use of any one of them, vaccines present an inherent risk that may not be acceptable. It may be preferable to rely on drugs in many situations; even though they have their own side effects and treatment may not be as effective as vaccine prevention, at least they would be used in the presence of a known risk (43). Certainly, vaccines will be important for a communicable disease such as smallpox, to protect at-risk laboratory workers, and selected populations or circumstances (44).

8. The aerosol mode of delivery presents us with a discipline that is both familiar and yet strangely forgotten. At one time, aerosols were studied as important mechanisms of spread of tuberculosis, measles, and other diseases; in the last two decades much of this knowledge has eroded from the medical curriculum. We need to resurrect this information and add new research findings. The importance in defense against catastrophic bioterrorism is undeniable. Observations on the use of *Bacillus thuringiensis* to kill arthropods have provided a chilling example of large area coverage by this relative of *B. anthracis* (28,*29*). Older observations based on liquid and powder aerosol biological warfare agents have given us a good perspective on the dissemination of airborne infection (*22*,24). However, the properties of the fine, hydrophobic powders that were the most dangerous weapons developed are not well understood by the medical community *(5)*, and the knowledge of their properties to form secondary aerosols is an area of some ignorance to all *(45)*.

CONCLUSIONS

The United States has just begun a long march toward effective biodefense measures. We should not suppose that this threat will disappear or that it is not significant because of the failure to find biological weapons in Iraq. The process will be expensive but will yield dividends through strengthening our national security, our posture toward emerging infectious diseases, and the public health system that protects us every day *(18)*. We still need a national dialogue and deeper thinking to resolve the elements of this complex problem (*20*,46).

FURTHER READING

The best single source for the principles of dissemination, history of biological warfare, and several of the diseases is the *Textbook of Military Medicine* edited by Sidell, Takafuji, and Franz *(22)*. Because many of the diseases are emerging or tropical diseases, that literature often has a more expansive treatment than texts oriented toward North American considerations *(47)*. The series of articles from the Johns Hopkins Center for Civilian Biodefense are excellent treatments of category A agents and are available through their Web site (http://www.upmc-biosecurity.org/). Some excellent Web-based aids are available at www.cidrap.umn.edu. Good popular books about biowarfare and bioterrorism cover the older history *(8)* and more recent events *(9)*. An excellent book for the intelligent layman who needs background is *Living Terrors: What America Needs to Know to Survive the Coming Bioterrorist Catastrophe* (48). It would be of interest to many to read at least one of the pre-9/11 commission reports predicting catastrophic terrorism and bioterrorism (32,*33*,*34*), as well as some of the more recent thinking on where we need to be going in biodefense (46).

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CHAPTER 102

The State and Local Response to Bioterrorism

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BACKGROUND

After the anthrax terrorist events of 2001, there was recognition at local, state, and federal levels of the importance of improving and maintaining the public health infrastructure as a primary defense against bioterrorism. In January 2002, the Department of Health and Human Services announced the availability of $1.1 billion in federal funding that would be made available to all states and four large urban areas (Chicago, District of Columbia, Los Angeles, and New York City) in federal fiscal year 2003 to address critical gaps in bioterrorism public health preparedness and response plans and infrastructure.

Federal funding for biodefense increased over the next several years through FY2006, trended down through FY2008, and has increased modestly in recent years. The FY2010 federal budget for biodefense totaled $6.05 billion *(1)*, with a significant portion applied to programs that serve multiple public health goals in addition to improving bioterrorism preparedness, according to an "all hazards" approach to disaster preparedness.

At the local and state levels, public health preparedness continues to develop on many fronts, creating expanded capacities for rapid and effective responses to incidents caused by intentional (e.g., bioterrorism) or accidental releases of biological threat agents (BTAs). Local and state health authorities must be able to recognize the occurrence of unusual disease manifestations, clustering, or increases in infectious disease illnesses through a variety of surveillance systems. Detection must be followed by prompt epidemiologic, environmental, and laboratory investigation, and an intentional source must be distinguished from a natural cause.

Once a BTA event is suspected, public health authorities need to be able to mobilize rapidly to identify the time, location, and method (e.g., aerosol vs. foodborne) of the release and conduct ongoing surveillance and epidemiologic investigations to characterize the extent of the outbreak. Local and state public health departments must be closely coordinated with the appropriate governmental agencies at the local and state (e.g., emergency management, police, emergency medical services), regional (neighboring state and county authorities, especially public health counterparts), and federal (e.g., Departments of Health and Human Services, Homeland Security, Defense, and Justice) levels. This coordination relies heavily on preexisting relationships and agreements with these agencies.

Local and state health authorities must also be able to communicate with and assist healthcare providers in the community through routine, well-established mechanisms. Linkages with the local healthcare provider, hospital, long-term care, home care, and laboratory communities are essential for successful engagement during a crisis. Public health authorities must determine whether antibiotic or vaccine prophylaxis is indicated and, if so, must be prepared to coordinate with emergency management agencies and the healthcare community to provide medications to potentially exposed persons.

In addition to effective communication with the provider community, local and state public health authorities must be prepared to communicate effectively with and engage the public at every step in the BTA investigation, even when information is limited.

By enhancing their capacities required for rapid and effective responses to outbreaks caused by potential BTAs, public health agencies are better prepared when naturally occurring public health emergencies occur (Table 102-1). This was evident in the local, state, and federal responses to the challenges of the 2009 H1N1 pandemic.

STATE AND LOCAL HEALTH DEPARTMENTS IN THE UNITED STATES

Public health authority in the United States resides mostly at the state and local levels, with the powers of our federal public health agencies being limited and specific to certain key areas (e.g., international and interstate quarantine, and regulation of drugs and vaccines). At the state level, the public health role focuses on ensuring that statutory authority is in place for both routine and emergency health activities, monitoring statewide disease surveillance in coordination with local health units, developing policy and guidelines for disease control activities, providing reference laboratory services, and supporting local public health agencies through financial or technical assistance. In contrast, local public health activities focus more directly on the collection of disease surveillance data; case and

TABLE 102-1

BTA Preparedness Checklist for Local and State Public Health Agencies

1. Coordination and communication
   a. Development and maintenance of an up-to-date contact list, with built-in redundancy, for all key personnel at responding local, state, and federal agencies (e.g., emergency management, police, fire, regional public health partners, FBI, and CDC)
   b. Regular interagency meetings with emergency management, law enforcement, and hazardous material responders to ensure that public health planning efforts are integrated with other agencies' plans
   c. Prepreparation of response protocols for each BTA, as well as various potential scenarios (e.g., threat incidents involving suspicious environmental samples vs. covert large-scale aerosol attack)
   d. Regular tabletop exercises and drills (include representatives from medical and laboratory communities)
2. Surveillance
   a. Illnesses caused by key potential BTAs should be included on the notifiable disease list; in addition, a clause to ensure that any unusual disease clusters or manifestations are reportable should be included in the local and/or state health code
   b. Ongoing provider outreach efforts to enhance knowledge of diseases caused by potential BTAs and to reinforce familiarity with all disease-reporting requirements
   c. Periodic bulletins on disease reporting and bioterrorism, with an emphasis on 24-h telephone contact information for reporting suspect cases of urgent concern
   d. 24-h/7-d response capability with appropriately trained medical staff to triage calls from providers regarding potential cases of public health concern
   e. Consider establishing syndrome-based or unexplained illness/death surveillance with protocols in place outlining response mechanisms if unusual disease activity is identified
3. Epidemiologic capacity
   a. Contingency plans for mobilizing health department staff to assist in a large and/or multiple epidemiologic investigations
   b. Template questionnaires and forms for chart reviews and other surveillance activities can be drafted beforehand; outbreak management database with electronic linkages to the public health laboratory
   c. Pre-established guidelines and procedures for conducting joint investigations with law enforcement
   d. Integrating environmental assessments and laboratory testing with the surveillance and epidemiologic response
4. Laboratory capacity
   a. Education of clinical microbiologists at local hospitals regarding criteria for reporting suspicious laboratory findings
   b. Training in chain of custody requirements and certification in proper packaging and transport of specimens according to government regulations
   c. Public health laboratories should participate in the CDC's LRN—for example, as reference laboratories—and should facilitate integration of clinical hospital and commercial laboratories into the LRN as sentinel laboratories
5. Guidance regarding clinical management of illness due to BTAs
   a. Clinical guidelines for the medical management of diseases caused by potential BTAs drafted before an event
   b. Communication infrastructure to ensure rapid distribution of guidelines and protocols to providers and hospitals, if needed (e.g., broadcast facsimile and e-mail, Web site, and Health Alert Network)
   c. Pre-event planning for establishing a medical hotline to assist clinicians in the management of patients and contacts and to triage reports on suspect cases, including surge capacity and just-in-time training for staff
6. Mass medical and mortuary care
   a. Contingency plans for enhancing capacity for acute medical care and mass mortuary needs (including plans for how federal DMAT and DMORT teams will be used)
   b. Contingency plans for rapidly establishing and maintaining community-based clinics for mass prophylaxis using antibiotics and/or vaccines (including plans for providing prophylaxis to difficult-to-reach populations, such as the homebound and homeless)
   c. Determination of need and feasibility of establishing a local antibiotic stockpile to ensure adequate supplies while awaiting federal reserves (antibiotic stockpiles need to include alternative regimens for pediatric, pregnant, and immunocompromised patients, when indicated)
   d. Prepreparation of multilingual patient information sheets and vaccine consent forms
   e. Contingency plans for establishing and enforcing quarantine of potentially infectious contacts (e.g., contacts of smallpox cases)
   f. Guidelines to assist local medical care institutions' planning for responses to citywide infectious disease emergencies, including treatment of mass casualties and fatalities, staffing, and other resource shortages and the integration of facility-specific plans into regional emergency management. Planning should include providers of acute care, long-term care, home care, and outpatient and emergency medical services
   g. Contingency plans for mass mortuary care including tracking, storage, and disposal of potentially infectious remains

(*Continued*)

TABLE 102-1

BTA Preparedness Checklist for Local and State Public Health Agencies (*Continued*)

7. Communication and mental health issues
   a. In coordination with other responding agencies, predesignation of primary spokesperson(s) and/or agency
   b. Pre-event drafts of fact sheets on potential BTAs for the general public
   c. In partnership with mental health agencies, develop capacities for providing crisis counseling for escalating numbers of potential victims, their families, first responders, the medical and public health community, and the general public
   d. Broadcast facsimile and e-mail capacity (e.g., Health Alert Network) to facilitate urgent communications and notifications of the medical community
8. General infrastructure issues
   a. Establishment of a public health incident management system with training of all staff regarding their expected emergency response roles and responsibilities
   b. Sufficient capacity to support emergency communication (cellular phones, two-way radios, BlackBerries), transportation, information technology, and personal protective equipment requirements

BTA, biological threat agent, CDC, Centers for Disease Control and Prevention; DMAT, Disaster Medical Assistance Team; DMORT, Disaster Mortuary Relief Team; FBI, Federal Bureau of Investigation; LRN, Laboratory Response Network.

contact management activities to control disease spread (e.g., provision of immune globulin for hepatitis A contacts or directly observed therapy for tuberculosis); and, in some localities, direct provision of healthcare *(2)*. However, great heterogeneity exists with respect to personnel capacity, services offered, and organizational structure among state and local health departments in the United States. In some states, public health is decentralized, with most activities and services occurring at the local level, and with state officials providing more of an oversight and advisory role. In other states, there are no local health units, and all public health activities are conducted by the state. An even greater diversity of capacity and services exists among local health departments. In some large urban areas, the local health agencies are larger than many state health departments and function independently, whereas in more rural counties, resources may be quite limited with minimal professionally trained staff, thus requiring a greater reliance on state-level support.

ROUTINE LINKAGES BETWEEN PUBLIC HEALTH AND THE HEALTHCARE SECTOR

Public health authorities routinely interface with the healthcare sector on many levels. One of the core missions of public health agencies is the control of communicable diseases. This legal mandate requires the close coordination between public health officials and their local healthcare provider, hospital, and laboratory communities. Traditionally, disease surveillance activities depend on prompt reporting by healthcare providers and laboratorians concerning suspect or confirmed cases of notifiable diseases to local and state health departments.

One of the most important linkages at the local level is between public health officials, infection preventionists (IPs), and healthcare epidemiologists. IPs and healthcare epidemiologists serve as the primary points of contact in hospitals for surveillance and disease control activities during both community- and healthcare-associated outbreaks and serve a critical role in any hospital's ability to respond to a BTA event. Case investigations by public health officials often require communication with the reporting clinician or hospital IPs, whether for more detailed clinical and/or epidemiologic data or to help facilitate the collection, packaging, and transport of appropriate clinical specimens for testing at public health reference laboratories (e.g., rabies or botulism).

In addition to reliance on IPs and healthcare epidemiologists for surveillance and case investigation, public health officials routinely request assistance from the provider community when postexposure prophylaxis is indicated for contacts at risk of potential secondary transmission (e.g., hepatitis A or invasive meningococcal disease).

Partnerships between health departments and the medical provider community are also essential in implementation of public health prevention campaigns. Examples of this successful partnership include the response to the epidemic of multidrug-resistant tuberculosis in the early 1990s *(3)*; perinatal hepatitis B prevention programs; HIV counseling, testing, and partner notification programs; and vaccination campaigns for seasonal influenza and high-risk groups for hepatitis A *(4)*.

BIOTERRORISM PREPAREDNESS REQUIRES ENHANCED LINKAGES

Bioterrorism preparedness requires building on linkages between the public health, hospital and medical care sectors that are already in place to confront routine public health problems. The terrorist events of 2001 highlighted gaps in the capacity of the healthcare system to respond to large-scale health events. In 2002, the Congress created the Hospital Preparedness Program in the U.S. Department of Health and Human Services. One of the significant outcomes of this program has been the development of healthcare coalitions (5) composed of healthcare facilities and response agencies (including and often led by local and state public health authorities).

Healthcare coalitions work together regionally to create comprehensive response plans tailored to the specific capacities and needs of the local communities. Hospital preparedness programs and healthcare coalitions enable the local medical and public health communities to become familiar with each other before a public health emergency occurs. Recent examples of linkages between public health authorities and the healthcare community include enlisting primary care clinic staff to deliver vaccinations or prophylactic antibiotics, training emergency medicine physicians and nurses to recognize and initiate treatment of BTA-related diseases, and partnering with intensivists to plan for surge capacity in critical care. Additionally, providers from pediatrics, obstetrics, and geriatrics were targeted to increase vaccination among their high-risk patients during the recent 2009 H1N1 pandemic.

Medical providers and key hospital staff (e.g., infection preventionist and microbiology staff) should know the local and state health departments' 24-hour, 7-day-a-week emergency contact numbers and Web site information and should be registered for public health electronic communication systems (e.g., Health Alert Network, broadcast facsimile, and e-mail health alert systems such as the Centers for Disease Control and Prevention's (CDC's) Clinician Outreach and Community Activity Listserv at *http://www.bt.cdc.gov/coc*a) that provide urgent notification of the community during acute events.

Key aspects of plans that need to be in place for the public health response to suspected or confirmed incidents involving BTAs parallel what should be used for naturally occurring infectious disease outbreaks. The 2009 H1N1 pandemic was a naturally occurring outbreak that demonstrated the need for many of these capacities and highlighted some of the ongoing challenges for public health emergency preparedness planners (6).

INTERAGENCY AND INTERSECTOR COORDINATION AND COMMUNICATION

Just as established linkages between public health authorities and the healthcare sector must be enhanced before an emergency occurs, strong relationships must be in place between public health agencies and other relevant local, state (e.g., emergency management, police, emergency medical services, fire/hazmat, and poison control centers), and federal (e.g., CDC and Federal Bureau of Investigation [FBI]) agencies prior to a public health emergency, whether a BTA event or a natural outbreak. A centralized emergency operations center is essential to facilitate intra- and interjurisdictional coordination and communication. In the event of an emergency, predesignated representatives from all involved agencies and any local or state hospital associations should be assigned to this center to ensure effective coordination of the overall response.

The public health sector's communication, transportation, and other equipment or infrastructure needs for disaster response should be assessed prior to an emergency. Essential resources include reliable and redundant communication capacity (e.g., cellular telephones, handheld devices [with e-mail/Internet access], laptop computers with modem, two-way and 800-MHz radios, and satellite telephones); broadcast facsimile and e-mail capability; secure Internet sites (e.g., Health Alert Network) to rapidly notify and inform the healthcare sector regarding events of public health concern; and computer systems that are networked between the local and state health department, the local emergency management command center, and appropriate state and federal agencies. Additionally, hospitals and some primary care clinics have enhanced their own redundant communication systems to improve and ensure internal and external communication with employees, public health authorities, and first responder agencies. Backup generators should be available not only in healthcare settings but also for use by public health authorities, as demonstrated by the 2003 blackout in New York City when a delay in obtaining generators limited the public health response *(7)*. Finally, an alternative location for emergency operations personnel to meet must be identified, in the event that the primary emergency operations center is damaged or otherwise unavailable.

If personnel are expected to use specific equipment and procedures during an emergency, they must be trained and demonstrate proficiency beforehand. To the extent possible, these response measures should be based on routine operations. It is unreasonable to expect unfamiliar plans, protocols, procedures, or equipment to be implemented or used effectively during an emergency.

While training for public health staff should include the clinical, laboratory, and epidemiologic features of disease caused by exposure to potential BTAs, it should also focus on the expected roles and responsibilities of agency staff during response activities. Key challenges facing public health officials once a BTA incident is detected include characterizing the scale and scope of the biological hazard; estimating accurately and rapidly those populations at risk from exposure to the biological hazard; distributing effective countermeasures efficiently and within a time frame that will prevent infection among those exposed; supporting the healthcare system that will be treating potentially thousands of casualties; and disseminating accurate and frequent guidance and updates for the public and providers. Importantly, these activities must be performed within an incident management structure that is consistent with national standards.

Effective training tools include tabletop and field exercises, with involvement of representatives from all key local, state, and federal agencies and representatives from the local medical and laboratory communities. These exercises provide the opportunity to test assumptions in existing plans and work out issues related to decision-making authority and respective roles and responsibilities among the disciplines that would be involved in responding to a BTA event. A successful exercise includes a written after action report that highlights gaps in preparedness that should be addressed through follow-up meetings and revision of written plans, if indicated, and reevaluated with periodic exercises.

DETECTION OF A BTA EVENT: TRADITIONAL AND NONTRADITIONAL SURVEILLANCE SYSTEMS

If there were a delay in detecting an outbreak caused by a BTA release, public health preventive interventions might be less effective than if started sooner, and the impacts on morbidity and mortality could be substantial (8). The

diseases caused by potential BTAs may not be suspected or diagnosed rapidly for a number of reasons: initial presentations may be nonspecific (e.g., influenza-like prodrome of anthrax); most physicians in the United States have little or no clinical experience with the diseases caused by these agents (e.g., anthrax, tularemia, botulism, or smallpox); laboratory diagnosis may require days or longer for presumptive identification (e.g., tularemia); the epidemiology and clinical presentation of diseases caused by intentional dissemination may differ from what is found in naturally occurring disease; and more common microorganisms could be used that might not be associated immediately with criminal intent (e.g., enteric pathogens).

State and local public health officials should consider the different surveillance strategies for detection of BTA-related incidents and need to be alert to potential ways in which they could present. A potential BTA dissemination should be considered by public health authorities or healthcare professionals if any of the following occurred:

1. A single suspected or confirmed case of an illness resulting from exposure to a potential BTA occurring in a patient without a plausible explanation for his or her illness (e.g., a case of plague in the absence of a recent travel history to a recognized endemic area).
2. Multiple patients presenting with a similar clinical syndrome that has unusual characteristics (e.g., unusual age distribution or previously healthy individuals), is clustered by time and/or space (e.g., all became symptomatic within the same approximate time period or attended the same special event), or involves unusually severe illness, without an obvious etiology or explanation.
3. An *unexplained* and marked increase in the incidence or severity of a common syndrome above seasonally expected levels (e.g., a sudden increase in influenza-like illness especially if during the summer and if rapid diagnostic tests were negative for influenza and other common respiratory viruses).

If a potential BTA incident is suspected, an investigation should be initiated immediately to determine the etiologic agent and the likely source of infection, including whether or not a natural route of transmission exists. Because the above circumstances could result from intentional, accidental, or natural exposures, it is important for those evaluating and managing routine cases and/or outbreaks to keep an open mind to all possibilities. Investigations of what appeared to be routine foodborne outbreaks, upon further epidemiologic and laboratory investigation were found to have resulted from intentional contamination of food with enteric pathogens *(9,10)*. In contrast, when diseases associated with exposure to a potential BTA occur in a nonendemic area, intentional dissemination (e.g., bioterrorism) could be a possibility; however, a natural explanation also must be considered. In 2002 in New York City, two bubonic plague cases occurred in residents of New Mexico who were exposed to plague bacilli shortly before traveling to New York *(11)*. Inhalation, cutaneous, and gastrointestinal anthrax also have occurred in recent years following exposure to contaminated animal hides and African *(12–14)*.

There are a number of surveillance methodologies used for detecting BTA incidents that focus on recognizing or detecting (a) a suspected or confirmed case or illness cluster resulting from exposure to a potential BTA; (b) community-wide or localized increases in influenza-like illness activity or other nonspecific syndromes or increases in potential markers of early prodromal illness (e.g., over-the-counter drug sales); (c) an increase in unexplained, severe infectious illnesses or deaths; or (d) nucleic acid from select bacteria or viruses in air samples collected routinely by environmental biomonitoring programs.

Traditional Public Health Surveillance

Traditional public health surveillance for BTA-associated illness relies on enhancing the medical and laboratory communities' familiarity with these agents, with the goal of improved reporting of suspected or confirmed illnesses potentially caused by a BTA, as well as reporting of unusual disease manifestations or illness clusters. Most local and state health codes require that physicians, hospitals, and laboratories report a defined list of notifiable infectious diseases. Many state public health agencies have added all CDC Category A and most Category B agents that were not already included on their reportable disease lists *(15)*. In addition, recognizing the need to detect newly emergent diseases that are not yet listed on the health code, most states also require reporting of any unusual disease clusters or manifestations.

Early recognition of a BTA-associated event depends in large part on astute clinicians and laboratorians recognizing one of the index cases based on a suspicious clinical, radiologic, or laboratory presentation (e.g., a febrile illness associated with chest discomfort and a widened mediastinum on chest radiograph in an otherwise healthy adult suggests inhalation anthrax). Isolated cases presenting at separate hospitals will not be recognized as a potential outbreak unless they are reported promptly to the local health department, where the population-based aberrations in disease trends are more likely to be noticed. Previous examples of astute clinicians recognizing and reporting unusual disease clusters or manifestations that led to the detection of a more widespread outbreak includes an outbreak of hantavirus in the southwestern United States *(16)*, Legionnaires disease associated with the whirlpool on a cruise ship *(17)*, an outbreak of *Cyclospora* associated with contaminated raspberries imported from Guatemala *(18)*, and the initial outbreak of West Nile virus in New York City in 1999 *(19)*. Similarly, the initial detection of anthrax in 2001 was due to a physician who recognized that large gram-positive rods in a patient's cerebrospinal fluid could be *Bacillus anthracis (20)*. By reporting this suspected case of meningeal anthrax, rapid confirmation was facilitated in a state public health reference laboratory. Weeks later, a suspected case of inhalation anthrax was recognized and promptly reported to and confirmed by public health authorities in New York City *(21)*.

To inform clinicians and laboratorians regarding their essential role in recognizing and reporting suspected or confirmed illness caused by exposure to potential BTAs, public health officials need to promote the importance of disease reporting through ongoing educational efforts. Targeted outreach efforts should focus on specialists in key areas, such as infectious diseases, infection control, microbiology, emergency medicine, dermatology, and neurology. Educational

outreach should emphasize the clinical presentations and diagnostic clues for specific BTA-associated illnesses (e.g., anthrax, plague, and smallpox) and unusual illness patterns suggestive of an intentional outbreak. One lesson learned during the 2001 anthrax outbreak was that public health and medical professionals need to keep in mind all potential clinical manifestations caused by BTA exposure. Cutaneous anthrax—not inhalational disease—was the sentinel illness in New York City. Educational materials also should emphasize prompt reporting of any unusual disease clusters or manifestations to the local or state health department as paramount to the early recognition of natural, intentional, and accidental outbreaks caused by BTA releases. Educational outreach is also needed for key members of the local first responder community (e.g., hazmat, police, and emergency medical services).

The following methods can be used to help increase awareness of BTA-associated illnesses in the medical and laboratory communities:

1. Oral presentations targeting specialists in internal medicine, emergency medicine, pediatrics, dermatology, neurology, family practice, infectious diseases, geriatrics, pathology, laboratory medicine, intensive care, pulmonary, radiology, and primary care physicians; physicians-in-training and medical students; medical examiners; veterinarians; and microbiologists.
2. Public health bulletins (22), newsletters, posters, or pocket cards that present overviews of the clinical aspects of infections caused by potential BTAs (e.g., clinical presentation, laboratory diagnosis, treatment, and prophylaxis) and emphasize the importance of promptly reporting any unusual disease clusters or manifestations to the local and state health departments. These educational materials should be updated and redistributed periodically to maintain ongoing awareness of and sensitivity to these issues.
3. Posting educational materials on the health department's public Web site with links to other useful resources (23), including the CDC (*http://www.cdc.gov*), the Infectious Disease Society of American (*http://www.idsociety.org*), the American Society for Microbiology (ASM; *http://www.asm.org*), and the Center for Infectious Disease Research and Policy at the University of Minnesota (*http://www.cidrap.umn.edu*).
4. Development of teaching slides and videos that can be distributed to academic and community-based physicians (train-the-trainer modules). Because many health departments may not have sufficient staff with the expertise or time to meet every request for a talk on the clinical aspects of the BTA and the threat of bioterrorism, efforts should be made to provide teaching materials (e.g., slide presentations with speaker notes) to interested local colleagues in infectious diseases, infection control, or other specialties to do presentations to medical staff at their own institutions or organizations.

Improving the overall relationship between the health department and the medical community is an important element that makes it more likely that providers will report promptly. Efforts to improve provider relations and streamline physician reporting should be prioritized. Web-based and other electronic methods can be offered for routine case reporting. During emergencies, a consistent telephone number could be used for provider hotlines (e.g., 1-800-MD-REPORT). This would facilitate efficient and timely triage of provider and laboratory calls to clinically trained health department personnel. Dissemination of surveillance data routinely and during emergencies also can foster the ongoing, collaborative relationship between public health and the medical and laboratory communities. These efforts have the additional benefit of improving all aspects of local public health surveillance.

Outbreaks of West Nile virus *(24)* and monkeypox *(25)* underscored how public health departments could benefit from establishing and maintaining active collaborations with the animal health community. Many potential BTAs cause zoonotic disease (e.g., anthrax, plague, and tularemia), and animal populations might be affected in unpredictable ways.

Historically, with the exception of rabies-related issues, local and state infectious diseases epidemiologists have not had strong relationships with clinical veterinarians and wildlife specialists in their community. However, with the continued emergence of new zoonotic disease threats, including those related to bioterrorism, local, state, and federal public health agencies have taken steps to improve communication between these communities. Veterinarians have been hired within communicable disease programs to foster collaboration. Requirements have been expanded to include reporting by animal health specialists of suspected or confirmed illness in an animal that might be caused by a potential BTA *(26)*. Similar to the list of notifiable diseases in humans, these regulations also can require reporting of any unusual disease clusters or manifestations in animals.

Nontraditional Surveillance Systems (Syndromic Surveillance)

In the event of an unknown, intentional, or accidental BTA dissemination with the potential to cause thousands of casualties, rapid detection and characterization of the outbreak would be crucial. The swift mobilization of surveillance and epidemiologic resources to determine the place, time, extent, and method of the release would help target preventive measures, speed the epidemiologic and criminal investigation, and reduce public anxiety. For diseases with short incubation periods such as inhalation anthrax, the window of opportunity to respond and to reduce morbidity and mortality is narrow. Therefore, surveillance systems that rapidly provide information on the potential magnitude and geographic scope of a BTA incident, that is, "situational awareness," are paramount.

The traditional public health surveillance system, based on passive reporting of a limited number of defined, notifiable diseases, may not be sufficient for early detection of a large accidental BTA release or for early recognition of the extent of its impact. Some diseases caused by these pathogens (e.g., tularemia) have nonspecific and protean clinical presentations, and laboratory diagnosis may be time-consuming. Thus, alternative systems that allow prompt recognition of unusual disease manifestations, clusters of illness, increases above expected seasonal levels of common syndromes (e.g., influenza-like illnesses), or deaths resulting from unknown infectious causes are potentially useful components of bioterrorism surveillance.

Surveillance for nonspecific clinical syndromes using data available in existing electronic health databases is considered a potentially valuable adjunct system for the timely detection of illness caused by exposure to a BTA. Although many of the most concerning potential infections (e.g., anthrax, plague, smallpox, and viral hemorrhagic fever) have distinct clinical characteristics once the disease is fully manifest, initial symptoms include a nonspecific febrile prodrome similar to influenza-like illness. Large numbers of botulism cases, on the other hand, would present with symptoms pointing to autonomic and voluntary motor nerve dysfunction. Nonspecific gastrointestinal symptoms would predominate if a food item was contaminated with an enteric pathogen.

Because many medical providers and laboratorians in the United States have limited experience with these pathogens, diagnosis may be delayed. Therefore, the first indication that large-scale exposure to a potential BTA has taken place might be an increase in nonspecific symptoms at the community level. Surveillance for these increases in nonspecific syndromes (e.g., respiratory, gastrointestinal, or neurologic) constitutes the cornerstone of syndromic surveillance used for emergency response purposes *(27)*.

The ideal features of a syndromic surveillance system for early detection of a BTA-related outbreak include the ability to detect changes in disease trends that are based on health event information available continuously, in close to real time or at least in 12- to 24-hour increments. Health event information is most timely when it is electronic, gathered routinely for other purposes, and not limited by diagnostic or recording delays. Syndromic surveillance systems based on clinical data have proven most popular, but other sources such as over-the-counter drug sales may also have utility.

Electronic data that may provide a reflection of community-wide illness are increasingly available, including emergency department visit logs *(28)*, ambulance dispatches *(29)*, ambulatory care encounters (30), data from electronic health records (31), and sales of prescription and over-the-counter pharmaceuticals *(32)*. The most reliable electronic data sources are those that already exist (e.g., emergency department and outpatient visits) and that do not rely on additional collection or reporting of data by medical providers. In many systems, these data include geographic information (e.g., home or work zip code or location of store), theoretically enabling the detection of localized disease outbreaks and monitoring of the geographical extent at a given point in time of a potentially widespread event.

Operation of syndromic systems for outbreak detection and situational awareness purposes should be at least daily (including weekends and holidays) and should use statistical algorithms to rapidly detect increases in disease syndromes compared with expected seasonal trends (33). Some systems have the additional sensitivity to detect geographic clusters *(34)*. Hospitals and medical care systems may be able to share data with their local or state health departments, including information on emergency department or primary care clinic visits or hospital admissions. If the data do not contain confidential patient information (e.g., de-identified data limited to age, date of visit, chief complaint, or provider diagnosis), then potential restrictions in the Health Information Privacy and Accountability Act would not apply *(35)*.

When an aberration in a particular syndrome is identified, either a jurisdiction-wide increase or a geographic-specific signal, public health officials need to assess the situation to determine if the finding may represent the first indication of a community outbreak and, if so, conduct an investigation. Similar to traditional outbreak investigations, syndromic signal investigations must determine whether the aberration represents common, background illness versus illness explained by a common exposure. To help separate genuine incidents from statistical anomalies, it is generally assumed that a continued increase in the incidence of the syndrome over two data collection periods is evidence of a genuine event. Interim data from involved facilities (e.g., the most recent 12-hour chief complaint log) can be useful in this evaluation. An aberration generated by one data source may represent unexpected artifacts (e.g., increases in the sale of an antidiarrheal medication resulting from a corporate promotion). However, when multiple signals occur in systems based on independent data sources, the aberrations are likely to reflect a genuine increase in community illness and further investigation would be indicated.

Inspection of the aberrant data may reveal unexpected coding mistakes or the presence of commonalities in demographic variables. Emergency department staff, as directed by geographic clustering, also can be called and asked whether increases in certain illnesses have been seen. As the providers on duty may not be those who worked when the analyzed data were collected, these anecdotes, though reassuring, may have limited value. If aberrations include sudden, marked increases in signal amplitude over baseline, unusual age clustering, or other unexpected features, health department staff can be dispatched to review medical records, conduct interviews, or conduct telephone follow-up on discharged patients. Prospective surveillance also can be augmented with enhanced diagnostic testing for newly presenting patients, as indicated by the syndrome of concern (e.g., rapid antigen tests for influenza, chest radiographs, or blood cultures).

Although initially conceived for early detection of a large, aerosolized covert BTA dissemination, these systems also can be used to monitor natural infectious disease outbreaks and trends in noninfectious events of public health importance. In New York City, syndromic surveillance has been in place since the 1990s, and since that time, numerous other state and local health departments have adapted or developed syndromic surveillance systems for use in their jurisdictions (*36*,37). Information from syndromic systems has proven to be useful for detecting, monitoring, and characterizing seasonal outbreaks of influenza *(38)*, winter gastroenteritis (e.g., norovirus and rotavirus), and asthma, and it has facilitated more timely notification of the medical community and public that preventive measures (e.g., vaccination) were recommended. Furthermore, syndromic systems were utilized extensively during the novel H1N1 influenza pandemic of 2009, along with other methods, to estimate the scale of community-wide influenza transmission (Fig. 102-1).

Health officials in New York City and elsewhere have also found syndromic surveillance useful for providing reassurance that localized to widespread outbreaks were not being missed during times of heightened concern. During the international outbreak of severe acute respiratory

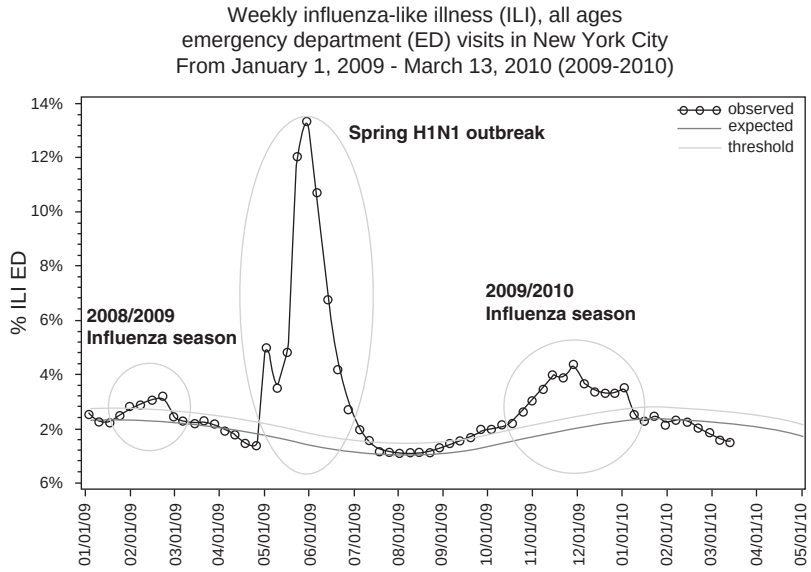

FIGURE 102-1 Weekly ILI syndrome visits to New York City emergency departments (EDs) showing the 2009 H1N1 pandemic and the previous influenza season for comparison. Expected and threshold values are derived from a Serfling model using influenza isolate data and ED syndromic information. ILI visits are defined as visits where the patient's presenting chief complaint include fever and cough *or* fever and sore throat *or* flu.

syndrome (SARS) in 2003, the absence of a persistent city-wide increase or geographic clustering of respiratory or febrile syndromes in any of the current systems in place in New York City provided some assurance that unrecognized SARS transmission was not occurring in the city. Similarly, when cases of inhalation anthrax *(39,40)* and bubonic plague *(11)* were confirmed in New York City, the lack of signals from these systems suggested that these were isolated, not city-wide, events.

Syndromic surveillance data also have been used to monitor trends in noninfectious diseases or conditions of public health concern. Recent applications in New York City have included assessing the cardiovascular morbidity associated with temperature and air pollution; correlating sales of nicotine prevention products—a marker of intent to stop smoking—with increases in the local cigarette sales tax; and identifying areas with increased rates of drug overdose death and domestic violence, through analysis of emergency medical service and emergency department data.

Though the utility of syndromic surveillance systems is well established in many state and local health department settings, particularly for situational awareness for a variety of public health problems, challenges remain. The interpretation of signals and evaluation of syndromic systems for early detection of outbreaks has been complicated by ongoing point-of-care difficulties, including the lack of rapid diagnostic testing of common viral and bacterial respiratory pathogens. As one of the main strategic goals of syndromic surveillance is to detect early signs of BTA-related illness, it would be valuable for emergency department practitioners in locations with syndromic signals to have access to reliable and rapid assays that could rule in the common etiologies of influenza-like illness.

It is not yet clear that syndromic surveillance would detect BTA-related outbreaks of varied scale and scope as there have been no large-scale BTA-related outbreaks to analyze in formal validation studies. Correlations have been seen between large-scale syndromic aberrations and infections from circulating viruses such as influenza and norovirus but small clusters identified by syndromic systems have not been matched to specific microorganisms that may have been causing the disease. However, the benefits beyond early detection of a BTA-related event, including improved situational awareness, may make the investment of resources in syndromic surveillance worthwhile *(41)*. Most importantly, these systems complement but cannot replace traditional disease surveillance for early detection based on disease reporting from astute medical providers. Recent outbreaks of BTA-related disease have been detected after concerned providers rapidly notified the local or state public health authorities regarding a single concerning case or small cluster *(11,20,21)*. Syndromic surveillance has been very helpful in these situations for providing assurance that a larger scale event was not occurring.

Unexplained Deaths and Severe Illnesses Potentially Resulting From Infectious Causes

Surveillance for unexplained deaths or severe illnesses that may be due to unrecognized infectious causes also might prove useful for detecting infectious disease outbreaks caused by BTAs. Sources of data include intensive care unit admissions, vital records (if electronic registrations systems are in place so that death certificates are available for analyses within 24 hours of filing), and medical examiner surveillance *(42)*. These systems also have potential usefulness for detecting new or reemerging infectious diseases with higher rates of morbidity and mortality, such as hantavirus pulmonary syndrome or SARS.

Existing systems focus on potentially infectious deaths or severe illnesses among otherwise healthy adults between the ages of 18 and 65 years, as unexplained infectious deaths are less common in this age group (43). Surveillance for unexplained infectious illness requires establishing collaborations with the critical care community and IPs; providing clear criteria for reporting suspect cases; and ideally including a strong laboratory component that encourages submission of appropriate clinical samples, including

tissue biopsies, for comprehensive testing at reference laboratories. Similar collaborations should be in place with the local medical examiner for unexplained infectious death surveillance, with protocols in place to obtain tissue samples from multiple organs for microbiologic, molecular, and/or antibody-based testing (e.g., immunohistochemical staining).

Simpler systems for monitoring potential infectious deaths involve the use of death certificate data, which are already being collected at the state and some local health department levels. These systems require clear criteria regarding which causes of death should be included (e.g., sepsis without a specific etiology). However, limitations to this method of surveillance include the typical 2- to 3-day delay between the time of death and filing of the death certificate, the lack of electronic death certificate data in most jurisdictions, and the inability to detect clusters at the time of illness onset because the data are restricted to fatal cases only. The usefulness of these systems are also limited by usual concerns regarding the reliability and accuracy of these data and the inability to obtain additional diagnostic testing unless clinical specimens were still available or autopsies were performed.

Although these systems in and of themselves may not be useful for the initial detection of a BTA-related event, they have potential usefulness as adjunct systems. If a suspicious case or cluster were detected, it would be valuable to have these systems in place to assess whether there had been any recent fatalities with similar presentations that could be part of the suspected outbreak. Finally, these systems encourage public health officials to forge relationships with partners in the intensive care and medical examiner/coroner communities—linkages that should be in place prior to the occurrence of a large, infectious disease outbreak of public health concern, whether natural, intentional, or accidental.

Environmental Monitoring for Intentional or Accidental BTA Releases

In 2003, the Department of Homeland Security (DHS) began deployment of BioWatch, an environmental monitoring system for detection of specific potential BTAs in approximately three dozen urban areas. It was meant to function as a biological early warning system, detecting evidence of aerosol dissemination before persons presented with acute illness. The system uses standard environmental air samplers that pump air across a filter membrane. The filters are collected and transported to local or state public health laboratories, where polymerase chain reaction testing is used to identify specific nucleic acid signatures for each of the potential BTAs. Third-generation systems have been planned that would be more automated, allowing for more timely detection using fewer public health laboratory resources.

DHS recently commissioned the National Academy of Sciences to examine the BioWatch program and to characterize the contribution of this system relative to public health and healthcare systems (44). Several areas of concern were identified and recommendations were issued that are intended for implementation prior to the deployment of the third-generation technology. These recommendations include improved integration of the system with the public health systems in jurisdictions where BioWatch is deployed and increased DHS support for local public health agencies so that they can respond more effectively to signals generated by BioWatch. A key report finding was the recognition that deployment of any environmental monitoring system must be accompanied by bolstering of local and state capacity to respond to potential public health emergencies detected by that system. In particular, health authorities must be equipped to rapidly determine whether a signal is real and, if so, define the geographic area affected and identify the potentially exposed individuals.

COORDINATION AND LAW ENFORCEMENT

An outbreak that is suspected or confirmed to be associated with dissemination of a potential BTA may be a criminal event. It requires careful consideration of when and to what extent coordination and collaboration with local, state, and federal law enforcement would be indicated. FBI is the primary agency charged with coordinating with other law enforcement agencies for all criminal investigations of incidents that are suspected to have resulted from the intentional use of a BTA *(45)*. Law enforcement agencies have not historically worked closely with the public health community. One of the lessons learned from the 2001 anthrax incidents was the value of public health and law enforcement officials knowing each other and being familiar with their respective investigational responsibilities *before* a crisis (46). FBI has established a nationwide network of Weapons of Mass Destruction Coordinators in key urban areas. These experienced investigators have been very successful in forming and sustaining valuable and effective collaborations with their public health counterparts.

Public health officials should establish consensus agreements with local law enforcement and FBI that address how all parties will communicate and coordinate activities during the investigation of any incident involving the suspected intentional use of a BTA. Protocols and procedures should acknowledge both shared and separate interests and can involve general counsel from each agency *(47)*. For example, it is crucial for public health to establish standards for joint investigations that minimize potential detrimental impacts on patients and on the routine activities within healthcare facilities. Otherwise, longstanding and critical relationships with providers and the public—necessary for carrying out core public health missions—could be damaged. Procedures can be implemented that acknowledge and protect this public health requirement and that also afford law enforcement sufficient flexibility to respond in ways that would not compromise a criminal investigation. For law enforcement, it is important to be notified by public health investigators whenever the possibility of a BTA release is being considered, to have immediate access to the patient's demographic information, and to be confident that public health investigators can deploy rapidly and at any time and respect the importance of crime scene investigations.

Joint investigation protocols can establish agreements in the following areas: circumstances when one party to the agreement will notify the other(s); response times;

information sharing; and parameters for joint interviews of ill patients and/or friends and household members (e.g., limited to where, when, and how exposures took place). The threshold for providing law enforcement with confidential patient information must be high and consistent with local, state, and federal statutes and regulations.

Clearly designated points of contact should be established between both local and federal law enforcement and local public health agencies, so that information can be shared confidentially, securely, and with confidence. Though it is not required for information sharing between trusted parties in most emergencies, a limited number of federal security clearances also might benefit local public health departments, so that certain officials can maintain work-related access to relevant classified information.

During a joint investigation of a suspected covert BTA release, public health and law enforcement staff will press to determine rapidly and efficiently the time, location, and method of dissemination. With that information, public health authorities may tailor interventions to those persons with specific exposure risk factors, enabling more effective use of finite personnel and material resources. For law enforcement, this collaboration could lead to more efficient determination of the crime scene, evidence collection, and arrest of suspected perpetrators.

Collaborative public health and law enforcement investigations would involve joint interviews of patients and families in hospitals, sharing of potentially sensitive data, and active liaison with and contribution to the respective epidemiologic and criminal investigations. Laboratory specimens obtained as part of the public health investigation, including both clinical and environmental samples, would need to be handled as potential evidence and collected with full attention to chain of custody and Select Agent Program documentation requirements *(48)*.

INITIAL INVESTIGATION AND NOTIFICATION OF ALL KEY PARTNERS IN THE EVENT OF A SUSPECTED OR CONFIRMED BIOTERRORIST EVENT

The initial investigation into a potential BTA-associated event should proceed according to preestablished protocols, as much as possible. Separate protocols may be needed to address the response to at least five potential scenarios: (a) suspected (i.e., by public health authorities) or confirmed cases of illness resulting from exposure to a potential BTA that are reported by a provider or laboratorian; (b) an unusual disease cluster or manifestation reported by a provider or laboratorian (e.g., rapidly progressive respiratory failure in a group of students from the same school); (c) marked statistical aberrations detected by syndromic surveillance (e.g., sudden, extraordinary increase in the number of patients with influenza-like illnesses presenting to emergency departments or unexplained infectious deaths); (d) a suspicious environmental sample identified in the field (e.g., package containing a written threat and a suspected disseminating device); or (e) a positive laboratory result generated by BioWatch or another environmental monitoring system.

When a suspected or confirmed BTA incident is detected by traditional public health surveillance, plans, protocols, and procedures should be used that address the following issues: internal and external notification, including other local agencies (e.g., the mayor's office, police, fire, and emergency management) and state and federal preparedness and response partners (e.g., state health and emergency management departments, CDC, and FBI); rapid diagnostic testing to confirm the presence of a BTA; communication hotlines for medical providers, the media, and the general public; disease-specific information to the healthcare community that addresses medical management of and infection control precautions for case-patients and potentially exposed persons; enhanced passive surveillance through the reporting of suspect cases; active surveillance and epidemiologic investigations that estimate the scale and scope of the incident and the risks associated with it; support for the healthcare sector's treatment of casualties; distribution of mass prophylaxis, when indicated; and addressing mental health needs, environmental recovery, and community resilience. Emergency call-up lists should be maintained to ensure that sufficient public health staff can be mobilized to assist in all aspects of the emergency response.

Depending on circumstances, notification of federal authorities might include a request for support as provided by the National Response Framework. This could include epidemiologic and laboratory assistance from the CDC; medical, pharmaceutical, and/or vaccine supplies from the Strategic National Stockpile; Disaster Medical Assistance Teams (DMATs); or Disaster Mortuary Relief Teams.

The initial responses to syndromic surveillance aberrations and to results from environmental monitors would be different. If the first indication of a BTA release came from a statistical anomaly or a tested air sample, it is possible that patients with suspected BTA-related infections would not yet have been reported to public health authorities. Accordingly, it would be challenging to determine whether or not the aberrant signal or air sample reflected a genuine public health concern. If a syndromic surveillance aberration was sufficiently unusual (e.g., marked increase in amplitude over what had been seen in the past), it is likely that hospitals would be contacted and asked to enhance diagnostic testing of persons meeting a specific surveillance case definition. Public health investigators also might be deployed to hospitals to review charts and to prospectively conduct active surveillance.

The field responses to an environmental monitoring test result or to a suspicious substance would resemble a hazardous material event, involving first responders from the fire, law enforcement and emergency management agencies. Government environmental monitoring programs use specific and federally validated laboratory assays. Positive results could, depending on circumstances, lead to an intensive investigation that assumed that a BTA release had taken place, including interagency notifications and coordination of interagency responses.

Suspicious substance investigations (e.g., powder in mail), though managed as hazardous material incidents, would not result in a full-scale environmental investigation unless a potential BTA were identified in the tested material. Protocols and procedures for evaluating suspicious

substances should address (a) coordination with other responding local agencies (e.g., emergency management, police, and fire hazmat); (b) collecting, packaging, and transporting samples for rapid testing at public health reference laboratories; (c) appropriate protective gear for first responders; and (d) if and when decontamination and prophylaxis of potentially exposed persons would be indicated.

Although there are commercially available kits that can screen suspicious substances for potential BTAs, FBI, DHS, and CDC have advised against using them for field testing because of the potential risks from both false-positive and false-negative results *(49)*. Reference laboratory testing at state or local public health laboratories is available within a matter of hours in most jurisdictions. Therefore, it is currently advised to withhold any preventive measures, such as antibiotics or vaccinations, pending test results. In the event of extenuating circumstances suggesting that an intentional BTA release was likely (e.g., intelligence information or suspicious disseminating device found at the scene), the field response might include additional measures.

The federal government has not published personal decontamination recommendations for suspicious substance incidents, and it is likely that standards vary between jurisdictions. One state has recommended that the decision should be based on both the law enforcement threat assessment and whether there had been direct contact with the suspicious letter or package *(50)*.

Response personnel at the scene should collect accurate, 24-hour emergency contact information for all potentially exposed persons. If polymerase chain reaction results confirmed the presence of DNA from a potential BTA or if cultures grew the microorganism, they would be contacted immediately to arrange administration of postexposure prophylaxis. Antimicrobial prophylaxis should not be started without first consulting the local health department. In most cases, that decision should be based on the results of tests conducted by public health reference laboratories.

Educational sessions and mental health counseling may also be required on-site and should be included in the interagency response plan to suspicious environmental samples. Potentially exposed persons do not require hospital evaluation unless they report symptoms needing immediate evaluation (e.g., chest pain or difficulty breathing).

PUBLIC HEALTH REFERENCE LABORATORY TESTING OF SUSPICIOUS CLINICAL SPECIMENS

A close and active partnership between the public health laboratory and local clinical laboratories is essential to any infectious disease emergency response. Laboratorians in sentinel laboratories must be trained to identify potential BTAs and demonstrate proficiency, including procedures used for reporting suspicious isolates to the local public health authority. Clinical laboratories also must be certified to pack and transport clinical specimens according to government regulations.

In 1999, the Laboratory Response Network (LRN) was established through collaboration of the CDC, the Association of Public Health Laboratories (APHL), and the FBI to ensure an effective and coordinated laboratory response to bioterrorism at the federal, state, and local levels. The LRN is a tiered-response system for testing and confirmation of potential bioterrorist agents and is composed of sentinel, reference, and national laboratories.

Sentinel laboratories include many hospital and commercial laboratories and follow established protocols for the initial testing of suspicious specimens. Protocols have been developed by the ASM in coordination with the CDC and the APHL to assist sentinel laboratories with techniques to rule out potential BTAs. These guidelines are available on the ASM Web site (*http://www.asm.org*) and provide detailed information regarding the staining properties, growth characteristics on routine media, and preliminary biochemical test results for the bacterial agents. If a potential BTA is suspected at the sentinel laboratory level, samples must be referred to a reference laboratory. Reference laboratories include >140 state and local public health, military, federal, and international laboratories (Australia, Canada, and the United Kingdom) as well as veterinary, agriculture, food, and water testing laboratories. These biosafety level 3 laboratories have the ability to confirm agents such as *B. anthracis* and *Clostridium botulinum*. National laboratories, including the CDC and Department of Defense laboratories, have biosafety level 4 capabilities and perform definitive testing of certain exotic microorganisms (such as smallpox) in high-containment environments *(51)*.

At the state and local levels, training should be routinely offered that addresses laboratory diagnosis and biosafety precautions for potential BTAs and chain of custody requirements, with the target audience being clinical microbiologists and laboratorians in local sentinel laboratories. Training materials should emphasize the potential critical role of laboratorians in the early detection of BTA-related incidents, through recognition of suspicious isolates and prompt reporting to local public health authorities.

Despite the establishment of the LRN and the development of protocols for local and state clinical microbiologists, challenges to the laboratory response to a large-scale outbreak remain. The over 2,000 sentinel laboratories in the United States vary in their preparedness (52). In the event of a large-scale BTA dissemination or naturally occurring outbreak, sentinel and reference laboratories may be quickly overwhelmed by demand for testing. They must be ready to coordinate quickly with public health officials in the implementation of incident-specific guidelines that explain which specimens to obtain, referral criteria for confirmatory testing in the local or state public health laboratory, and handling and shipping requirements. The 2009 H1N1 influenza outbreak demonstrated the potential for rapidly overwhelming sentinel and reference laboratories with the increased demand for testing.

ACTIVE SURVEILLANCE AND EPIDEMIOLOGIC INVESTIGATIONS AFTER THE INITIAL DETECTION OF A CONFIRMED BIOTERRORIST EVENT

Once a BTA-related event is recognized and confirmed by laboratory testing, public health officials have two immediate objectives: (a) to determine who was exposed and

potentially at risk by accurately estimating the scale and extent of exposure to the BTA and (b) to track the health impacts of the incident. To accomplish the former, it will be necessary to determine where, when, and how the dissemination occurred. Data will be collected, analyzed, and interpreted from epidemiologic and criminal investigations and from any environmental sampling that is conducted. Data and analyses must be shared between agencies. In some cases, interstate and international coordination of the epidemiologic investigation may be necessary depending upon the scope of the event. Outlier cases occurring among residents of neighboring or other jurisdictions may provide valuable information to help identify the site, time, and manner of release.

Enhanced passive and active surveillance must be initiated immediately to support epidemiologic investigations that rapidly identify risk factors and track ongoing impacts from the incident. Template materials can be prepared before a BTA event—and revised as necessary—to expedite an investigation. Ready-to-go draft documents can include surveillance instruments (e.g., generic questionnaires for case ascertainment and chart review that can be rapidly modified to the specific circumstances under investigation) and public health alerts that could be mass e-mailed and faxed to all hospitals, primary care settings, and key subspecialists throughout the jurisdiction. This would increase the reporting of illness suspected of being associated with the incident to public health authorities. Generic surveillance instruments should include variables that capture patient demographics; clinical illness; exposures to ill contacts; commuter routes (e.g., subway or bus lines); food histories, if warranted; and potential exposures during the likely incubation period of the specific BTA, such as time spent at stores, restaurants, theaters, museums, tourist attractions, parks, places of worship, schools, sports events, other entertainment venues, and other special events. Both paper and electronic copies of these surveillance materials should be readily available.

Efficient and accurate data management is one of the highest priorities and challenges during any high-profile outbreak investigation. Effective outbreak data management requires the linking of clinical and epidemiologic data with laboratory information, to track specimen collection, laboratory testing results, and the patient's case status (i.e., suspect or laboratory-confirmed). Appropriate public health decisions depend on having up-to-date, accurate information about the evolving outbreak, and the healthcare community, political leaders, the news media, and the public need and expect accurate information describing the event's impacts. This requires having flexible, tested databases that can be modified to the specific incident. These systems should be exercised during routine outbreak investigations to facilitate efficient use during emergencies.

GUIDANCE FOR HOSPITAL AND MEDICAL PROVIDERS

Most medical and laboratory professionals in the United States have had minimal clinical experience with the most concerning potential BTAs (e.g., anthrax, smallpox, and plague). In the event of a BTA release, public health authorities must provide timely information that guides the identification, reporting, and medical management of these diseases and how providers, hospitals, clinics, and others in the healthcare sector can coordinate with local, state, and federal public health partners. The launching of the Hospital Preparedness Program in 2002 made available federal monies to all states and four large urban areas (Chicago, District of Columbia, Los Angeles, and New York City). The monies went to hospitals, outpatient centers, long-term care facilities, emergency medical service agencies, and poison control centers to enhance their surge capabilities. Over time, healthcare coalitions were created among hospitals and other nonhospital healthcare facilities to share plans, medical supplies, and personnel through signed memoranda of understanding (5).

During a BTA-related event, it is possible that healthcare workers would be less likely to present for work out of concern for their own health or the health of their families or because of challenges related to transportation or childcare *(53)*. To expand the pool of available healthcare workers, volunteer medical systems have been created in each state. Another source of medical personnel during an emergency is DMATs deployed through the federal government.

Detailed and frequently updated resource libraries for diseases caused by key potential BTAs have been developed and made available online by the University of Minnesota's Center for Infectious Disease Research and Policy (*http://www.cidrap.umn.edu*) and other governmental and academic institutions. These resources address the microbiology, epidemiology, clinical presentations, diagnosis, treatment, prophylaxis, and infection and exposure control considerations for anthrax, plague, tularemia, botulism, smallpox, and viral hemorrhagic fever, and they can serve as an introduction to BTAs and as an ongoing resource for providers and healthcare facilities.

State and local health officials should build upon existing materials when developing guidance specific to the circumstances of an event. Documents can be disseminated to medical providers via varied and redundant mechanisms, including a Health Alert Network; local or state health department public Web sites; Listservs maintained by hospital and provider trade organizations; and other medical groups. Guidance for hospitals and medical providers should include clear criteria for reporting suspect cases (including clinical and epidemiologic features that meet the public health surveillance case definition), instructions for submitting clinical specimens to the public health reference laboratory, treatment and prophylaxis, infection control precautions to prevent healthcare-associated exposures to a contagious disease, and advice on where to find reliable, frequently updated public health information.

In addition to protocols, model tabletop exercises to test an institution's response to BTA incidents have been made available *(54)*.

Health departments also must be able to rapidly mobilize medical hotlines for providers using clinically trained staff to triage calls reporting suspect cases. Questions regarding the medical management of cases, contacts, and asymptomatic exposed persons also must be answered. The staffing, training, and telephone equipment needs for this unit should be predefined. Ideally, preexisting provider hotlines that are used routinely for public health questions

would be supplemented. However, given the potential for a marked increase in calls to this hotline during emergencies, contingency planning should address the likelihood that escalating capacity and training would be needed.

In addition to hotlines, conference calls for healthcare partners provide the opportunity for immediate updates and question-and-answer sessions and may be hosted by local or state health departments or another coordinating group within a regional healthcare coalition. Once again, preexisting relationships among the health department officials, providers, hospital administrators, and emergency management officials facilitate this exchange of information in a time of crisis.

MASS CASUALTY, MASS PROPHYLAXIS, AND MASS MORTUARY PLANNING

Local and state public health authorities should play an active role in planning for how the treatment of mass casualties will be coordinated from a jurisdiction-wide perspective, in collaboration with area hospitals, nonhospital healthcare facilities, emergency medical services, and emergency management agencies. For planning purposes and during responses, accurate and frequently updated information is needed from all acute care facilities within the jurisdiction that capture available staffed beds (i.e., adult, pediatric, medical, surgical, and intensive care), isolation and emergency department capacity, and inventories of key equipment (e.g., ventilators) *(55)*. Local public health officials and area hospitals should work together to evaluate preparedness activities, using tabletop and field exercises to assess the adequacy of planned institutional responses to a BTA release.

Individual hospitals or hospital networks must develop institutional-specific plans for how they would respond to an area-wide infectious disease emergency, including activating the hospital's incident management system; implementing rapid patient discharge plans and bed capacity expansion strategies; managing marked increases in emergency department visits and admissions; outdoor triage—including safe and acceptable personal decontamination, if necessary; canceling all nonemergent admissions and procedures; mobilizing additional personnel and determining emergency staffing strategies; reopening patient units that had been closed; and establishing temporary isolation units, if needed. A number of mass casualty triage tools have been created, initially conceived for rapid assessment of soldiers during wartime, and more recently developed for civilian use. These tools are intended to allow for rapid classification of large numbers of patients according to several physiological parameters associated with clinical presentation. However, these instruments have not been adequately studied, standardized, or universally accepted, limiting their use during a public health emergency or disaster (57).

During incidents of this kind, healthcare facilities are likely to be inundated with "worried well" and strategies to limit the impact of "low-risk patients" have been developed *(57)*. These strategies include dissemination of rapid, clear, and concise information to the public, including who should and should not seek medical attention; rapid updating of health department Web sites with current information on the outbreak; the use of telephone-based consultation with healthcare providers; public hotlines that are staffed by nurses to guide callers on if and where to seek care for their symptoms; and the use of set criteria for rapidly triaging patients at the entry to hospitals or primary care practices to distinguish those requiring immediate evaluation and treatment from those who may be referred back to their homes with planned follow-up by telephone.

Other important, difficult issues that must be addressed ahead of time include the manner in which critical resources (e.g., ventilators) would be fairly distributed if there were insufficient supplies (58), whether alternate treatment sites would be established in certain situations, emergency credentialing procedures for nonaffiliated medical staff and volunteers, and whether specific facilities would be designated to care for contagious patients and their contacts. Mass care planning should be coordinated with local relief agencies, such as the American Red Cross, and public health authorities in neighboring counties and states. Nontraditional use of home care agencies and long-term care facilities may be needed to make hospital beds available. Mutual aid agreements are useful to have in place and to exercise before emergencies, as done routinely by fire and police departments and emergency medical services. Because there also may be a need to request federal support (e.g., DMATs), local authorities need to consider how these resources could be integrated most efficiently with existing acute care facilities.

In addition to medical treatment of mass casualties, health authorities may need to provide mass prophylaxis to potentially exposed persons and/or close contacts (e.g., in the case of anthrax or smallpox). Planning for the rapid provision of antibiotics and/or vaccines to large populations requires the involvement of public health, emergency management, and the local medical community. Efforts should focus on (a) predetermination of which antibiotics and vaccines would be needed in a variety of circumstances, (b) how these medications could be mobilized and distributed rapidly and efficiently, and (c) considerations for certain potentially vulnerable populations, such as children, pregnant women, and those who are isolated and without resources and social supports. Mass prophylaxis plans need to consider the specific challenges in distributing antibiotics and vaccine to difficult-to-reach populations, such as the homeless and homebound. Multilingual medical information sheets and vaccine informed consent forms should be prepared in advance. Although there is currently a federal stockpile of medications and supplies, the Strategic National Stockpile, local and state officials need to consider whether a smaller stockpile should also be maintained locally to ensure supplies are available in the first hours or days after an attack is detected, given cost issues and limited shelf life of many pharmaceutical agents. Specifically, contingency plans for setting up community-based, mass prophylaxis clinics that address staffing resources, equipment and space requirements, and patient flow must be developed ahead of time *(59,60)*.

The capacity of health officials to rapidly vaccinate the community was recently tested in many regions during the 2009 H1N1 pandemic. The effort to provide vaccine

to large numbers of city residents in New York City, including thousands of schoolchildren, demonstrated the need for flexibility and coordination in distribution of vaccine, which included school-based programs, community health centers, pharmacies, and large health department–sponsored vaccination clinics.

Finally, mass mortuary issues (including tracking, storage, and disposition of decedent's remains) must be addressed by the local and state medical examiners, in coordination with local public health officials, emergency management, and hospital associations. Guidance for the safe handling and disposal of potentially infectious remains should be developed *(42)* and may be adapted from established plans already developed for pandemic influenza *(61)*.

In regards to potential BTAs, the standard procedures used to prevent infections during autopsies would be sufficient. Embalming should not be performed in decedents associated with BTA incidents. Cremation without embalming would be recommended following death from anthrax, smallpox or a viral hemorrhagic fever. If cremation were not possible, burial in a sealed container would be an alternative. Smallpox vaccine should be offered to any persons providing direct medical care for—or postmortem examination of—patients with suspected or confirmed smallpox *(42)*.

Any deaths associated with the intentional release of a BTA would be classified as homicides. An efficient mechanism must be established urgently to ensure that all deaths thought to result from bioterrorism are reported to the appropriate local authorities, such as the medical examiner's or coroner's office.

LEGAL ISSUES RELATED TO THE PUBLIC HEALTH RESPONSE TO BIOTERRORISM OR OTHER INFECTIOUS DISEASE EMERGENCIES

In 2002, the CDC asked the Center for Law and Public Health at Georgetown and Johns Hopkins Universities to draft a model state public health law (the Model State Emergency Health Powers Act or Model Act) for jurisdictions to use in addressing a BTA-related event (e.g., bioterrorism) or naturally occurring disease outbreaks (62). The Model Act outlines five major public health functions to be allowed by the law: preparedness, surveillance, management of property, protection of persons, and communication.

In addition to ensuring sufficient authority to collect disease surveillance data, conduct contact tracing, and provide preventive measures to those at risk, public health laws must enable health officials to implement quarantine measures, if needed, to control a contagious disease outbreak with epidemic potential and that could lead to severe morbidity or mortality (e.g., smallpox). This authority should be linked with specific criteria that were scientifically appropriate and that would be met before quarantine could be implemented. In addition, public health laws should provide for due process measures to protect those affected *(63)*. Ideally, quarantine strategies would be determined and operational procedures would be in place prior to an emergency.

Public health agencies should be satisfied that they have operational capacity to implement and enforce quarantine, which could be done in homes, hospitals, and other facilities. Complex operational details that would need to be addressed include thresholds that would trigger decisions regarding implementation of quarantine; situations that would merit home versus facility-based quarantine; and logistics needed to provide food, medical care, and financial compensation (i.e., lost wages) to those who were quarantined.

It may be necessary to request that the federal government temporarily suspend specific laws and grant emergency waivers so that hospitals would not be considered noncompliant with acts such as the Health Insurance Portability and Accountability Act and the Emergency Medical Treatment and Active Labor Act during declared states of emergency. Legal standards of care that are used normally may not be applicable or achievable during emergencies. For example, lay vaccinators might need to be employed for a mass vaccination campaign even though this would not be allowed routinely. Because of shortages of critical supplies, public health agencies also could ask providers and hospitals to make individual treatment decisions that might differ from how they would practice medicine during nonemergencies. Unless temporary "crisis standards of care" are used during emergencies and disasters that protect clinicians from subsequent liability claims, public health agencies may not be able to manage finite emergency resources equitably or effectively *(64)*. It is also essential that these modified standards be developed at a federal level to ensure consistent approaches and criteria are used nationally.

ENVIRONMENTAL ISSUES

Following the dissemination of certain potential BTAs, public health and environmental agencies would be challenged by a number of potentially significant environmental health concerns. The released pathogen might be stable in most or some environmental matrices (e.g., *B. anthracis*, *Francisella tularensis*, and *Yersinia pestis*). Environmental contamination could result in long-term biological hazards, in which case remediation and recovery issues would predominate after the immediate disease control interventions (e.g., prophylaxis for presumed inhalational exposures) had been addressed.

Some potential BTAs are zoonotic pathogens that are normally part of complex life cycles that include insect vectors and nonhuman mammalian reservoirs (e.g., *Y. pestis*, *F. tularensis*, and the virus that causes Rift Valley fever). If one were released in a nonendemic region or where only sporadic human disease was found, entomologists, rodentologists, livestock veterinarians, pest control experts, and others might need to be engaged to assess complicated environmental and ecological issues and address them.

The extensive and prolonged public health responses to the 2001 anthrax clusters underscored some important public health gaps. Enhanced methods are needed to conduct timely environmental risk assessments and BTA remediation *(65)*. More public health expertise in this regard must be developed at the local, state, and federal levels

based on improved and scientifically validated methods for collecting and testing samples from a variety of environmental matrices and for interpreting findings to assess environmental risks. If buildings and other structures were contaminated, new, timely, and effective remediation strategies would be needed. With current tools, public health and other agencies can manage small incidents, such as the ones associated with the use of contaminated animal hides to make African drums *(12,13,66)*. However, these and other available methods would not be adequate if an urban jurisdiction faced large-scale and wide-area anthrax contamination *(67)*.

MENTAL HEALTH PREPAREDNESS AND RESPONSE

Both the 2001 World Trade Center attack and the outbreak of intentional anthrax resulting from contamination of the mail highlighted the dramatic psychological effects that a terrorist event can have on the public, even in sites far removed from the actual events. One of the primary targets of terrorism is the public's mental health, with the potential impact lasting long beyond the immediate event and involving persons far from the area affected. The media often plays an unwitting role in facilitating this with constant replays and graphic images shown frequently on television and in newspapers in the immediate aftermath of an event.

In New York City, soon after the World Trade Center attacks, a telephone survey revealed that between 7.5% and 40% of Manhattan residents had symptoms consistent with posttraumatic stress disorder; the prevalence was higher among those closer to the site or among those who had witnessed the attacks (68). The subsequent large number of "powder incidents" worldwide illustrated that one does not need sophisticated weapon delivery systems to cause public panic. In many of the affected jurisdictions, it was not the outbreak response at the worksite locations where the anthrax letters were delivered that overwhelmed local public health and emergency response authorities but the hundreds to thousands of calls reporting concerns about potential "powder threats." This illustrated the impact that public panic can have on the public health and medical care systems. More recently, the 2009 H1N1 pandemic demonstrated that large-scale naturally occurring infectious disease outbreaks may also result in significant anxiety, leading to overwhelming numbers of "low-risk patients" consuming limited healthcare resources, and especially in emergency department settings *(69)*.

Unfortunately, mental health preparedness is an area in which many local and state public health agencies have minimal experience. Further, hospital preparedness for mental and behavioral health interventions following the release of a BTA or a naturally occurring infectious disease outbreak has not been well studied or evaluated (70). It is essential that jurisdictional bioterrorism response plans address the community's mental health response to terrorism both before and after an event. Preplanning efforts for mental health preparedness should include development of a risk communication strategy with training of all potential public health spokespersons and the establishment of surge capacity for mental health services after an event occurs (71). Ideally, the public and media should be educated ahead of time about the risk of bioterrorism and relevant details of local government BTA response plans, so that they know what steps can be taken to improve personal, family, and community preparedness and what to do in the event of a BTA incident.

Planning for the potential demands on mental health programs and experts should not be limited to the persons directed affected by the incident but should also address the needs of their families and friends, those responding to the event, including traditional first responders and the medical provider community, and the general public. Strategies may include plans for rapidly establishing crisis hotlines and referral sites and for mobilizing additional assistance through creation of a mental health reserve corps. Involvement of community-based organizations, religious leaders, and local government officials in both preplanning and response efforts is essential. Clear and regular communication from public health officials should be prioritized and may address some of the public stress and fear related to the event.

COMMUNICATION WITH THE GENERAL PUBLIC

As with any major disaster, one of the most important components of the governmental response is a proactive, effective, risk communication strategy, essential features of which include preexisting and effective links with the news media (including local and national print, radio, and television outlets). The multidisciplinary nature of government's response to a BTA release may require coordination of media outreach through a joint information center that includes local, state, and federal officials. Public affairs staff at hospitals should coordinate any public messages with their counterparts at the local and state health departments.

Ideally, there should be one primary government spokesperson designated to provide consistent messages throughout the disaster response. This spokesperson should be clearly in charge (e.g., the top elected official); an effective, clear, and concise communicator; and available for frequent press briefings. Although the primary spokesperson does not have to be a medical or public health official, it is essential that persons with such expertise be present to answer or clarify health-related questions or issues. One of the most difficult risk communication challenges following a bioterrorist event and other incidents involving dissemination of a BTA would be the need for frank communication of uncertainty, given that it may take days or weeks before the full circumstances of the event become known. It is important for spokespersons to clearly explain the facts of the situation: what is known, what is not known, and what measures the government is taking to answer all key questions. The public is more likely to be reassured by government's frankness and competence when information is shared promptly and transparently. Frequent updates should be provided to the news media and public when new information becomes available.

Some of the communication strategies used in response to the 2001 anthrax incident underscored how public

confidence can be lost quickly and that spokespersons need to be credible and believable. Trying to reassure the public that the index case of inhalation anthrax might have been caused naturally had a decidedly negative public impact. Once the public and news media's trust has been lost, it is difficult to regain *(72)*.

In the past, the most efficient mechanism for communicating to the general public has been through print, television, and radio news media. More recently, the Internet has served as a major mechanism for public health officials to address the questions and concerns of the general public, by way of official agency Web sites and Internet-based news.

Establishing a hotline for the general public should also be a key component of the public health response planning efforts. Hotlines will likely need to respond to escalating demands during the immediate hours and days after an acute event. Surge capacity strategies and procedures with respect to both staff and telephone infrastructure should be identified before the emergency. Staff must be trained to handle calls from a concerned public, and mechanisms need to be in place to provide ongoing training as the outbreak evolves.

Finally, just as the Hospital Preparedness Program has encouraged public health officials to forge relationships with healthcare providers and emergency responders, public health officials should also develop relationships and agreements with various community-based groups *before* public health emergencies occur. By engaging communities during planning stages, public health policy can be informed through increased understanding of local beliefs and values. These efforts may increase the public's trust in health officials, may expand the capacity of members of the public to play crucial roles in attending to vulnerable members of the community during a crisis, and may enhance community resilience during public health emergencies (73).

SUMMARY

Since the terrorist events of 2001, the importance of improving and maintaining the public health infrastructure at the local, state, and federal levels has been prioritized, reflected by substantial federal funding provided by the Departments of Health and Human Services and Homeland Security. Jurisdictions have used these funds to address the following key areas: all hazards emergency planning and responses to biological, radiologic or chemical terrorism events, as well as for naturally occurring disease outbreaks and other emergencies (e.g., coastal storms); enhancing surveillance and epidemiologic capacity; expanding public health reference laboratory services, especially for confirmation of the CDC Category A and B agents; developing or enhancing environmental health expertise; planning for large-scale antibiotic and vaccine distribution clinics; establishing or enhancing local and state legal authorities for implementing and enforcing isolation and quarantine; ensuring that communication mechanisms and strategies are in place to provide up-to-date information to the medical community and general public; providing risk communication and media training for key public health staff; training medical providers to recognize, treat, and report diseases caused by potential BTAs; and mental health preparedness planning.

Integration of BTA-related surveillance, laboratory, environmental, and communication efforts into routine public health activities should enhance core public health functions and also improve local and state public health responses to large, naturally occurring disease outbreaks, such as the 2009 H1N1 pandemic. Enhancing our public health infrastructure to respond to BTA events is a long-term investment and one that is necessary to protect the public from natural, accidental, and intentional disease threats.

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CHAPTER 103

Agents of Bioterrorism

Michael Osterholm, Elizabeth Linner McClure, and C. J. Peters

THE HISTORY OF BIOTERRORISM

The weaponization of biologic agents is as old as recorded history *(1)*. Serpents, tossed onto enemy ships, were used in ancient times as weapons of warfare. The Tartar army, in 1346, used the bodies of plague victims as weapons of war, catapulting them into the city of Caffa. In 1763, the British army intentionally infected Delaware Indians by providing them with blankets used by smallpox victims. Various human and animal pathogens were used on a limited scale as biologic weapons in both World War I and World War II.

Both Twentieth Century World Wars stimulated research and development of biologic weapons. Although many countries, including the United States, Canada, the United Kingdom, and the Soviet Union, continued the development of biologic agents as weapons following World War II, most of these programs were abandoned in the late 1960s and early 1970s. In 1972, the Biologic Weapons Convention Treaty was ratified by >140 nations. This treaty prohibited the possession, stockpile, or use of biologic weapons, although no provisions for monitoring, inspection, or enforcement were made within that treaty.

In the mid-1990s, it became evident that the Soviet Union had secretly continued an aggressive program to weaponize biologic agents *(2)*. Major aspects of that program included the production of large amounts of smallpox virus and research surrounding a means to weaponize it. Other biologic weapons were developed by the Soviets and included *Bacillus anthracis* spores and botulinum toxin *(3)*.

The dissolution of the Soviet Union increased the vulnerability of the world to bioterrorism. Soviet scientists left the Soviet Union and have been actively recruited by rogue nations such as Iraq, Iran, Syria, and North Korea. Stockpiles of biologic agents from the Soviet program are also missing or inadequately contained *(4)*.

After the Gulf War, there was concern that Iraq may be developing an extensive biologic weapons program predominately involving anthrax and botulism. There is also concern that both Iraq and North Korea may have obtained smallpox virus.

Today, there is little doubt that biologic weapons of mass destruction lie within the grasp of many nations and groups. The recent terrorist attack on the United States in 2001 with aerosolized anthrax is just one example of the reality of biologic agents as weapons. Several commissions have recently reviewed the threat of bioterrorism on the United States (United States Commission on National Security/21st Century, 2001; National Commission on Terrorism, 2000; Gilmore Commission, 2000). In November 2001, the Institute of Medicine convened a workshop on *Biologic Threats and Terrorism: Assessing the Science and Response Capabilities*. All these expert panels have uniformly concluded that the United States is highly vulnerable to another bioterrorist attack potentially much more massive in scale than the anthrax attacks of 2001.

BIOLOGIC AGENTS AS WEAPONS

What are the agents that would be employed as biologic weapons or instruments of terrorism? One way to analyze the problem is to narrow the problem according to the scenarios that are most damaging. The modes of dissemination of a biological agent are numerous, but the optimum way to infect large numbers of persons with a lethal agent is to use infectious aerosols. This conclusion allows us to narrow the spread of agents of concern to those that can be grown in large quantities and that are infectious in aerosols, a relatively small subset of the total number of microorganisms that a terrorist might employ. Contamination of the food supply is another possible route of infection that is of great concern, but probably not as potentially severe as an aerosol attack. Other means of infection could be imagined, but none seem to be so effective in producing mass casualties by direct infection. Smallpox is particularly concerning, however, because in addition to its direct aerosol transmission it can be spread from person to person in ever-widening circles and thus could be a highly effective terror weapon even if the initial number of persons infected were relatively small. The Centers for Disease Control and Prevention (CDC) published a list of biologic agents in 2000 selected for their needs for public health preparedness and their likely health and social impact *(5)*. The list is divided into categories A, B, and C. Category A agents are characterized as being easily disseminated or transmitted from person to person. They are capable of causing high mortality, leading to public panic and government destabilization. They also require rapid public health response

TABLE 103-1

Critical Biologic Agents for Use in Bioterrorism

Category A agents: B. anthracis (anthrax), *C. botulinum* toxin (botulism), *Y. pestis* (plague), *F. tularensis* (tularemia), variola major virus (smallpox), Ebola, Marburg, Lassa, and South American hemorrhagic fever viruses (VHFs)

Category B agents: Coxiella burnetii (Q fever), *Brucella* species (brucellosis), *Burkholderia mallei* (glanders), alphaviruses (Venezuelan encephalomyelitis and eastern and western equine encephalomyelitis), ricin toxin from *Ricinus communis* (castor beans), epsilon toxin of *C. perfringens, Staphylococcus* enterotoxin B

Foodborne or waterborne agents also are included under category B. These pathogens include, but are not limited to, *Salmonella* species, *Shigella* species, *Escherichia coli* O157:H7, *Vibrio cholerae*, *Cryptosporidium parvum*

Category C agents: Nipah virus, Hanta viruses, tick-borne hemorrhagic fever viruses, tick-borne encephalitis viruses, yellow fever virus, multidrug-resistant *Mycobacterium tuberculosis*

(CDC. Biological and chemical terrorism: strategic plan for preparedness and response: recommendations of the CDC Strategic Planning Workgroup. *MMWR Recomm Rep* 2000;49(RR-04):1–14.)

and preparedness. Category B agents are moderately easy to disseminate. They cause lower morbidity and mortality and require important public health diagnostic capability and disease surveillance. Category C agents include emerging biologic agents that could be weaponized in the future due to their availability, ease of production and dissemination, and high morbidity and mortality (Table 103-1).

This chapter will focus on CDC category A agents including *B. anthracis*, *Clostridium botulinum* toxin, *Yersinia pestis*, *Francisella tularensis*, variola major virus (smallpox), and the viral hemorrhagic fever (VHF) viruses. Major clinical, microbiologic, and epidemiologic factors will be addressed, particularly within the context of the suitability of each agent as a potential biologic weapon. This list is by no means comprehensive. There are many other known biologic agents suitable for weaponization, which could become the source of a bioterrorist attack in the future. The Soviet Union alone is known to have weaponized at least 30 biologic agents, some of which focus on vaccine or drug resistance *(4)*.

ROUTES OF DISSEMINATION

Many different bioterrorist attack scenarios are possible. As noted above, two important modes of transmission include aerosol and foodborne attacks. Aerosols are an efficient mode of transport to a wide geographic area. The inhalation of small particles (1–5 μm) causes deposition deep in lung tissue, and some agents are capable of very efficiently setting up a systemic infection from that site. There are basically two mechanisms for developing these aerosols. One involves the generation of particles from liquids energized by passage of air over a nozzle, and the other is the production of fine powders that are treated to be electrically neutral and readily propelled into the air by small energy input and to continue to be carried by the air currents. Potentially available means for wide-scale dissemination of aerosolized particles could include the use of crop-dusting planes, small aerosolizing generators in closed spaces such as shopping mall or subways, the dissemination of particles through the ventilation systems of large buildings, and the contamination of items in the environment by fine powders as was the case with the recent anthrax attacks on the United States in 2001.

Foodborne bioterrorism, which could encompass a variety of biologic agents, is also a real threat. These agents are relatively easy to obtain and some agents can cause mortality at very low doses. They are also readily available in the environment and may in fact be the easiest bioterrorism agents to disseminate. Contamination of water sources is much less likely to be effective as the dilutional effect would be too great and most agents are vulnerable to chlorine, a standard additive to potable water.

AGENTS

Anthrax

B. anthracis is a large gram-positive bacillus. It forms long chains *in vitro* but exists in single cells or short chains *in vivo*. It is a nonmotile, catalase-positive aerobe or facultative anaerobe. Colonies are fast growing and exhibit a ground glass appearance. *B. anthracis* also exists as a spore. These spores germinate, forming vegetative cells in nutrient-rich environments. Anthrax bacilli are vulnerable and readily inactivated outside mammalian hosts and will sporulate when nutrients in their environment are exhausted. These spores are highly stable, existing in the environment for years at a time. Spores have been shown to survive in the environment >40 years *(6)*. These spores germinate, forming vegetative cells in nutrient-rich environments.

Laboratory diagnostic procedures beyond culture are not well-standardized. Blood cultures are usually positive in serious cases, but automated systems may reject the early-growing *Bacillus* as a contaminant. Late in infection, direct smears of peripheral blood or cerebrospinal fluid usually show the microorganism directly. Autopsy findings are pathognomonic and tissue Gram stains positive. Polymerase chain reaction (PCR) of tissues and direct tests for toxin in the blood are promising experimental approaches to microbiological diagnosis. Convalescent patients usually develop antibodies to anthrax toxins such as protective antigen.

Modes of Transmission Anthrax is primarily a disease of livestock or other herbivores. Infection is acquired through consumption of soil or feed containing *B. anthracis* spores. Illness in humans most often occurs following exposure to infected animals. Exposure to infected animals occurs from contact with contaminated tissue; the consumption of undercooked, contaminated meat; or the vigorous handling of tainted wool, hides, or other animal by-products during processing. Person-to-person transmission has occurred rarely with cutaneous anthrax, but not gastrointestinal (GI) or

inhalational disease *(7,8)*. Cutaneous disease from laboratory inoculation with *B. anthracis* has also been recognized *(9)*.

Clinical Syndromes Naturally occurring anthrax infection in humans can present as cutaneous anthrax, inhalational anthrax, or GI anthrax. The cutaneous manifestation is the most common presentation. Inhalational anthrax is the disease associated with aerosol dissemination in a bioterrorist attack, although cutaneous disease might result from environmental contamination.

Inhalational Anthrax Inhaled *B. anthracis* spores are deposited deep in the lung. Endospores are then phagocytosed by macrophages and transported to regional lymph nodes. Within the lymph nodes, spores germinate into vegetative cells, multiply, and enter the bloodstream. Bacteremia leads to septic shock and toxemia. Hemorrhagic mediastinitis and massive pleural effusions frequently occur. Secondary meningitis or involvement of other lymph nodes can be seen. The chest X-ray is a critical part of the diagnostic workup because of the typical widened mediastinum from regional lymph involvement *(10)*. It has become apparent that the use of thoracic computed tomography scans is a more sensitive way to detect and quantify the pathognomic node involvement as well as the effusions.

Illness may be biphasic, with an initial prodrome of fever and malaise. If left untreated, a second phase follows characterized by a sudden increase in fever and rapid-onset respiratory distress and cardiovascular collapse. Case-fatality rates decrease with prompt and aggressive antibiotic therapy.

The ID50 for inhalational anthrax has been estimated at 8,000 to 50,000 spores *(11)*, although the minimum infective dose may be considerably less. Extrapolation of dose–response curves from cynomolgus monkeys predict that the LD10 in humans may be as low as 50 to 98 spores, and the LD1 may be only a single spore *(12)*. Host factors may affect susceptibility, as well.

Cutaneous Anthrax Cutaneous anthrax is largely a localized infection caused by the introduction of endospores into a break in the skin. Germination at the site of entry causes localized infection, which appears as a papule with localized edema. Ulceration occurs after 1 to 2 days followed by the formation of a black eschar over the ulcerated lesion. These lesions heal without scarring in 80% to 90% of patients. Rarely, a more generalized lymphadenitis can occur; patients with multiple bullae deteriorate secondary to severe edema and shock. The overall case-fatality rate is extremely low with proper antibiotic therapy. Before the era of antibiotics, the case-fatality rate approached 20%. The infective dose for cutaneous anthrax is not known *(13)*.

Gastrointestinal Anthrax GI anthrax is rare and its etiology is poorly understood. Unlike the other forms of anthrax in which the endospore is the infecting agent, GI anthrax is thought to be secondary to the ingestion of vegetative cells from undercooked meat taken from ruminants dying of anthrax *(13)*. Patients infected with anthrax via the GI tract may exhibit symptoms ranging from oropharyngeal involvement to widespread edema, ascites, hemorrhage, and shock. The overall case fatality is between 25% and 60%. The impact of early antibiotic therapy is not known.

Epidemiology *B. anthracis* can be found in the soil of many areas around the world, particularly those that experience episodic periods of heavy rainfall followed by drought. It is a disease of animals primarily and is endemic in most areas of the Middle East, equatorial Africa, Mexico, Central and South America, and some Asian countries *(14)*. Globally, several thousand cases of anthrax are reported each year *(15)*. These are mostly cutaneous; inhalational and GI anthrax occur at much lower rates.

In the United States, naturally occurring anthrax is relatively rare in humans. Approximately 10 cases of human disease were reported in the United States each year since the late 1960s; a number that has declined from over 100 cases per year in the early 1900s. Since 1990, only two cases of naturally occurring anthrax were reported: one in 1990 and one in 2000. Both were cases of cutaneous anthrax *(16)*. Livestock and wild ruminant disease is common, particularly in the western states.

Anthrax as a Biologic Weapon *B. anthracis* is an ideal biologic agent for weaponization. It is stable in spore form, making it easy to store, transport, and aerosolize *(13)*. It is readily available in nature and has a long history of development as a weapon of mass destruction since the early 1940s. The impact of a massive aerosolized anthrax release attack is not known, but several agencies have conducted hypothetical scenarios that predict extremely large casualties. The Office of Technology Assessment in 1993, for example, concluded that deaths of over 3 million could occur following a 100-kg aerosol release dissemination of *B. anthracis*.

Although aerosolization release of anthrax spores is the most likely mechanism for its use as a biologic weapon, deliberate contamination of food is also a possibility. During World War II, the Japanese reportedly impregnated chocolate with anthrax to kill Chinese children. The apartheid government of South Africa also experimented with anthrax in chocolate *(17)*.

Weaponized anthrax has been the cause of disease outbreaks twice in history. In 1979, an accidental release of weaponized anthrax from a laboratory weapons factory in the Soviet Union caused 75 cases of inhalational anthrax and 2 cases of cutaneous anthrax. The overall case-fatality rate was 86% *(18)*. The release dose amount of anthrax was estimated by investigators to be as low as a few milligrams.

The United States, in 2001, experienced an outbreak of anthrax involving the intentional contamination of mail with anthrax spores. Four letters containing up to 2 g of powder, with over 500 billion spores per gram were mailed from Trenton, NJ, over a 3-week period. Twenty-two cases of anthrax (11 inhalational and 11 cutaneous) were reported. All cases involved the Ames strain of *B. anthracis* and shared identical molecular subtyping. The case-fatality rate for inhalational anthrax was 45% *(19,20)*.

Following recognition of anthrax in postal workers, the U.S. Postal Service initiated a pilot program called the Biohazard Detection System in July 2003, which involves placing anthrax detection systems at selected mail-processing centers around the country.

Therapeutic Countermeasures for Weaponized Anthrax Release

Vaccine Currently, BioPort Corporation manufactures a cell-free anthrax vaccine called AVA (Biothrax) *(21)*. Seroconversion following three doses of the vaccine is reported (in one study) to be 95% *(22)*; however, the correlation between antibody titer and protection against infection has not been defined. The duration of vaccine efficacy is also unknown, but thought to be approximately 1 to 2 years.

Randomized controlled trials on the clinical effectiveness, immunogenicity, and safety of anthrax vaccines were recently reviewed. The authors concluded that vaccines based on anthrax antigens are immunogenic in most vaccines with few adverse events, but data were limited *(22A)*. A recent review of anthrax vaccine-related VAERS (Vaccine Adverse Event Reporting System) reports from 1990 to 2007 showed no unusual pattern or high frequency of adverse events reported *(22B)*.

Preexposure: Biothrax is not available to the general public. Persons who should receive a preexposure vaccination series include the following: members of the military (or other select populations with a risk of exposure to weaponized anthrax), laboratory workers engaged in production of *B. anthracis* cultures, veterinarians or other high-risk persons handling potentially contaminated meat or animal products, and workers who may be making repeated entries into a *B. anthracis* contaminated site after a bioterrorist attack *(23,24,24A)*. Anthrax vaccine is not currently recommended for postexposure use, so it must be given under an investigational new drug application with the Food and Drug Administration (FDA).

Postexposure: Recent Advisory Committee on Immunization Practices guidelines recommend the use of anthrax vaccine in combination with antibiotics following an inhalational exposure to *B. anthracis (24A)*. Exposed persons should receive a three-dose regimen of Biothrax and a 30-day course of antibiotic therapy *(25)*. Anthrax vaccine is not currently licensed for postexposure use, so it must be given under an investigational new drug application with the FDA.

Research into new anthrax vaccines is ongoing. Most vaccines under investigation utilize either recombinant technology or employ novel adjuvant to increase the immune response. Combination vaccines, such as the one against both anthrax and plague, may represent an evolution in vaccine development against agents of bioterrorism *(25A)*.

Antibiotics The FDA has approved doxycycline, ciprofloxacin, and penicillin G procaine for use in postexposure prophylaxis against aerosolized anthrax. Prophylactic antibiotic therapy is recommended for persons exposed to an airspace contaminated with a suspicious material that may contain anthrax spores or those exposed to an airspace with known anthrax release. This includes unvaccinated laboratory workers exposed to suspected aerosolized *B. anthracis* in culture. Antibiotic prophylaxis is not recommended for autopsy personnel, for medical personnel caring for anthrax victims, or for the prevention of cutaneous anthrax *(25)*.

In the event of a massive aerosolized release of anthrax spores, rapid delivery of prophylactic antibiotics would be crucial in preventing large casualties *(26)*. States can request antibiotic and medical supplies from the Strategic National Stockpile through the CDC. State and local health departments should activate their bioterrorism preparedness plans to distribute antibiotics rapidly.

New Therapeutic Approaches In addition to antibiotic treatment protocols, several new therapeutic approaches are being researched; most involve the use of monoclonal antibodies *(26A–26C)*. The Department of Health and Human Services is working with Human Genome Sciences, Inc. to develop a human monoclonal antibody called ABthrax or raxibacumab *(26D)*. Another therapeutic approach under investigation is the use of human hyperimmune plasma and immune globulin from previously vaccinated persons undergoing serial plasmapheresis. Hyperimmune plasma and immune globulin isolated in this way could potentially serve as a basis for a new anthrax treatment *(26E)*.

Implications for Healthcare Workers Standard Precautions are considered adequate for patients with inhalational, GI, and oropharyngeal anthrax since person-to-person transmission for these forms of the disease has not been reported *(13)*. Although people with inhalational anthrax may have residual contamination of hair and clothing from their exposure event on presentation to a medical facility, this does not appear to be a transmission concern to healthcare workers. Standard Precautions are also recommended by most sources for cutaneous anthrax; however, because person-to-person transmission has occurred rarely for this type of anthrax, Contact Precautions have also been recommended *(7,27)*.

Complete information regarding the use of personal protective equipment for first responders and other healthcare workers can be found in the following documents (see Refs. *25* and *28*):

- *CDC:* Protecting investigators performing environmental sampling for *B. anthracis:* personal protective equipment
- *OSHA:* Anthrax in the workplace
- *OSHA:* Fact sheet and references on worker health and safety for anthrax exposure

Botulinum Toxin

Botulinum toxins are the most lethal human toxins known. They are colorless, odorless, and tasteless at concentrations that are lethal. The toxins are produced by vegetative cells following the germination of *C. botulinum* spores and released by cell lysis. In the case of wound botulism or infant botulism the microorganisms may be present in the wound or the bowel, but in foodborne disease or bioterrorist events the toxin is released from the microorganism prior to the intoxication. Several distinct antigenic toxin types are produced by *C. botulinum* and other *Clostridium* species. Types A, B, E, and F cause natural disease in humans; toxin type F accounts for <1% of naturally occurring disease. Other antigenic subtypes, including toxin types C, D, and G, can cause disease in other mammals and birds. Botulinum toxin is inactivated by heating it to 85°C for 5 minutes *(29)*. It is important to note that in the event of an intentional dissemination of botulinum toxin, the causative (vegetative) microorganisms may not be present.

Diagnostic procedures usually rely on the toxicity for mice confirmed by neutralization of the toxin by antiserum.

Toxin can be detected in food, gastric contents, or serum. Antibodies do not usually develop in convalescence because of the very small lethal dose.

Clostridium botulinum *C. botulinum* is a gram-positive spore-forming bacillus. It is "sluggishly" motile and anaerobic and can be found in soil and aquatic sediments. There are several strains of *C. botulinum*; subtyping is based on metabolic characteristics of the microorganism. Groups I and II are responsible for the toxin production, which is lethal to humans.

C. botulinum spores are resilient, resisting destruction with prolonged boiling at high temperatures and desiccation. They have been shown to survive in a dry state for over 30 years. The spores are susceptible to chlorine in dilute concentrations (as in chlorinated water). They undergo germination most readily by exposure to heat ("heat shocking") of 80°C for 10 to 20 minutes *(30)*.

Botulism Pathophysiology and Clinical Presentation Botulinum toxin can enter the body via ingestion or inhalation. Exposure can also occur through local production in the GI tract or necrotic tissue at the site of a wound. Botulinum toxin is activated by proteolytic cleavage; the activated structure contains a heavy and light polypeptide chain. The toxin is carried through the bloodstream to the neuromuscular junction where the heavy chain binds to presynaptic receptors causing permanent inhibition of acetylcholine release. After several months, muscle function is regained based largely on the production of new synapses at the neuromuscular junction.

Clinically, patients present with neuromuscular weakness, ranging from mild cranial nerve dysfunction to complete flaccid paralysis. The severity of disease corresponds to the toxin dose and the toxin subtype; type A creates a more severe clinical presentation than type B or E. The major differential diagnoses include Guillain-Barré syndrome, Eaton-Lambert syndrome, and polyneuropathies such as the recently recognized West Nile syndrome. Botulism is characteristically distinguished by initiation of involvement with the cranial nerves and descending in the neuraxis as it progresses.

Loss of respiratory and pharyngeal muscle function can require a prolonged period of mechanical ventilation. Death often results from complications of prolonged ventilatory support. Prior to mechanical ventilation, death rates approached 50% *(31)*. Case-fatality rates are now lower due to the advent of adequate supportive care including advanced respiratory support capabilities. The current overall case-fatality rate is 5% to 10% for foodborne disease and somewhat higher for wound botulism *(31,32)*.

Modes of Transmission/Epidemiology

Foodborne Botulism Botulinum toxin can be produced in food items that are contaminated with *C. botulinum* spores. Conditions including an anaerobic environment, acidic pH, minimum temperature of 10°C, and availability of a water source must exist to facilitate germination of spores and production of botulinum toxin *(33)*. Food containing the neurotoxin that is not sufficiently reheated to at least 85°C for 5 minutes becomes a potent toxin delivery source for humans *(29)*.

A single case of foodborne botulism is considered an outbreak and declared a public health emergency. All cases of botulism must be reported to the CDC immediately. In the United States, an average of nine outbreaks per year was seen in the late 1990s, with approximately two to three cases per outbreak *(33)*. Improperly home-canned vegetables are the most common source of foodborne botulism; however, over the past 20 years, a variety of commercially produced, preservative-free foods have caused outbreaks. Garlic in oil, baked potatoes in foil, jarred peanuts, and commercially processed cheese sauce have been associated with outbreaks *(34–38)*.

Botulinum toxin is rapidly inactivated by the chlorine, which is a standard additive to potable water. For this reason, cases of botulism have not been associated with contaminated water *(39,40)*.

Wound Botulism *C. botulinum* infection is usually associated with traumatic injuries of the extremities, especially those that involve contact with soil or another natural *C. botulinum* source. Although seen more rarely, cases of botulism following a postoperative infection, the use of intravenous or intranasal illicit drugs, or dental abscess have also been reported. Wound botulism is a rare event; only 78 cases were reported to the CDC for the period of 1986 to 1996 *(33)*.

Inhalational Botulism Inhalational botulism is caused by inhalation of aerosolized preformed botulinum toxin into the lungs and, subsequently, the circulation. It is a very rare exposure event, occurring only once in a veterinary laboratory setting in Germany in 1962 *(39)*. Inhalational disease has also been produced experimentally in primates. Results of this study showed disease onset occurring 12 to 80 hours after exposure *(41)*.

Botulinum Toxin as a Biologic Weapon Botulinum toxin has been manufactured as a potential biologic weapon since World War II. The United States produced the toxin during that time period, but abandoned production after signing the BWTC in 1972 renouncing use, stockpiling, or production of biological weapons in 1968. The Soviet Union, however, continued production into the early 1990s. At the time of the Gulf War, Iraq had produced over19,000 L of botulinum toxin, some of which was weaponized *(42)*. On three occasions between 1990 and 1995, the Japanese cult Aum Shinrikyo attempted to use aerosolized botulinum toxin in Japanese cities, but was not successful.

Botulinum toxin could be disseminated via the deliberate contamination of food or beverages, or as an aerosol. Experts believe that the foodborne route represents the most likely bioterrorist scenario. Deliberate contamination of a large source of commercially available and distributed food or beverage product, particularly one in which adequate heating would be unlikely, could cause massive extensive casualties across the country. The widespread nature of the attack would also create significant panic, economic loss, and social disruption.

The dispersal of aerosolized toxin is also possible and could result in extremely large numbers of casualties, in this instance, concentrated in a single urban setting. One gram of aerosolized botulinum toxin could theoretically

kill 1.5 million people *(43)*; however, it is likely that for practical considerations, the effects of a botulinum toxin attack would be relatively limited compared to one of the infectious agents.

Contamination of a water source is unlikely because of dilution as well as the vulnerability of the toxin to chlorine, a standard additive to potable water.

Therapeutic Countermeasures for Weaponized Botulinum Toxin

Botulinum Antitoxin Supportive care is the mainstay for treatment of botulism; prolonged intensive care, mechanical ventilation, and parenteral nutrition may be required. Botulinum antitoxin can be administered to treat forms of botulism (other than infant botulism) and is most effective when given early in the course of illness. It cannot reverse existing paralysis, but can prevent additional nerve damage if given before all the circulating toxin binds to the neuromuscular junction.

Botulinum antitoxin is of equine origin and has traditionally been developed for use against subtypes A, B, and E. The CDC formulary currently includes a botulinum antitoxin bivalent for types A and B (licensed by the FDA) and botulinum antitoxin equine type E (an investigational product). In the past, the CDC released a trivalent ABE antitoxin, but this product is not currently available. The CDC maintains an active surveillance program for cases of botulism and is responsible through state health departments for the distribution of antitoxin in suspected cases *(39,41)*.

Antitoxin (supplied by the CDC) is maintained at quarantine stations in various metropolitan airports and, once requested, can generally be delivered within 12 hours *(43A)*.

In the event of a bioterrorist attack with botulinum toxin, it is possible that other subtypes will be weaponized. The U.S. Army has developed an equine heptavalent botulinum antitoxin effective against all botulinum toxin types, but its efficacy in humans is not clear. Additionally, as for the licensed product, it carries with it the potential for serious allergic reaction. Additional research into heptavalent botulinum antitoxin has occurred through a U.S. Department of Health and Human Services development contract (Cangene Corp).

The dose of antitoxin required to reduce the effects of the neurotoxin varies with the inoculating dose. In the event of a mass release of weaponized botulinum toxin, the scarcity of antitoxin would be highly likely *(39)*.

Botulinum Toxoid Vaccine Vaccination with botulinum toxoid is currently recommended for laboratory personnel who work with *C. botulinum* and military personnel at risk for exposure to weaponized botulinum toxin *(44)*. The vaccine is not considered a viable countermeasure against a bioterrorist attack. It is not effective against all subtypes; it is painful to receive and requires a yearly booster; it also disallows the recipient from receiving botulinum antitoxin therapy for life.

Emergency Response to a Mass Exposure A single case of botulism is considered a public health emergency *(45)*. In the event of a suspected botulism outbreak, public health officials will assist with appropriate laboratory testing to confirm diagnosis, authorize use of antitoxin, and conduct aggressive surveillance investigations to identify the source of an outbreak to determine if there is evidence to suggest a bioterrorism-related event.

In the event of a mass exposure, such as a widespread aerosol release of botulinum toxin, the rapid administration of antitoxin to ill persons would be indicated. Although antitoxin does not reverse existing paralysis, it binds remaining circulating toxin, mitigating progression of the disease. Rapid mobilization of mechanical ventilators and other ancillary supportive care tools would be critical to successful management of any mass-exposure botulism outbreak.

Implications for Healthcare Workers In the hospital setting, Standard Precautions are adequate for patients with botulism since person-to-person transmission does not occur. In the laboratory setting, *C. botulinum* toxin detection should only be performed by trained individuals at level C or higher Laboratory Response Network laboratories *(46)*. The FDA also released biosafety recommendations for laboratories that test for *C. botulinum*. A partial list includes the following: placement of biohazard signage; the use of appropriate laboratory safety apparel including coats and safety glasses; restriction of solo work shifts; immediate autoclaving of all toxic material; and ready access to information on the location of an antitoxin source *(47)*.

Plague

Y. pestis is the causative agent of plague. It is a pleomorphic gram-negative bacillus, existing as single cells or short chains in direct smears. It is a nonmotile, nonsporulating facultative anaerobe, slow growing in culture. At 48 to 72 hours of incubation on solid media, colonies have a raised, "fried egg" appearance. Data banks for many commercial laboratory identification systems do not include *Y. pestis (*48*)*.

Y. pestis is thought to have evolved from *Y. pseudotuberculosis* 1,500 to 20,000 years ago *(49)*. Recent data suggest the continued evolution of the bacillus through the emergence of several new genotypes *(50)*.

Modes of Transmission Humans are an incidental hosts for *Y. pestis* and are not part of its natural life cycle. Many different animal species (mostly wild rodents) are natural reservoirs for the bacillus *(51)*. Like humans, other nonrodent mammalian species serve as incidental hosts for *Y. pestis*. These animals, however, can serve as sources of human exposure. Disease occurrence in humans is dependent on the frequency of infection in local rodent populations. Human outbreaks are usually preceded by epizootics with increased deaths in susceptible animal hosts *(52,53)*.

The vector for *Y. pestis* is the flea. Over 1,500 species of flea exist; approximately 30 are known to be vectors for *Y. pestis (53)*.

Humans can become infected with *Y. pestis* via the bite of an infected flea, a bite or scratch from an infected incidental host mammal such as a cat, or direct contact with infected animal carcasses or products. Inhalation of respiratory droplets from infected animals or humans can also cause infection *(54)*.

Pathogenesis/Clinical Syndromes The classic forms of plague are bubonic plague, pneumonic plague, and septicemic plague. Rarely, plague can be manifested as meningitis,

pharyngitis, or pestis minor, a milder form of bubonic plague.

Bubonic Plague Bubonic plague is transmitted to humans via the bite of an infected flea, a bite or scratch from an infected animal or direct contact with infected animal carcasses. Between 25,000 and 100,000 *Y. pestis* microorganisms are inoculated into the skin after a bite from an infected flea *(55)*. The microorganisms migrate through the cutaneous lymphatics to regional lymph nodes. Once in the lymph nodes they are phagocytized by polymorphonuclear leukocytes (PMNs) and mononuclear phagocytes. Microorganisms phagocytized by PMNs are largely destroyed, whereas those phagocytized by mononuclear cells proliferate intracellularly and are released when cell lysis occurs *(53)*. Initially, affected nodes contain a thick exudate composed of plague bacilli, PMNs, and lymphocytes. This pattern gives way to hemorrhagic necrosis, which creates the clinical picture of swollen, painful buboes that are characteristic of bubonic plague. Microorganisms also enter the bloodstream causing hemorrhagic lesions in other lymph nodes and organs throughout the body. Eventually septicemia disseminated intravascular coagulation (DIC) and shock ensues. Without prompt antibiotic therapy, death usually results from overwhelming septicemia.

Pneumonic Plague *Y. pestis* can enter the lungs directly through direct inhalation (primary pneumonic plague) or via hematogenous spread of bubonic plague (secondary pneumonic plague). Primary pneumonic plague is acquired by inhalation of approximately 100 to 500 microorganisms *(13)*. Clinically, patients present with fulminant lobar or multilobular pneumonia. Marked edema and congestion of the lungs are also common. Death from overwhelming sepsis, DIC, and multiorgan failure occurs rapidly without prompt antibiotic therapy; untreated mortality approaches 100% *(53)*.

Septicemic Plague Primary septicemic plague is defined as systemic toxicity caused by *Y. pestis* infection without apparent lymph node involvement. Secondary septicemic plague occurs commonly as part of bubonic or pneumonic plague. Septicemia is the syndrome that leads to multiorgan failure, DIC, and death. In the late stages of the disease, high-density bacteremia often occurs, with ready identification of microorganisms on peripheral blood smears or buffy coat preparations *(52)*.

Epidemiology

Historical Perspective Three plague pandemics have occurred during recorded history, causing an estimated 200 million deaths *(56)*. The first recorded pandemic began in Egypt in 542 AD, spread throughout Europe, Central and Southern Asia, and Africa, killing over 100 million people. The second pandemic, widely known as the Black Death, began in Italy in 1347 and spread rapidly across Europe killing one third of the population. The most recent pandemic began in China in 1894 and spread throughout the world over a 10-year period, presumably facilitated by ship travel. This pandemic was responsible for an estimated 12 million deaths, most occurring in India.

Naturally Occurring Plague in the United States Plague was first introduced to the United States in 1900 as part of the third pandemic and created an epidemic in the early 1900s in San Francisco *(57)*.

It was sporadically epidemic largely in urban settings secondary to infected rat populations *(58)*. After 1926, plague became endemic in wild animal populations in the Western United States. Cases have also been associated with infected domestic cats *(54)*.

Today, plague remains endemic in the United States. It is usually seasonal, with a higher case incidence during summer months *(57,58)*. From 1947 through 1996, 390 cases of plague were reported to the CDC with an overall case-fatality rate of 15.4% *(59)*. Bubonic plague accounted for 83.9% of those reported cases. An average of 8.9 cases per year were reported to the CDC from 1990 to 1999 *(60,61)*. Many of these cases developed secondary pneumonia, but no transmission to contacts has been seen. The disjunct between the pneumonic transmission that occurred during the Manchurian epidemics early in the century and the uncommon documentation of pneumonic spread in other settings may reflect the crowding and lack of basic hygiene during earlier epidemics.

Plague as a Biologic Weapon *Y. pestis* is a potentially suitable agent for use as a biologic weapon, because it can be aerosolized and/or transmitted person to person. The pneumonic form of plague is highly fatal, and its communicability could generate widespread fear and panic. Plague was used as a biologic weapon in the Middle Ages when armies catapulted the bodies of plague victims into cities in order to spread the disease *(1)*. In World War II, Japan used plague against the Chinese by dropping plague-infested fleas over populated areas, causing outbreaks of the disease *(1,62)*. *Y. pestis* has also been weaponized by the United States and the former Soviet Union, the latter having also engineered *Y. pestis* for increased virulence and microbial resistance *(63,64)*.

In 1970, the World Health Organization (WHO) modeled a biological warfare attack with *Y. pestis*. This report estimated that the aerosol dissemination of 50 kg of dried powder containing 6×10^{15} *Y. pestis* microorganisms over a city of 5 million people would generate 150,000 cases and 36,000 deaths. They speculated that subsequent person-to-person transmission would create another 500,000 cases and 100,000 deaths, but the actual pneumonic spread is not clearly established in modern times *(65)*.

The primary clinical presentation of persons infected by aerosolized *Y. pestis* would be pneumonic plague, although septicemic disease might occur. Previously healthy patients would present with severe and rapidly progressive multilobular pneumonia. Hemoptysis, GI symptoms, evidence of DIC, and a fulminant clinical course would be highly suspicious for pneumonic plague. Notably, characteristic buboes, associated with bubonic plague would be absent, and patients would not necessarily present with risk factors for plague exposure. This disease requires intensive medical and nursing support with rapid isolation and antibiotic therapy followed by hospitalization for several weeks of convalescence.

Therapeutic Countermeasures for Aerosol Dissemination of Plague A rapid, coordinated public health response is essential to minimize casualties during a bioterrorist attack of weaponized plague. The Working Group on Civilian

Biodefense developed consensus-based recommendations for the treatment of pneumonic plague for two scenarios: In a setting with limited potential casualties, and an adequate medical care delivery system, parenteral antibiotics (streptomycin or gentamicin) should be administered to all patients whenever possible. In a mass casualty setting, in which the medical care resources are outstripped, oral antibiotics (doxycycline or ciprofloxacin) should be administered for a period of 10 days. Antibiotics must be administered early in the course of the infection (perhaps within 24–48 hours of onset), or death occurs in 3 to 6 days. In addition, close contacts of untreated patients should also receive prophylactic oral antibiotics for a period of 7 days *(63)*.

Plague Vaccine A licensed, killed whole-cell vaccine was available in the United States until 1999 *(66)*. It was used by the military and showed some efficacy against bubonic plague, but not pneumonic plague. It is no longer manufactured, and its lack of efficacy against pneumonic plague would limit its usefulness in the event of a bioterrorist attack. A live, attenuated vaccine was developed in the early 1900s and has been used in some parts of the world. The vaccine strain is not avirulent, however, and is associated with significant safety concerns.

Research is ongoing to develop new plague vaccines. Two approaches include the development of a live, attenuated mutant *Y. pestis* vaccine strain and the use of antigenic subunit vaccine *(67,68)*. This recombinant vaccine has shown the best protection against both bubonic and pneumonic plague. It is currently unavailable, but research is ongoing.

Decontamination In general, environmental decontamination following an aerosol event has not been recommended, since experts have estimated that an aerosol of *Y. pestis* microorganisms would be infectious for only about 1 hour *(63)*. A recent study demonstrated that *Y. pestis* can survive on selected environmental surfaces for at least several days, although the potential for reaerosolization of these microorganisms was not addressed *(69)*.

Implications for Healthcare Workers Healthcare workers need to be protected from transmission of *Y. pestis*. Droplet Precautions with eye protection in addition to Standard Precautions are indicated for patients with pneumonic plague *(70)*. Patients should be considered infectious for 48 to 72 hours after appropriate antibiotic therapy has been initiated with evidence of clinical improvement *(9,64)*. The detailed mechanisms of transmission of pneumonic plague are unknown. The Manchurian and Indian epidemics early in the 20th century were associated with crowding and a lack of hygiene and are thought to reflect droplet spread, a conclusion supported by the protection provided to medical staff by surgical masks. There has been no interhuman transmission of plague in the United States since 1924 in spite of numerous bubonic and a smaller number of pneumonic cases. The possibility of aerosol transmission of pneumonic plague, particularly in the unexplored setting of a bioterrorist attack, is unknown but believed to be unlikely *(70)*. Nevertheless, medical staff, like other contacts, who are in close contact with plague patients should receive antibiotic prophylaxis.

Smallpox

Variola viruses are orthopoxviruses from the family Poxviridae. They are DNA viruses, brick shaped and large in size (200-nm diameter). The average genome is 200 kbp, and several strains have been completely sequenced. Efforts are ongoing to determine genetic diversity of existing variola viruses *(71)*. Variola viruses have been classified as variola major or variola minor based on the severity of their clinical manifestations.

Many viruses in the Poxviridae family do not include humans as a natural host. Some, however, in addition to variola virus, can cause natural human infection. These include members of the *Orthopoxvirus* species, including monkeypox, vaccinia, and cowpox viruses. Other poxviruses that cause human infection include *Yatapoxvirus*, *Parapoxvirus*, and *Molluscipoxvirus* (the causative agent of molluscum contagiosum).

Laboratory diagnosis is most readily made from skin lesions by electron microscopy, which can correctly identify viruses as orthopoxviruses, and by PCR and sequencing, which can arrive at a species identification. Cultivation of virus and other approaches are also useful.

Epidemiology/Modes of Transmission Smallpox virus no longer exists in nature. Several important epidemiologic properties of the virus helped facilitate its eradication in the 1970s. Of primary significance is the fact that humans represent the only natural reservoir for the virus. Additionally, the infectivity of naturally occurring smallpox is not generally as high as that for other common exanthems such as measles, usually requiring close contact for transmission. Maximal infectivity also occurs during the height of clinical illness, a time during which infected persons are bedridden and severely ill, limiting contact with uninfected populations. After recovery, infectivity wanes with the resolution of pustules; smallpox cannot exist in a chronic carrier state *(72)*. Currently, declared variola major virus exists in only two WHO-approved facilities: The CDC in Atlanta and the Russian State Centre for Research on Virology and Biotechnology in Novosibirsk *(73)*.

Smallpox is transmitted from person to person via large droplet nuclei or aerosols generated from oropharyngeal secretions of smallpox victims *(72)*. Airborne transmission is unusual but was documented in two hospital outbreaks in Germany in the 1960s *(74)*. Transmission of the virus via fomites has also occurred. This was, in fact, an intentional transmission mode during the French–Indian wars of the mid-1700s *(75)*.

Smallpox is a moderately contagious disease. The infectious dose is presumed to be low (10–100 microorganisms) *(13)*. Unlike some other viruses, persons with the disease are not considered infectious in the prodromal stage of the disease *(76)*. The highest risk for transmission occurs 1 week after the onset of rash when oral lesions ulcerate and release large amounts of virus into the saliva. Patients should be considered infectious at the time of fever onset, however, because some virus may be present in oral secretions shortly before the onset of the rash. Virus is present in skin lesions and scabs so communicability lasts until the pustules have scabbed over and fallen off.

In the pre-eradication era, the average number of cases infected by a primary case was approximately 3.5 to 6 *(77)*.

The secondary attack rate among close contacts varied from 37% to over 70% *(78–80)*. Transmission outside the family and the hospital (patients and medical staff) was uncommon. Random spread to less intimate contacts was not a feature of the European epidemiology in the era in which vaccination was waning and occasional introductions occurred.

Clinical Features Variola major virus can cause several distinct clinical disease manifestations. In the pre-eradication period, distinguishing between these types was based on rash pattern, clinical illness, epidemiology, and laboratory findings. Major types will be reviewed briefly. Monkeypox, a related *Orthopoxvirus*, has some similarities in presentation and will also be reviewed.

Ordinary Smallpox Ordinary smallpox accounted for over90% of variola major infections in the pre-eradication period. After a 10- to 13-day incubation period, a prodrome of fever, chills, and prostration ensues. This lasts 2 to 4 days and is often followed by the appearance of a few skin lesions on the face called "herald spots." Painful, hard lesions progress synchronously on the face and distal extremities including the palms and soles. Fewer lesions are found on the trunk. These are initially maculopapular, then vesicular, and finally pustular, leaving pitting scars after recovery.

Patients may undergo massive fluid shifts, hemodynamic instability, and skin desquamation, resembling a massive burn clinically. The overall case-fatality rate is 15% to 45% in unvaccinated persons *(72)*.

Flat-Type (Malignant) Smallpox Flat-type smallpox is a highly fatal disease, affecting children primarily. It accounted for <10% of variola major presentations in the pre-eradication period. Malignant smallpox has a similar incubation period and clinical prodrome to ordinary smallpox. In this disease, however, lesions develop slowly and have a confluent, flat, velvety pattern. The nonpustular appearance of the rash can obscure the diagnosis. This type of smallpox is almost uniformly fatal.

Hemorrhagic Smallpox Hemorrhagic smallpox was rare in the pre-eradication period, accounting for <5% of overall cases. Pregnant women experienced the greatest mortality among patients with this type of smallpox. The clinical picture of hemorrhagic smallpox is that of DIC, shock, and organ failure. The case-fatality rate for hemorrhagic smallpox exceeds 96%, and death can occur before the development of the rash *(81)*. Because of the atypical presentation and the very high virus levels in blood and throat wash, this clinical form is particularly dangerous epidemiologically.

Monkeypox Monkeypox virus is an *Orthopoxvirus*, which causes an infection similar to smallpox, but generally milder. It occurs sporadically in Western and Central Africa.

Clinically, patients experience a similar prodrome (fever, chills, headache, backache) to smallpox *(82)*. After 1 to 3 days, a smallpox-like rash appears, which lasts 2 to 4 weeks. Lymphadenopathy is a more prominent feature in monkeypox than in smallpox *(82–84)*.

The case-fatality rate for monkeypox is lower, reflecting a milder clinical course. In two reported outbreaks, the case-fatality rate varied from 3% to 11%. All deaths in these two outbreaks involved children under the age of ten with no prior smallpox vaccination *(82)*.

Monkeypox virus can be spread from animal reservoirs (squirrels, rabbits, rodents, prairie dogs) or person to person. The secondary attack rate for household contacts is low; rates ranging from 7% to 15% have been reported among unvaccinated close contacts *(83,85,86)*.

In June 2003, an outbreak of monkeypox occurred in the United States. The outbreak was traced back to infected prairie dogs, which had contracted the virus by close contact during shipping with imported Gambian rats from Africa. Seventy-one cases were reported; 26% were hospitalized, but no deaths occurred. Thirty exposed persons received smallpox vaccine to prevent monkeypox; one of these was later confirmed with the disease *(87)*.

Smallpox as a Bioweapon Smallpox has been considered the most devastating of all global infectious diseases, and its intentional reintroduction would be a "crime of unprecedented proportions" *(4)*. This fact alone makes it an attractive agent of terror.

Smallpox has several features that enhance its potential as a biologic weapon: it is contagious, and at this point in time, most of the population has no immunity to the disease; it is stable and infectious when aerosolized; the virus carries a high rate of morbidity and mortality and would undoubtedly cause widespread panic and social disruption *(88,89)*. Ongoing global vigilance is necessary to detect any recurrence of smallpox through accidental or intentional release *(84)*.

Therapeutic Countermeasures for Weaponized Smallpox

Treatment Supportive care including fluid management, pain alleviation, and surveillance for bacterial superinfection is the only available treatment for patients with smallpox. In the pre-eradication period, there was no available antiviral therapy against smallpox. Today, there have been over 200 antiviral compounds tested for therapeutic benefit against variola virus and other Orthopoxviruses *(72)*. Among those tested, cidofovir, adefovir, dipivoxil, and ribavirin have shown significant *in vitro* activity *(13)*. Animal model testing is the next stage toward the development of a clinically effective antiviral therapy. At least one study has suggested that cidofovir might be useful in postexposure prophylaxis or perhaps treatment.

Vaccination The vaccinia vaccine available from 1970s to 2008 was a lyophilized preparation called Dryvax (Wyeth Laboratories). All lots of Dryvax vaccine expired on February 29, 2008, and all programs that held supplies of Dryvax were instructed to destroy them.

A new cell culture–derived live vaccinia vaccine, produced by Acambis, was licensed by the FDA in 2007. ACAM2000 has been shown to elicit a successful immune response in a similar proportion of subjects when compared with the Dryvax vaccine *(89A)* ACAM2000 has replaced Dryvax smallpox vaccine due to withdrawal of the Dryvax license.

CDC will continue to provide ACAM2000 smallpox vaccine to protect responders as part of state public health

preparedness programs and laboratory personnel at risk for exposure to smallpox and other orthopoxviruses. In terms of new vaccine development, one approach has been to develop vaccines from attenuated vaccinia–derived viruses *(89B,89C)*. The highly attenuated modified vaccinia Ankara (MVA) is a possible vaccine alternative that may be safer than the existing vaccine, but immunogenicity studies are ongoing. Phase 1 and 2 trials IMVAMUNE (an MVA vaccine) showed a high level of immunogenicity with no unexpected side effects or serious adverse events among healthy humans, immunocompromised patients, or those with atopic dermatitis. More attenuated vaccines are under development.

Use of Vaccine for Postexposure Prophylaxis Immunity to variola virus generally develops within 8 to 11 days after vaccination. Since the incubation period for smallpox averages 12 days, vaccination soon after exposure (up to 4 days) may confer some immunity and reduce overall mortality. This may be particularly true for persons who received smallpox vaccination in the pre-eradication period due to the anamnestic immune response that occurs with revaccination *(90)*. The true efficacy and timing of postexposure vaccination prophylaxis remain unclear.

Use of Vaccine During a Smallpox Emergency A "ring vaccination" strategy has been used successfully during the smallpox eradication campaign and is the approach incorporated by the current CDC smallpox plan *(91)*. This strategy involves rapid identification and isolation of smallpox cases, identification and vaccination of contacts with monitoring for symptoms, and vaccination of household members of contacts (where no contraindications exist). In addition to ring vaccinations, rapid voluntary vaccination of a large population may be necessary to aid containment control strategies. Large-scale voluntary vaccination would only be initiated in certain situations under the recommendation from the Secretary of Health and Human Services. Vaccination of the general population before the threat of a smallpox attack is better defined; it would be associated with an unacceptable number of serious and fatal adverse effects.

Vaccination only provides solid immunity if given within the previous 3 to 5 years. However, there is amelioration of severity and protection from mortality for many years, depending on the number of vaccinations. Because infection with rash and spread of virus may occur and because some patients with distant vaccination will be expected to die, history of vaccination should not dissuade revaccination when indicated for protection.

Targeted quarantine of selected high-risk exposures would be expected to have a place in control of smallpox under certain circumstances. Wide-scale quarantine of communities would likely not be effective and are not recommended *(92)*.

Implications for Healthcare Workers Patients with suspected smallpox should be cared for using strict isolation procedures including placement in negative pressure rooms with external air exhaust or high-efficiency particulate air filters where available. In the event of a massive outbreak, smallpox patients should be cohorted and isolated. All healthcare workers caring for patients with suspected smallpox should be vaccinated immediately *(93)*. Contraindications for the vaccination of healthcare workers included history of eczema or atopic dermatitis, persons with other exfoliative skin diseases or burns, immunocompromised patients, and patients with known cardiac risk factors *(94)*.

In October 2002, the Advisory Committee on Immunization Practices and the Healthcare Infection Control Practices Advisory Committee at the CDC recommended smallpox vaccination for persons designated by the appropriate bioterrorism and public health authorities to conduct investigation and follow-up of initial smallpox cases (i.e., smallpox medical response teams). According to CDC, as of October 31, 2005, over 39,608 persons were vaccinated through this program. This represented <17% of smallpox vaccine doses distributed to states for healthcare workers *(94A)*. Reasons for nonparticipation included relatively low risk of a smallpox outbreak, risks associated with the vaccine, hospital costs, and high rates of contraindications to vaccination *(94B)*. (For additional information on smallpox as a bioterrorism agent, see Chapter 104.)

Tularemia

F. tularensis is the causative agent of tularemia. It is a small gram-negative rod, often mistaken visually on Gram stain for *Hemophilus* species. It is a nonsporulating, nonmotile aerobe. There are several subspecies of *F. tularensis*, which are differentiated by biochemical tests and antimicrobial resistance. These microorganisms flourish in moist environments (water, mud, animal carcasses) and can survive for extended periods of time in these settings *(95–97)*. There are several biovars, but the *F. tularensis* biovar tularensis or type A is the most virulent.

Laboratory diagnosis is possible by cultivation from blood or other relevant clinical samples although growth may be slow and conventional media may not be optimum. Investigational techniques include PCR and antigen detection.

Epidemiology/Modes of Transmission The primary vectors for *F. tularensis* are ticks, mosquitoes, and biting flies *(98,99)*. The principal reservoirs include a variety of small animal species including rabbits, rats and mice, lemmings, squirrels, and aquatic rodents *(98–100)*. Humans and other mammals as well as some species of birds, fish, and amphibians serve as incidental hosts. An outbreak of tularemia in commercially distributed prairie dogs was reported in the United States in 2002 but did not result in human cases *(101)*.

F. tularensis can be transmitted to humans by several routes: the bite of an infected arthropod vector *(102)*; ingestion of contaminated food or water *(103,104)*; the handling of infected animal tissue *(105)*; the inhalation of aerosolized bacteria during the mowing of hay or grass *(106,107)*; or during processing of bacteria in the laboratory *(108)*. The average incubation period is 3 to 5 days; *F. tularensis* is highly infectious, but not contagious from person to person.

Most cases in the United States in recent years have been associated with bites from infected arthropods, although animal exposure continues to be a common

source of infection in the southeastern United States *(109)*. States with the highest number of reported cases include Arkansas, Kansas, Missouri, Montana, Oklahoma, and South Dakota *(110)*. Most cases occur in rural or semirural settings and show seasonality, presenting between May and August. Sporadic cases may rarely occur in urban settings with no identifiable source, but would justify additional scrutiny.

Although the number of cases reported each year is declining, tularemia can occur in outbreaks, the most recent of which occurred in Martha's Vineyard in 2000. Fifteen cases of primarily pneumonic tularemia occurred, presumably secondary to aerosolized exposure to *F. tularensis* via lawn mower clippings. There was one fatality in that series *(107)*. Worldwide, tularemia is seen most often in Scandinavian countries and Russia *(98)*. It is endemic in latitudes that include North America, Europe, states of the Russian Federation, China, and Japan *(98)*. Outbreaks have been reported intermittently in Europe as well.

Clinical Syndromes Infection with *F. tularensis* can cause several clinical syndromes ranging from a mild, localized infection to a life-threatening systemic illness. Poor outcomes occur in patients with significant comorbidity or in those in whom diagnosis and antibiotic therapy have been delayed *(98)*.

Glandular, ulceroglandular, and pneumonic tularemia are the most common naturally occurring manifestations of tularemia. Other rare presentations of *F. tularensis* include oculoglandular and oropharyngeal tularemia *(98)*. Typhoidal tularemia is a term used historically to describe pneumonic tularemia. Experts in this field now recommend the term "typhoidal tularemia" to denote systemic infections with *F. tularensis* that lack a clear anatomic focus.

Glandular and Ulceroglandular Tularemia Ulceroglandular tularemia is the most common manifestation of *F. tularensis* infection accounting for over half of all clinical presentations of *F. tularensis* infection. Glandular tularemia represents 25% of cases. In both illness manifestations, microorganisms enter the body through unapparent breaks in the skin or via the bite of an infected arthropod. The infectious dose for humans following percutaneous or inhalational inoculation is 10 to 50 microorganisms *(11)*. Patients with these forms of tularemia usually present with a painful, localized cutaneous infection and tender, regional lymphadenopathy. Fever, chills, axillary adenopathy, and myalgias are also common. Complications of this type of infection include secondary pneumonia, hematogenous spread to other organs, and, rarely, sepsis. Glandular tularemia is distinguished by lymph node involvement, but lack of ulceration at the site of inoculation *(96)*. The case-fatality rate is generally low (<2%), but some subtypes are more virulent than others.

Pneumonic Tularemia Pneumonia caused by *F. tularensis* can result from inhalation of infectious aerosols or via hematogenous spread. Primary pneumonic tularemia often presents as an atypical pneumonia unresponsive to conventional therapy. Symptoms include fever, nonproductive cough, myalgias, and occasionally nausea and vomiting. The disease course is extremely variable. Complications include the adult respiratory distress syndrome, lung abscesses, sepsis, or involvement of other organs through hematogenous spread. Recovery is prolonged, and relapses can occur even with antibiotic therapy. The case-fatality rate with prompt antibiotic treatment has been reported at <3%.

Secondary pneumonia occurs frequently in patients with typhoidal tularemia. Case-fatality rates of this pneumonia presentation have approached 50% in the preantibiotic era but are significantly reduced with appropriate antibiotic treatment.

Tularemia as a Biologic Weapon There is information and evidence to support the use of *F. tularensis* as a biologic weapon *(109)*. During World War II, the Japanese conducted research on *F. tularensis* as a biologic weapon. *F. tularensis* was also investigated for weaponization by the United States in the 1950s and 1960s, although these stockpiles were destroyed in 1973 as part of the BWTC act. The former Soviet Union also weaponized *F. tularensis*, including the development of antibiotic resistant strains. In 1969, a WHO modeling scenario estimated that a 50-kg release with dissemination of *F. tularensis* over a city of 5 million people would cause 250,000 illnesses and 19,000 deaths *(111)*.

A bioterrorist attack with aerosolized *F. tularensis* would be expected to cause primarily pneumonic tularemia; however, some cases of typhoidal (nonspecific) and glandular tularemia may occur as well. Tularemia is highly infectious, and it should be assumed that weaponized *F. tularensis* would be selected for high virulence and engineered for antimicrobial resistance and high virulence.

An outbreak of tularemia from a bioterrorist attack would be differentiated from a naturally occurring outbreak in that persons infected would have no known exposure to the bacteria, and cases would likely present in an urban rather than rural setting *(109)*.

Therapeutic Countermeasures for Weaponized Tularemia Exposure

Postexposure Prophylaxis The prompt initiation of a prophylactic antibiotic treatment regimen is critical for reducing morbidity and mortality as well as providing a community-wide sense of calm and control.

Current recommendations by the Working Group on Civilian Biodefense include the following: If the release of *F. tularensis* becomes known before clinical cases occur (i.e., during the incubation period), persons in the exposed population should be placed on prophylactic oral antibiotics (doxycycline or ciprofloxacin) for a period of 14 days.

In a situation of a known terrorist attack with documented clinical cases, all persons should be watched for signs of fever; any person who develops fever or flu-like symptoms should be placed on parenteral antibiotics, if available, or oral antibiotics in mass casualty settings *(109)*.

Antibiotic Treatment Antibiotic therapy for patients with documented tularemia is similar to prophylactic treatment regimens. The Working Group on Civilian Biodefense has made the following recommendations for treatment during a bioterrorist attack: If parenteral therapy is available, patients should be given streptomycin or gentamicin intramuscularly for 10 days. In a situation of mass casualties where the medical delivery system is unable to meet patient care demands, oral

antibiotics should be administered for a period of 14 days. It is important to watch for posttreatment relapse and consider the possibility that a weaponized form of *F. tularensis* may be engineered for antimicrobial resistance *(109)*.

Tularemia Vaccine There is no licensed vaccine currently available for tularemia. Several vaccine prototypes are under development; however, challenges to develop new, effective vaccines against *F. tularensis* include lack of a complete understanding of the immunodominant antigens and virulence determinants as well as the fact that generation of both humoral as well as cellular immune responses may be necessary for protection against infection.

In addition, postexposure vaccination against tularemia is also not a feasible strategy; the short incubation period of the disease (3–5 days) negates the benefit of vaccine-based immunity, which requires 14 days to develop after injection.

Implications for Healthcare Workers

Healthcare workers exposed to aerosolized *F. tularensis* should undergo postexposure prophylaxis as described above. In caring for patients with diagnosed tularemia, the use of Standard Precautions *(70)* is adequate since the agent, while highly infectious, is not contagious from person to person.

F. tularensis does pose a significant potential threat in the laboratory setting since tularemia can be easily aerosolized and requires an extremely small dose for infectivity. In addition, the agent may be present in virtually any human specimen *(112)*. A recent report described the exposure of 12 laboratory workers after a delay in identification of *F. tularensis (113)*. This led to a recommendation by the authors that any bacterial microorganisms with properties suggestive of *F. tularensis* on initial evaluation be evaluated under a biologic safety cabinet until the microorganism is further identified.

Viral Hemorrhagic Fever

Hemorrhagic fever viruses are a collection of taxonomically distinct viruses that cause the hemorrhagic fever syndrome. Because the clinical presentation of these viruses is similar, they are all considered hemorrhagic fever viruses.

They share commonalities in composition; they are all single-stranded RNA viruses and possess a characteristic lipid envelope. The four taxonomic families represented in this clinical group include Filoviridae, Flaviviridae, Arenaviridae, and Bunyaviridae. Some key characteristics of specific hemorrhagic fever viruses within these families are shown in Table 103-2.

Laboratory diagnosis is specialized and can be achieved by detection of viral RNA through RT-PCR or viral antigen by enzyme-linked immunosorbent assay. Viral isolation is also useful in a longer time frame. After the disappearance of virus-related markers as the patient enters convalescence, immunoglobulin M appears. Hantaviruses are an exception in that patients present with immunoglobulin M antibodies in serum.

Clinical Syndromes/Epidemiology Although each virus family has unique clinical and epidemiologic characteristics, the overall clinical picture for the group of hemorrhagic fever viruses is similar *(122)*. The infectious dose for hemorrhagic fever viruses appears to be extremely low (1–10 microorganisms) *(11)*. Regardless of the route of infection, they induce a systemic illness with fever, capillary dysfunction, prostration, and, in their most severe manifestations, shock and central nervous system dysfunction. Many patients experience hemorrhagic manifestations that occur as a result of thrombocytopenia or severe platelet dysfunction along with endothelial dysfunction *(122)*. A hemorrhagic or purpuric rash, epistaxis, menometrorrhagia, hematemesis, hemoptysis, blood in stools, and nondependent petechiae are common bleeding manifestations.

The Working Group on Civilian Biodefense has compiled a list of hemorrhagic fever viruses that pose the most serious threat as biologic agents of terror. Notable clinical features of these specific viruses will be reviewed briefly *(123)*.

Ebola Hemorrhagic Fever Ebola belongs to the Filoviridae family of viruses. It is an important emerging infectious disease, with increasingly frequent outbreaks documented in Central Africa since its discovery in 1976 (124). Much about the transmission, reservoirs, and pathogenesis of this disease remain unclear; however, its high case-fatality rate (50%–90%) and its potential for weaponization have made it an increasing focus of public health interest in recent years.

Clinically, Ebola hemorrhagic fever presents with fever, maculopapular rash (especially on trunk), myalgias, chest pain, jaundice, and severe prostration. After several days, bleeding ensues, followed by DIC, shock, and end-organ failure. Death occurs usually within 10 days of symptom onset (124,*125*).

Modes of transmission in nature include person to person, via contact with blood or body fluids (including semen), or direct contact with nonhuman primates, and possibly via aerosolization *(126–128)*.

Marburg Hemorrhagic Fever Marburg virus is a member of the Filoviridae family and shares many similarities to Ebola virus. It was discovered in 1967 following an outbreak in laboratory workers in Marburg, Germany (as well as Yugoslavia) *(129)*. It has been responsible for several outbreaks in Central Africa, the largest in the Democratic Republic of the Congo in 1998 *(130)*.

It has a similar but less lethal clinical picture than Ebola virus; case-fatality rates are generally <25%. Like Ebola, its pathogenesis, modes of transmission, and reservoirs have not been completely elucidated.

Lassa Fever Lassa fever virus is a member of the Arenaviridae family of viruses. It is a disease that has become endemic in West Africa over the past 30 years. It was discovered in 1969 in Northern Nigeria and has been responsible for 100,000 to 300,000 yearly infections since that time *(131)*. Occasionally, it is imported into the United States or other Western Countries *(132)*.

Clinically, Lassa fever is characterized by a prodrome of fever and general malaise, followed by severe exudative pharyngitis, occasionally maculopapular rash, prostration, and, in about one-third of cases, bleeding manifestations. The case-fatality rate is about 15%. Ribavirin therapy is helpful in management of severe cases.

TABLE 103-2

Characteristics of Hemorrhagic Fever Viruses

Family	*Agents*	*Characteristics*
Filoviridae	Ebola virus Marburg virus	• Filamentous virions (from the Latin "filo" for "thread") • Genome contains single-stranded nonsegmented RNA • Size: 19 kbp, 80 nm in diameter, variable length • Transmembrane spike glycoprotein produces antigenically distinct viral species
Arenaviridae	Old World arenaviruses: • Lassa virus New World arenaviruses: • Junin virus (Argentine hemorrhagic fever) • Machupo virus (Bolivian hemorrhagic fever) • Guanarito virus (Venezuelan hemorrhagic fever) • Sabia virus (Brazilian hemorrhagic fever) • Whitewater Arroyo virus	• Spherical or pleomorphic virions with "sandy," granular ultrastructural appearance • Genome contains single-stranded RNA with two segments • Size: 11 kbp, generally 110–130 nm in diameter • Distinct club-shaped or spike glycoprotein projections on viral envelope • Lassa fever viruses exhibit four distinct genetic lineages (three in Nigeria, and one in Guinea, Liberia, and Sierra Leone) • New World arenaviruses differ by neutralization tests and rodent reservoirs
Bunyaviridae	• *Phlebovirus* (Rift Valley fever virus) Nairo virus (Crimean Congo hemorrhagic fever) Hanta virus (Hantaan virus; Sin nombre virus)	• Spherical or slightly pleomorphic virions • Genome contains single-stranded RNA with three segments • Size: 11–19 kbp, 80–120 nm in diameter
Flaviviridae	Yellow fever virus Kyanasur Forest disease virus Omsk hemorrhagic fever virus Dengue virus (primary infection only rarely causes hemorrhagic fever)	• Family name from Latin "flavus" for "yellow" • Icosahedral virions • Single-stranded nonsegmented RNA • Size: 10–12 kbp, 40–50 nm in diameter • Virions covered with surface projections composed of M (membrane) and E (envelope) glycoproteins

(Data from References 114–121.)

New World Arenavirus Hemorrhagic Fevers Several different viruses from the Arenaviridae family are responsible for the New World hemorrhagic fevers. Most cases occur in South America, although one strain, Whitewater Arroyo virus, has been identified as a cause of disease in California *(133)*. The virus is transmitted from asymptomatically infected rodents that serve as a reservoir for the virus. The disease is common in the endemic regions of Bolivia and Argentina; however, some viruses have been responsible for only a very small number of cases.

New World hemorrhagic fever viruses that cause disease in humans include Junin virus (Argentine hemorrhagic fever), Machupo virus (Bolivian HF), Guanarito virus (Venezuelan HF), Sabia virus (Brazilian HF), and Whitewater Arroyo virus.

Clinically, they are similar; most cases are notable for fever, sore throat, myalgias, conjunctivitis, petechiae and other bleeding manifestations, neurologic involvement, and occasionally shock. Recovery occurs over 2 to 3 weeks; the overall case-fatality rate is 15% to 30% *(134)*.

Rift Valley Fever Mosquitoes serve as the vector for Rift Valley fever virus, a bunyavirus (family Bunyaviridae, genus *Phlebovirus*), which is endemic in sub-Saharan and North Africa. The virus was first discovered in sheep in 1930 in Kenya *(135)*. Livestock and humans are most often affected. Epizootics in animals characteristically involve high rates of sheep or cattle mortality especially in the young animals and very high rates of abortion in infected animals. Outbreaks are episodic and most often follow heavy rainfall that results in flooding of previously dry areas, allowing for extensive hatching of the primary mosquito vector *(136)*.

Human illness is usually relatively mild, although most infections are subclinically evident. In <1% of cases, VHF with marked hepatitis and bleeding manifestations can occur. Encephalitis is also an infrequent manifestation of the disease. Retinitis occurs in perhaps 10% of cases, is associated with secondary blindness, and may be associated with permanent visual impairment. The overall case-fatality rate is around <1%, but is as high as 50% in cases of hemorrhagic fever.

Yellow Fever Yellow fever virus is a member of the Flaviviridae family of viruses. It has been described as early as the 1600s and continues to be endemic in sub-Saharan Africa and tropical South America *(137)*. A variety of mosquito species serve as vectors for yellow fever virus. The

WHO estimates 200,000 cases per year and 30,000 deaths worldwide, although many of these are unreported.

Many cases of yellow fever are mild or even subclinical. Cases of severe disease are characterized by fulminant hepatitis, bleeding, renal failure, shock, and death. The overall case-fatality rate is from 5% to about 20%, but increases to 50% or more for patients with severe disease.

Kyasanur Forest Disease and Omsk Hemorrhagic Fever Kyasanur Forest disease is a rare, tick-borne infection found only in one region of India. Outbreaks occur periodically and parallel epizootics are found in the local monkey population. Omsk hemorrhagic fever is also a rare form of VHF, limited to regions of Central Asia and Siberia. It is associated with episodic outbreaks that have been documented since the 1940s and 1950s (138). Recently another flavivirus, Alkhurma virus, has shown activity in Saudi Arabia. It is a variant of Kyasanur Forest disease and can cause severe disease, although aerosol infection has not been evaluated *(138A)*.

The clinical picture is similar to other hemorrhagic fever viruses; many cases are mild, but severe disease can be associated with meningoencephalitis and VHF. The overall case-fatality rate for Kyasanur Forest disease is 3% to 10% and Omsk hemorrhagic fever is 0.5% to 10%.

Hemorrhagic Fever Viruses as Biologic Weapons VHF viruses have been the subject of considerable research and development as biologic weapons; the United States, prior to 1972, conducted research on a variety of agents, and the Soviet Union weaponized Marburg virus and conducted research on Ebola, Lassa, and Rift Valley fever viruses as well as others. There is concern that North Korea may have weaponized yellow fever virus *(139)*.

These viruses have characteristics that make them attractive as biologic agents of terror: they are infectious by aerosols at low doses and can be aerosolized; they can cause high fatality rates with a dramatic clinical syndrome that could contribute to subsequent widespread panic and social destabilization; many are readily available and have been extensively researched by several countries. In addition, treatment options are limited or nonexistent.

The CDC, in 2000, listed Ebola, Marburg, and Lassa viruses and New World arenaviruses as category A agents, those most likely to cause mass casualties if deliberately disseminated. In 2002, the Working Group on Civilian Biodefense added Rift Valley fever virus, yellow fever virus, Kyasanur Forest disease virus, and Omsk hemorrhagic fever virus to the list compiled by the CDC *(123)*.

Therapeutic Countermeasures for Weaponized VHF

Treatment The mainstay of treatment for VHF is supportive, intensive care as indicated by the complications of the disease. Management of bleeding diatheses is controversial but generally involves the administration of blood and clotting factor components as indicated by the laboratory findings. Heparin or tissue factor antagonists may be useful therapeutic choices in cases of DIC *(140)*. Steroids have not been shown to be effective, but should be considered with evidence of adrenal involvement *(141,142)*.

Ribavirin has significant *in vitro* activity against members of the Arenaviridae and Bunyaviridae (*123,143,144,145*,146). *In vivo*, the major established therapeutic utility of the drug is in the arenavirus hemorrhagic fevers. Human data are available for Lassa fever, but for the Bolivian, Argentine, and Brazilian viruses there is only animal data with anecdotal clinical reports (*147*,148,149,*150*). There are a number of experimental approaches that are impractical or insufficiently developed, including passive antibody therapy or interferon prophylaxis. Antiviral agents have not been shown to be effective against diseases caused by filoviruses or flaviviruses *(123)*.

Postexposure Prophylaxis There is no effective postexposure prophylaxis for asymptomatic persons exposed to weaponized hemorrhagic fever virus. The Working Group on Civilian Biodefense instead recommends that exposed populations be placed under surveillance for signs of fever or other symptoms suggestive of VHF. In the event of a documented fever >101°F, persons should be given intravenous ribavirin unless the agent is a confirmed filovirus or flavivirus *(151)*. This is an off-label use, and intravenous ribavirin is mainly accessible for compassionate use. Surveillance should continue for 21 days following exposure *(123)*.

Vaccine The only effective licensed vaccine against VHF is yellow fever vaccine. It is a live virus vaccine and has been associated with adverse events including fever, jaundice, and multiple organ system failure on rare occasions. The vaccine is in limited supply and is only recommended for travelers to areas endemic for yellow fever and laboratory personnel with an ongoing exposure risk to yellow fever *(152)*.

In the event of a bioterrorist attack, yellow fever vaccine would not be effective as a prophylactic treatment following exposure, because the disease incubation period is significantly shorter than the time required for developing immunity following vaccination *(123,153)*.

Vaccines against Argentine hemorrhagic fever and Rift Valley fever are known to be efficacious but are available only as investigational drugs *(154)*. Efforts to develop additional vaccines against various hemorrhagic fever viruses are ongoing *(155–157)*.

Implications for Healthcare Workers Transmission within healthcare settings has been documented for several VHF viruses, including Ebola, Marburg, Lassa, Machupo, and Crimean-Congo viruses *(7)*. Healthcare-associated transmission has usually occurred by contact with infected body fluids or blood (158,*159*). Needlesticks or the reuse of needles has also been associated with viral transmission *(155,160)*. Although these viruses form stable infectious aerosols, person-to-person airborne transmission is distinctly uncommon; the potential for airborne transmission in a healthcare setting cannot be ruled out (*123*,161). There is one documented case of airborne transmission of Machupo virus to a nursing student observing a bed linen change. The student had no physical contact with the patient or any associated fomites *(162)*. Contact with cadavers has also been a documented source of infection during outbreaks with Ebola hemorrhagic fever *(163)*.

Healthcare workers must exercise appropriate isolation procedures for patients with suspected or confirmed VHF including a combination of Airborne and Contact

Precautions *(7)*. The Working Group on Civilian Biodefense recommends the following precautions for healthcare settings *(123)*:

- All healthcare workers must have appropriate personal protective equipment, including N95 masks or personal air-purifying respirators.
- Patients must be placed in a negative pressure room, with restriction of nonessential staff and visitors.
- All healthcare workers who have had high-risk close contact with patients suspected of having VHF should be placed under medical surveillance for 21 days following exposure *(123)*.
- If multiple patients suspected of having VHF are admitted to a healthcare facility, they should be cohorted to minimize exposure to healthcare workers and other patients.

All cases of suspected VHF should be reported immediately to state or local public health officials, according to disease reporting requirements.

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CHAPTER 104

Preparedness for a Bioterrorist Attack with Smallpox

Whitni B. Davidson, Andrea M. McCollum, and Inger K. Damon

Smallpox is an infectious disease caused by an orthopoxvirus, variola virus, and efforts of a worldwide program led to its eradication. Historical accounts have long placed smallpox as the cause of many epidemics and deaths. Smallpox has a high interhuman transmission rate, multiple transmission routes, and a high case fatality rate. Jenner's inoculation with cowpox in 1798 demonstrated that protection against smallpox could be achieved using dermal infection with a related orthopoxvirus. Shortly thereafter, vaccination with live vaccinia virus was introduced as an individual and population-based method to prevent infection with smallpox. An extensive global campaign including vaccination, surveillance, containment, and infection control practices was led by the World Health Organization (WHO) beginning in 1967. The last case of "natural" smallpox was reported in a Somalian patient in 1977, and two persons were infected as a result of a laboratory exposure in 1978. Worldwide eradication was pronounced in 1980. Childhood vaccination programs ceased before, or shortly after, the declaration of disease eradication.

Smallpox, as known in the historical medical literature, did not have an animal reservoir; thus, there is no risk of "natural" human infections appearing again, and this, in part, contributed to the ability to eradicate the disease. However, the virus itself has not been eradicated. Declared stocks of the virus are securely maintained in two WHO reference laboratories, one at the U.S. Centers for Disease Control and Prevention (CDC) and the other at the State Research Center of Virology and Biotechnology (Vektor Institute) in Russia. There is some belief that undeclared stocks may also exist *(1)*. Thus, the chance of an accidental or intentional release of smallpox is not zero. This, along with an increasing susceptible, unvaccinated, mobile population, causes great concern about the dangers posed by variola virus in the world today.

Large-scale public health efforts have resulted in the development of emergency plans, response guidelines, and acquisition of vaccine stocks. For example, the United States has enough smallpox vaccine in its stockpile to vaccinate each U.S. citizen in the event of a release of the virus. This chapter will review the biology and epidemiology of smallpox, vaccination information including adverse events, and hospital control and prevention of transmission of the disease.

VIROLOGY AND PATHOLOGY

Variola virus belongs to the *Poxviridae* family, subfamily *Chordopoxvirinae*, as a member species of the *Orthopoxvirus* genus. Chordopoxviruses infect a wide variety of animals including birds, rodents, ruminants, and humans, and these viruses can exhibit wide to narrow "host" species specificities and host ranges. The *Orthopoxvirus* genus includes four virus species known to infect humans, variola, monkeypox, vaccinia, cowpox, as well as others not currently known to naturally infect humans. Orthopoxviruses are closely related and immunologically cross-reactive. Edward Jenner demonstrated cross-protection against variola in humans first using cowpox in 1798 and then using vaccinia virus.

Poxviruses have large virions, approximately 140 to 260 nm × 220 to 450 nm. Oval- or brick-shaped virions encapsulate linear, double-stranded DNA genomes of approximately 200 kb in length. There are two epidemiologically characterized variants of variola infection: "variola major" and "variola minor"; each differs in case fatality rates and some viruses associated with the less severe disease manifestations can be distinguished in the laboratory or by genetic markers (2).

Much of the information about smallpox pathogenesis has been gleaned from using animal models with a variety of orthopoxvirus challenges. In human smallpox disease, epidemiologic information indicated that the common route for infection was via the respiratory tract; transmission via the skin or congenitally occurred less frequently. The virus asymptomatically replicates in the endothelium and enters the reticuloendothelial system. Additional replication occurs in the lymph nodes. Macrophages migrate to infected lymph nodes early in infection, and the production of cytotoxic T cells and B cells limits the spread of infection. Neutralizing antibodies can be found during the first week of infection. Secondary viremia followed by initial onset of symptoms occurs on average 12 days after transmission. Hemagglutination inhibition and complement fixation antibodies are present approximately 16 and 18 days postinfection, respectively. These antibodies may dissipate after 1 year; however, neutralizing antibodies are present for many years postinfection (2–4). Currently, humoral immune responses to orthopoxvirus infections are more commonly measured

via immunoglobulin M and/or G enzyme–linked immunosorbent assays and neutralizing responses *(5)*.

A rash develops over the entire body and goes through several stages (described below) as macrophages migrate to the epidermis. Aside from oropharynx and skin lesions, virus can be found in lymph nodes, bone marrow, spleen, liver, kidney, urine, and conjunctival secretions (2,3). In fact, virtually all organs are affected. Endothelial cells lining the sinusoids of the liver swell and can become necrotic, and parenchymal cells swell. The spleen enlarges with increased lymph involvement. Hemorrhaging of renal, gastric, and pharyngeal membranes and endocardium and myocardial tissue occurs. Thrombocytopenia, encephalitis, and necrosis of testis are also occasionally noted. Prominent pitted scarring is likely due to the destruction of sebaceous glands (6).

The exact cause of death due to smallpox is not completely understood. Secondary bacterial infections have been posited to play a role in death, but recent data do not support their role in fatalities. One retrospective study attributed many deaths to cytotoxicity or immune complex disease *(7)*.

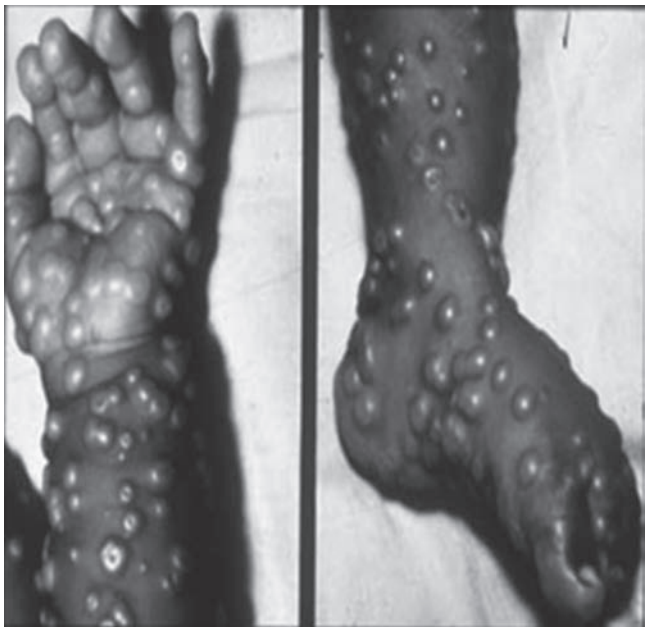

FIGURE 104-1 Smallpox: lesions on palms and soles. (From World Health Organization.) (*See color insert.*)

CLINICAL DISEASE AND EPIDEMIOLOGY

Presentation

Clinical presentations of smallpox can vary depending on the patient's vaccination status, level of nutrition, and infectious strain, among a host of unknown factors. Smallpox illness has three phases: incubation, prodrome, and rash. Infection occurs via the respiratory mucosa, and an incubation period of 10 to 14 days on average occurs before a prodromal period of 2 to 4 days. The prodrome is characterized by fever, malaise, vomiting, headache, backache, and myalgia. The prodromal phase can be severe enough to confine many patients to bed and has been described to resemble a severe influenza illness (2,*8*).

Rash initially presents as an enanthem on the mucous membranes of the mouth, tongue, and oropharynx; within 24 hours, a rash, ultimately with centrifugal distribution, develops. Usually, the rash is first evident on the face, then proximal extremities, distal extremities (including palms and soles), and trunk (Fig. 104-1). The rash develops from macules to papules to vesicles to pustules over the course of 1 to 10 days postprodrome (Fig. 104-2). Lesions on any one part of the body generally present in the same stage of development during the course of the rash, and lesions present with a centrifugal density. Lesions are deep, firm, and become umbilicated (Fig. 104-3). Lesion numbers can be denser in areas of trauma or inflammation—the "garter effect"—and are noted in areas where there are scratches or irritation. Scabs eventually form and fall off approximately 2 to 3 weeks postinitial rash onset and leave pronounced deep scars and hypo- and/or hyperpigmentation (2,6,*8*). Nonfatal severe complications associated with variola infections include panophthalmitis, blindness, keratitis, corneal ulcers, osteomyelitis, arthritis, orchitis, and encephalitis.

Forms of Variola

Smallpox has been categorized in a number of different ways including variola major and minor, based on epidemiological criteria such as case fatality rates. Variola major and variola minor, on average, have case fatalities of about 30% and ≤1%, respectively. Variola–alastrim strains (which caused disease in Brazil in the 20th century) have been discretely biologically and genetically discriminated from variola major. However, certain African variola minor isolates by laboratory assays are more like variola major than alastrim *(9)*. Surveillance data (which may be biased by health-seeking behaviors) suggest that nearly 90% of patients develop variola major. Variola major was categorized by the WHO into eight clinical types. Three types of "ordinary" disease are discriminated by the density of rash presentation on the face and body: ordinary discrete, ordinary semiconfluent, and ordinary confluent. In hospitalized patients, these forms are characterized to have mortality rates of 30%, 37%, and 62%, respectively, in unvaccinated individuals and mortality rates of 3%, 8%, and 26%, respectively, in vaccinated individuals. The terms discrete, semiconfluent, and confluent refer to the density of the lesions (6,*10*).

Less severe, somewhat atypical disease, described as modified smallpox, exhibits a faster disease time course with more superficial lesions when compared to ordinary forms of variola major. Another less pathogenic form, variola *sine eruption*, is characterized by a febrile illness without rash and little to no viral transmission. Modified smallpox and variola *sine eruption* occur mainly in vaccinated individuals with little associated mortality (2,6).

The most severe, and rare, manifestations of disease (<3–5% of hospitalized patients) are flat and hemorrhagic forms of smallpox. Flat-type smallpox describes a disease in which the lesions appear flat, likely because of significant tissue edema. In hospitalized patients, the mortality rate is approximately 97% in unvaccinated and 67% in vaccinated individuals. Hemorrhagic smallpox is characterized to have two variants: early and late. In early disease, the characteristic discrete, raised pustules seen in ordinary smallpox do not develop. Instead painful, erythematous,

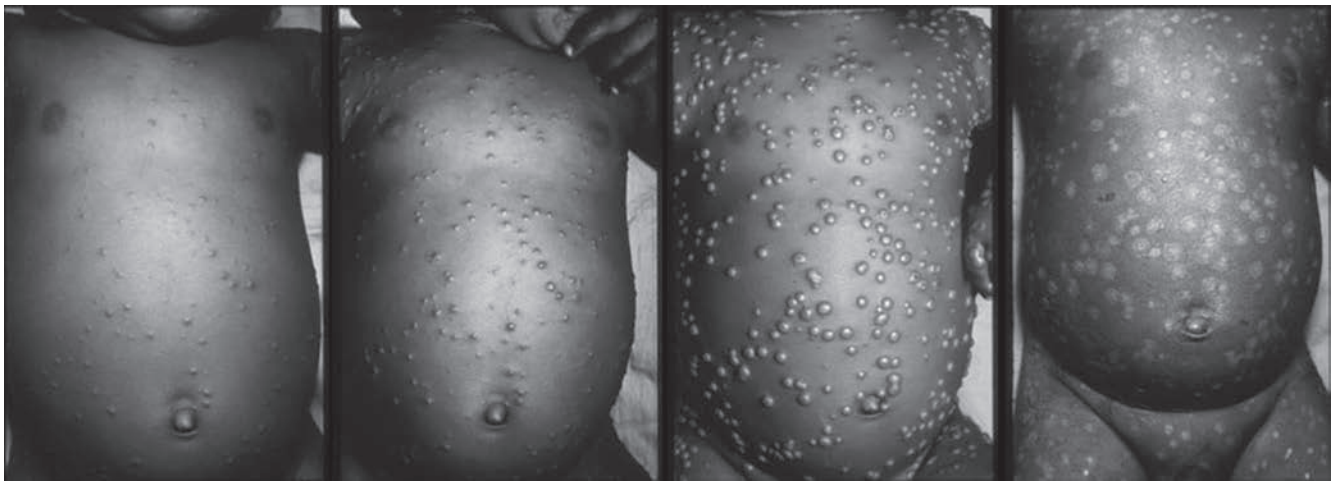

FIGURE 104-2 Smallpox: progression of lesions on the abdomen of child days 4, 5, 8/9, and 20. (From World Health Organization.) (*See color insert.*)

petechial lesions appear. In late hemorrhagic disease, some characteristic lesions develop, and hemorrhage is noted at the base of the lesions. The incubation period for early hemorrhagic smallpox is relatively short and death occurs within 5 or 6 days of rash onset. Death, regardless of vaccination status, occurs in approximately 95% of hospitalized individuals and is most likely due to massive mucosal hemorrhage (2,6,*10*).

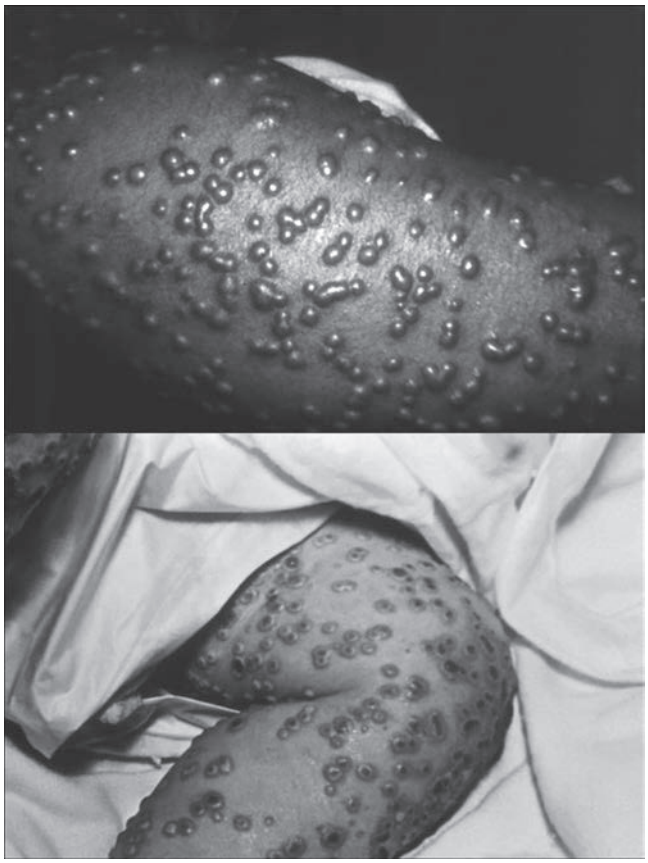

FIGURE 104-3 Firm, deep-seated pustular lesions on right arm (*top*) and umbilicated lesions on the leg of a 1-year-old (*bottom*). (*Top*: From CDC/Dr. John Noble Jr. *Bottom*: From CDC/Dr. Robinson.) (*See color insert.*)

Diagnosis

There are a number of illnesses that can be misdiagnosed as smallpox. These have included, and continue to include, varicella (chickenpox), monkeypox, disseminated herpes zoster and herpes simplex, impetigo, drug-induced rashes, erythema multiforme, Stevens–Johnson syndrome, scabies, molluscum contagiosum, and enteroviral infections, especially hand, foot, and mouth disease. The disease most commonly mistaken for smallpox during and after eradication is varicella. Clinical features of varicella that distinguish it from smallpox are a short prodromal phase lasting 1 to 2 days, fever with onset of rash, centripetal rash distribution, lesions in varying stages of development, and shortened lesion progression from vesicles to crusting (3). Human monkeypox, a zoonotic disease endemic to central and western Africa, resembles smallpox in appearance, but patients will typically experience lymphadenopathy as part of their clinical course. Human monkeypox has not been seen in the United States since the 2003 outbreak related to importation of African rodents *(11)*.

Many medical professionals have no experience with smallpox; therefore, an algorithm was developed by CDC that separates patients into three risk categories for smallpox—high, moderate, or low (Fig. 104-4) (3). This algorithm (a) provides information about the symptoms of smallpox and other causes of febrile, vesicular/pustular rash illnesses likely to be confused with smallpox and (b) limits laboratory testing to high-risk patients reducing the likelihood of false-positive test results *(12)*. The algorithm can be found at *http://emergency.cdc.gov/agent/smallpox/diagnosis/evalposter.asp*.

Because of bioterrorism concerns for the potential malevolent use of variola, screening for variola virus from specimens of high-risk individuals can be performed in the U.S. at specific Laboratory Response Network (LRN) reference laboratories. Absent circulating disease, if screening at an LRN facility is positive for variola virus, more extensive testing and confirmation is performed at CDC before results are released. Real-time polymerase chain reaction is the gold standard for detection of variola virus. Previously, unique viral growth on chorioallantoic membrane

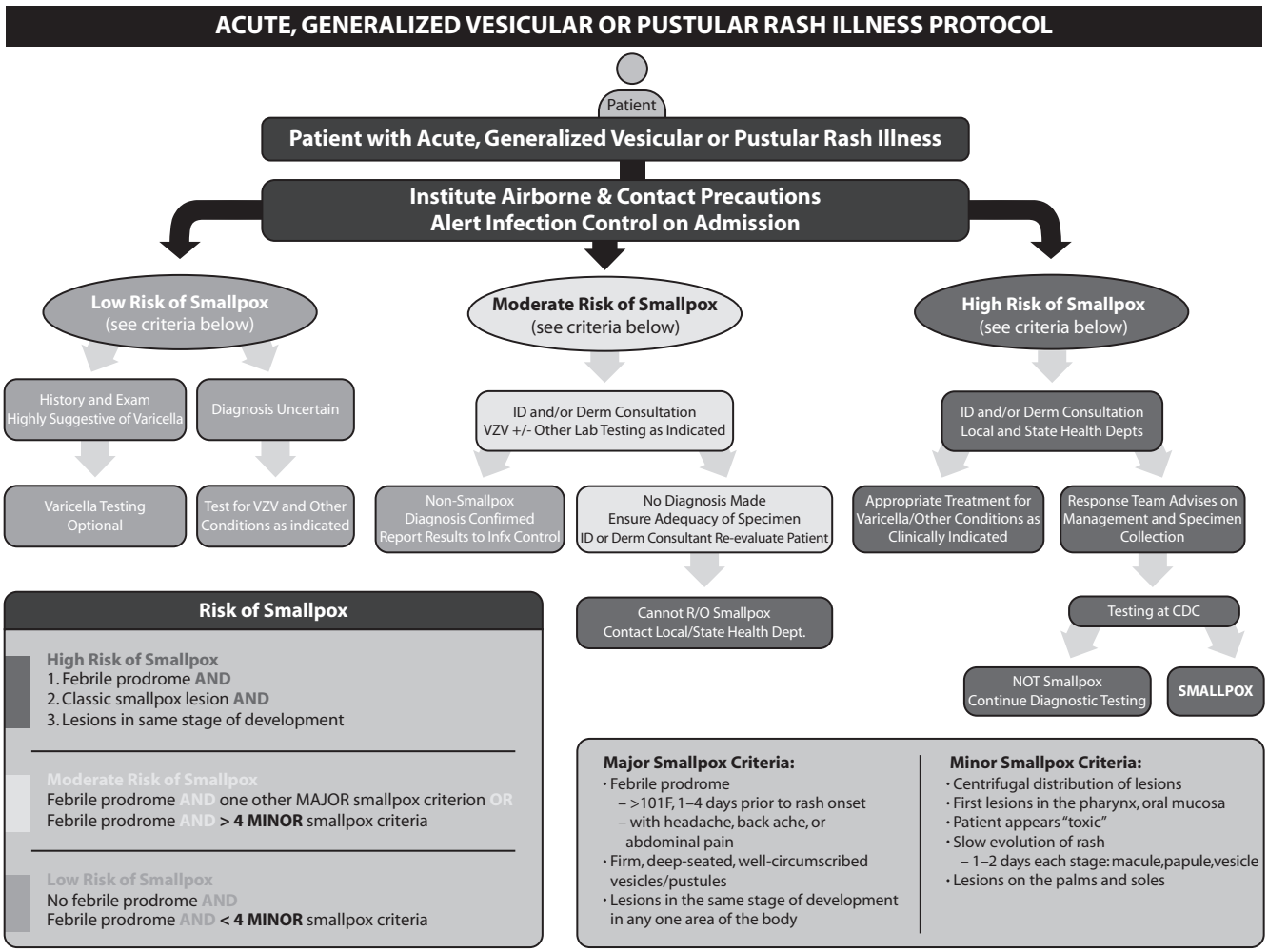

FIGURE 104-4 Evaluating patients for smallpox: acute, generalized vesicular, or pustular rash illness protocol. (From Centers for Disease Control and Prevention. Acute, generalized vesicular or pustular rash illness testing protocol in the United States. Available at *http://emergency.cdc.gov/agent/smallpox/diagnosis/pdf/poxalgorithm11-14-07.pdf.* Accessed June 1, 2011.) (*See color insert.*)

provided definitive confirmation. Other laboratory testing diagnostics such as enzyme-linked immunosorbent assay, electron microscopy, and immunohistochemical staining can diagnose a poxvirus infection; however, these tests are not specific for variola virus. With the exception of parapoxviruses, poxviruses have identical morphology by electron microscopy making it impossible to differentiate one species from another. Assays relying on immune reagents will, at least, identify all members of a poxvirus genus; orthopoxviruses share >90% genetic similarity causing antibodies to cross-react among member species (3).

Therapy

Currently, no antivirals are licensed for the treatment of any orthopoxvirus infection. There are active research programs evaluating various compounds against orthopoxviruses, including variola, in *in vitro* tissue culture, and in various orthopoxvirus-challenge animal disease model systems. Supportive therapy should be offered to smallpox patients. The time period between exposure and case identification or symptom onset is a critical factor in consideration for the use of postexposure prophylaxis (in the form of vaccination) or the use of investigational antiviral medications (2,4,13).

Patterns of Transmission

The infectiousness of a smallpox case depends upon the amount of viral shedding in oropharyngeal secretions and the number and distance of face-to-face contacts with susceptible persons. Smallpox patients have maximum infectivity during the first week of rash when large amounts of virus are being shed from the mouth and pharynx. Severe cases of smallpox typically shed larger amounts of oropharyngeal virus than those with modified-type smallpox. Although a large amount of virus can be detected in smallpox scabs, their infectivity is considerably less due to the enclosure of viral particles within hard dry scabs (4). Transmission rarely occurs before the first day of rash *(14)*. Epidemiologic studies have found that most cases of secondary smallpox caused by importation from an endemic area occurred within 3 weeks of initial exposure *(15)*.

The most frequently infected group is the household or family because of the significance of face-to-face contact in transmission. The secondary attack rate of variola major has

ranged from 1.2% to 88% in close contacts and is significantly affected by the vaccination status of the contact. Because patients with variola major in the prodromal phase usually fall quite ill, they separate themselves from the community, but not from their household contacts. The average attack rate for unvaccinated family contacts was 58.4%, and 3.8% in vaccinated contacts. On the other hand, cases infected with variola minor are more mobile causing more disease within the community despite less viral shedding (4).

Smallpox shows a seasonal variation in incidence with a predilection for winter and spring. However, seasonal fluctuation is limited in areas with uniform temperature and humidity. Aside from the environmental factors that may prolong the viability of virus, cool temperature and low humidity, other considerations have been given to the seasonal incidence of smallpox. These include (a) changes in mucous membrane permeability, (b) alterations in resistance because of changes in diet, and (c) the effect of climate on social activities (4).

VACCINATION

Edward Jenner demonstrated the principles of vaccination in 1796 when he used material from human cowpox lesions to protect individuals against smallpox. Today, live vaccinia virus is used to vaccinate against smallpox. Vaccinia virus is a closely related, yet distinct *Orthopoxvirus* species from variola. Routine vaccination was common in many countries until the early 1970s (4).

Variola virus has no nonhuman animal reservoir, and infection can be prevented with a single-dose, recent vaccination: these two characteristics made eradication a feasible accomplishment. WHO began an intensive surveillance, containment, and eradication campaign in 1967. Surveillance and containment consisted of the following five steps: (a) identification of cases, (b) isolation of patients, (c) identification of ring or close contacts, (d) vaccination of the ring contacts, and (e) vaccination of the associates of the ring contacts. This approach was used to eradicate smallpox and is recommended by WHO for use today if smallpox reappears (2,4). However, if a reintroduction occurs, widescale vaccination may occur in several countries.

In late 2007, the Food and Drug Administration licensed a new smallpox vaccine to replace Dryvax®. This new vaccine, ACAM2000®, is a cell culture grown, fully replicative vaccinia virus derived from a clonal isolate of Dryvax®. ACAM2000® was chosen based on its similar efficacy to Dryvax® *(16)*. Focus of current research on smallpox vaccines is the further development of replication competent cell culture–derived vaccinia; replication deficient, highly attenuated vaccinia; and DNA- or protein-based vaccines. Preclinical and clinical trials are currently underway for some of these newer vaccines to determine their efficacy *(17)*.

The preferred site for vaccination is the upper arm over the deltoid muscle. Vaccine is delivered by scarification using a sterile bifurcated needle that has been dipped into the rehydrated suspension. Fifteen perpendicular strokes to the skin are given through the droplet within a diameter of about 5 mm. The appearance of a drop of blood indicates that the strokes were vigorous enough to puncture the skin. Following successful primary vaccination, a major cutaneous reaction should appear at the site of inoculation by day 6 to 8 (Fig. 104-5). Within 2 to 5 days postvaccination, a papule will appear that will become vesicular, then pustular, and reach maximum size at day 8 to 10. The pustule will dry forming a scab which typically separates within 14 to 21 days, often leaving a pitted scar, and hypo- or hyperpigmentation is not unexpected. Persons who are revaccinated after successful primary vaccination may have a modified cutaneous response but this does not necessarily indicate an unsuccessful vaccination (18).

Because the current smallpox vaccine is a live, fully replicative vaccinia virus and can cause secondary transmission,

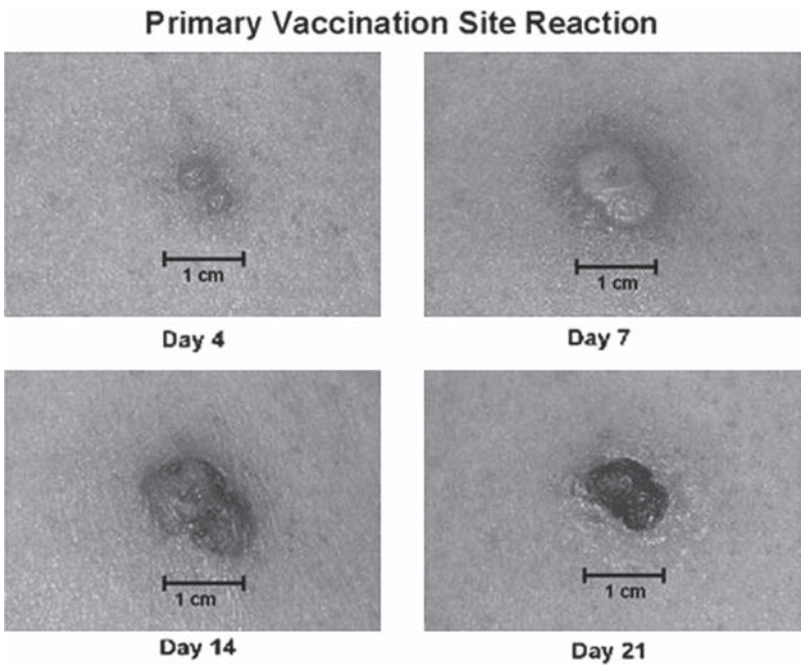

FIGURE 104-5 Vaccination site progression sequence in a normal primary vaccinee days 4, 7, 14, and 21. (From Centers for Disease Control and Prevention.) (*See color insert.*)

the inoculation site must remain covered until the scab has completely detached and a new epidermal layer has formed. A gauze bandage held in place by adhesive tape should loosely cover the site. If the vaccinee has an occupation that puts him or her in direct contact with patients, the gauze should be covered with an additional barrier using a semipermeable dressing and a layer of clothing. The use of only a semipermeable dressing is not recommended as it might lead to maceration of the vaccination site. Maceration can cause prolonged irritation and itching, potentially leading to increased touching or scratching and therefore contamination of hands. If maceration does occur, the lesion should be left uncovered to allow the site to dry. This is only suitable when a healthcare worker has no direct contact with patients or other persons. The vaccination site must remain covered until the scab separates *(19)*. Contaminated bandages should be sealed in a plastic bag and thrown in the trash. After direct contact with the vaccination site, hands should be washed with soap and warm water or with alcohol-based hand rubs. Potentially contaminated clothes, towels, or sheets should be washed separately in warm water (18).

The Advisory Committee on Immunization Practices lists a number of contraindications to smallpox vaccination in a routine nonemergency setting for both vaccinees and their household contacts. For both, these include a past or present history of eczema or atopic dermatitis; acute, chronic, or exfoliative skin conditions such as burns, chickenpox, or Darier's disease; immunodeficiency or those currently on immunosuppressive therapy; inflammatory eye diseases leading to use of steroid eye drops; and pregnancy or plans to become pregnant in the next 4 weeks. Additional contraindications for vaccinees only include: allergy to smallpox vaccine components, including polymyxin B, neomycin, streptomycin, and phenol; symptomatic or asymptomatic heart disease or three or more cardiac risk factors (hypertension, diabetes, hypercholesterolemia, heart disease at 50 years of age in a first degree relative, or current smoker); breastfeeding; persons under 18 years of age, especially infants <12 months, and those older than 65 years; severe allergy to latex; or "moderate" to "severe" illness at vaccination time. There are no absolute contraindications to vaccination for a person with a high-risk exposure to smallpox (18,*20*,21).

In the United States, routine smallpox vaccination of civilians was discontinued in 1971 following reduction of smallpox importations in the 1960s. In 1976, routine vaccination of healthcare workers was also discontinued *(22)*. In 2002, a preparedness plan was initiated to protect the United States against a possible smallpox bioterrorist attack. This plan calls for vaccination of both military and civilian personnel. Under the U.S. Civilian Smallpox Preparedness and Response Program, groups of public health and medical response teams who would care for smallpox patients during the first 7 to 10 days of an outbreak were voluntarily vaccinated (Table 104-1). Approximately 40,000 civilian personnel received licensed vaccine from January to December 2003 *(23)*. Since 2003, CDC continues to provide smallpox vaccine to state public health authorities for vaccination of smallpox response team members. CDC recommends revaccination of volunteer responders on an "out-the-door" basis, meaning only after a smallpox outbreak has been confirmed or is highly suspected, or there is credible evidence of a release or imminent release *(24)*. The US military continues to vaccinate personnel who serve in high-risk parts of the world. Additionally, laboratory researchers who work with or may be exposed to nonhighly attenuated vaccinia virus are often vaccinated (21,*25*,*26*).

TABLE 104-1

Recommended Members of Smallpox Response Healthcare Teams (per ACIP and HICPAC)

1. Physicians, nurses, and unit staff providing inpatient medical care for children and adults, including those in emergency room departments, intensive care units, general medical units, and primary-care facilities
2. Medical subspecialists, including infectious disease specialists, dermatologists, pathologists, ophthalmologists, surgeons, anesthesiologists, or those with previous smallpox experience
3. Infection control professionals
4. Respiratory therapists
5. Radiology technicians
6. Security personnel
7. Housekeeping staff (e.g., those staff involved in maintaining the healthcare environment and decreasing the risk for fomite transmission)

ACIP, Advisory Committee on Immunization Practices; HICPAC, Healthcare Infection Control Practices Advisory Committee. (Adapted from CDC. Recommendations for using smallpox vaccine in a pre-event vaccination program. *MMWR Morb Mortal Wkly Rep* 2003;52(RR-07):1–16.)

Reactions and Adverse Events to Smallpox Vaccination

Successful primary vaccination correlates with the activation of both the humoral and cellular immune responses in >95% of individuals. This includes production of neutralizing antibodies, vaccinia-specific memory B cells, and CD8+ and CD4+ cytotoxic T lymphocytes. Neutralizing antibodies appear approximately 10 days postvaccination. Both peak antibody levels and vaccinia-specific memory B cells decline during the first year postvaccination but then stabilize and can be detected >50 years later. Both CD4+ and CD8+ T cells can be detected by 1 month postvaccination and slowly decline over time but may be detectable for decades (3,*27*). Vaccination against smallpox does not confer complete lifelong immunity. A successful primary vaccination confers full immunity in >95% of individuals for 5 to 10 years (4).

In most cases, vaccination is safe and effective against the prevention of smallpox; however, adverse reactions can occur in individuals with or without preexisting conditions (Table 104-2). Some of these reactions are mild, others serious but treatable, and a rare few can be life threatening (28). Most data regarding adverse reactions to smallpox vaccination were gathered in the 1960s when the public was still routinely vaccinated. Rates of adverse reactions are expected to be higher in today's population given the increase in the number of immunocompromised individuals, such as those with HIV/AIDS, and the widespread use of immunomodulatory medications.

TABLE 104-2

Adverse Events Associated with Smallpox (Vaccinia) Vaccine

Adverse reactions in vaccine recipient or contact of vaccine recipient

1. Local skin reaction and hypersensitivity
   Allergic reaction to bandages/adhesives, robust take, bacterial infection
2. Nonspecific rashes
3. Dermatologic manifestations of hypersensitivity reactions
   Erythema multiforme; Steven–Johnson syndrome
4. Inadvertent inoculation
   Contact inoculation, autoinoculation, ocular vaccinia, eczema vaccinatum
5. Congenital vaccinia (fetal vaccinia)
6. Generalized vaccinia
7. Progressive vaccinia (vaccinia necrosum, vaccinia gangrenosa, and disseminated vaccinia)
8. Cardiac complications
   Myocarditis, pericarditis, atypical chest pain
9. Central nervous system complications
   Postvaccinial encephalitis, myelitis, acute disseminated encephalomyelitis

(Adapted from CDC. Smallpox vaccination and adverse reactions. *MMWR Morb Mortal Wkly Rep* 2003;52(RR-04):1–28.)

Approximately 1 week postvaccination, individuals may experience systemic symptoms such as fever >37.7°C lasting up to 3 weeks, malaise, myalgia, headache, chills, nausea, and fatigue. Soreness at the vaccination site, local lymphadenopathy, and erythema are also common. Expected normal variants include the appearance of satellite lesions close to the vaccination site, viral lymphangitis with a visible track toward the regional nodes in the axilla, local swelling, and intense inflammation surrounding the lesion. These types of local reactions typically only require supportive treatment *(29)*.

Many vaccinees will develop an exanthema 1 to 2 weeks after vaccination that may have multiple etiologies including hypersensitivity to a component of the vaccine. These rashes vary in appearance and often spontaneously resolve on their own. Rarely, individuals develop Stevens–Johnson syndrome with mucosal involvement. These rashes are typically pruritic and, with the exception of Stevens–Johnson syndrome, do not require hospitalization. Bacterial infections can occur at the vaccination site causing lymphangitis and regional lymphadenitis, but most often are superficial in nature (28).

A stringent screening program and exclusion of persons at risk for adverse events before the administration of vaccine coupled with educational information on infection control practices postvaccination can markedly curtail the number of adverse events in both vaccinees and their contacts (21). Inadvertent inoculation (accidental implantation) is the most common adverse event following primary vaccination due to the high titer of virus on the surface of the skin (Fig. 104-6). Inadvertent inoculation

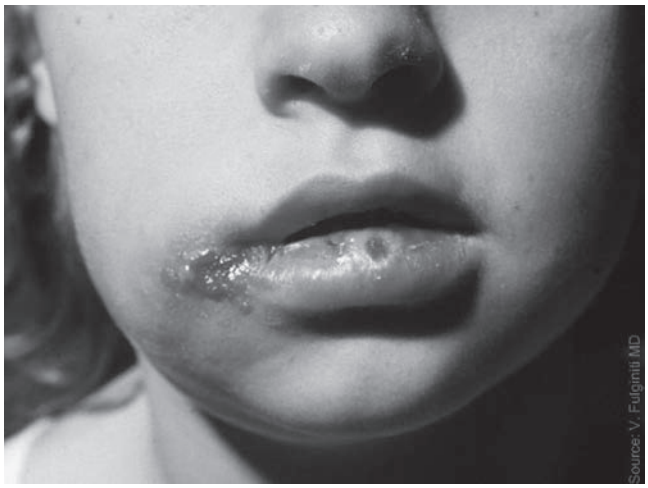

FIGURE 104-6 Inadvertent inoculation of the lip. (From CDC/V. Fulginiti, MD.) (*See color insert.*)

can vary from development of single lesions to massive involvement depending on the degree of skin involvement. Corneal implantation can cause vaccinia keratitis, which results in ulceration, scarring, and vision loss (Fig. 104-7). Eczema vaccinatum (EV) can occur in patients with a previous or current history of atopic dermatitis (Fig. 104-8).

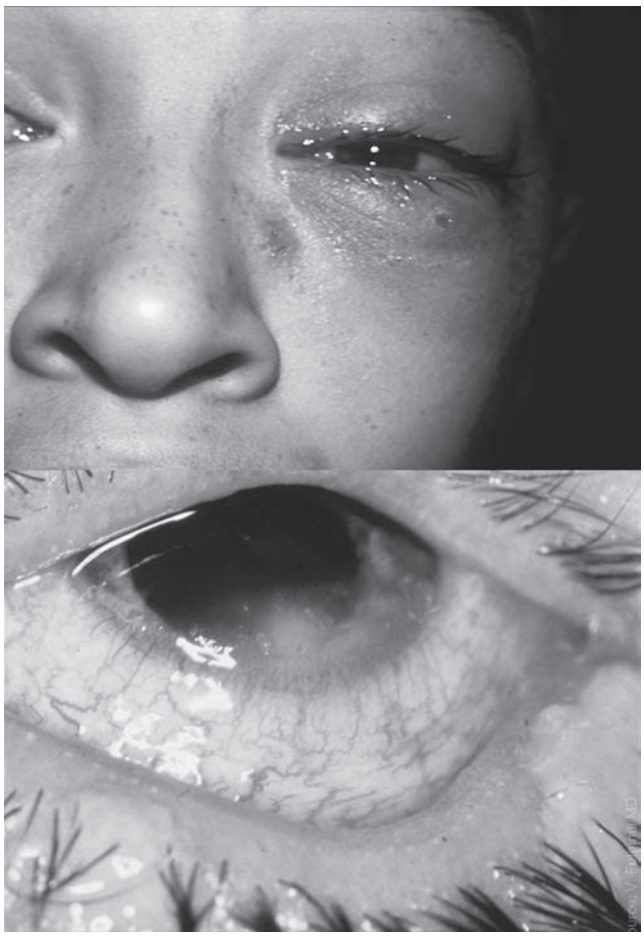

FIGURE 104-7 Inadvertent inoculation of the eye in a 12-year-old boy (*top*) and cloudy corneal lesions in a woman (*bottom*). (*Top*: From CDC/Dr. Weyand. *Bottom*: From CDC/V. Fulginiti, MD.) (*See color insert.*)

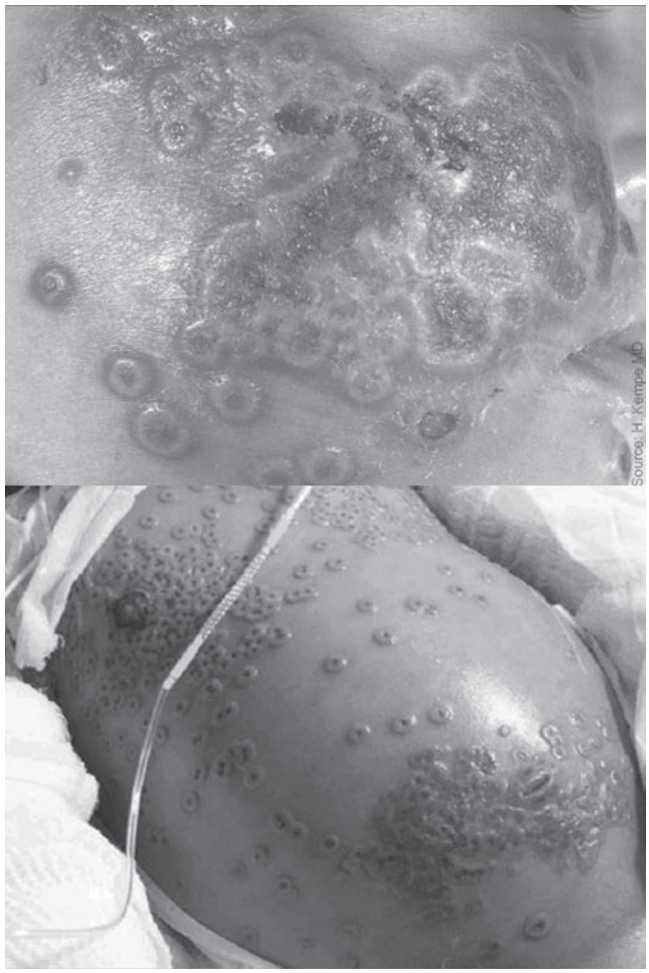

FIGURE 104-8 Eczema vaccinatum: vesicles with surrounding erythema and crusting on the cheeks of an infant (*top*) and umbilicated lesions on abdomen and chest of a 28-month-old child (*bottom*). (*Top*: From CDC/H. Kempe, MD. *Bottom*: From *MMWR Morb Mortal Wkly Rep* 2007;56(19):478–481.) (*See color insert.*)

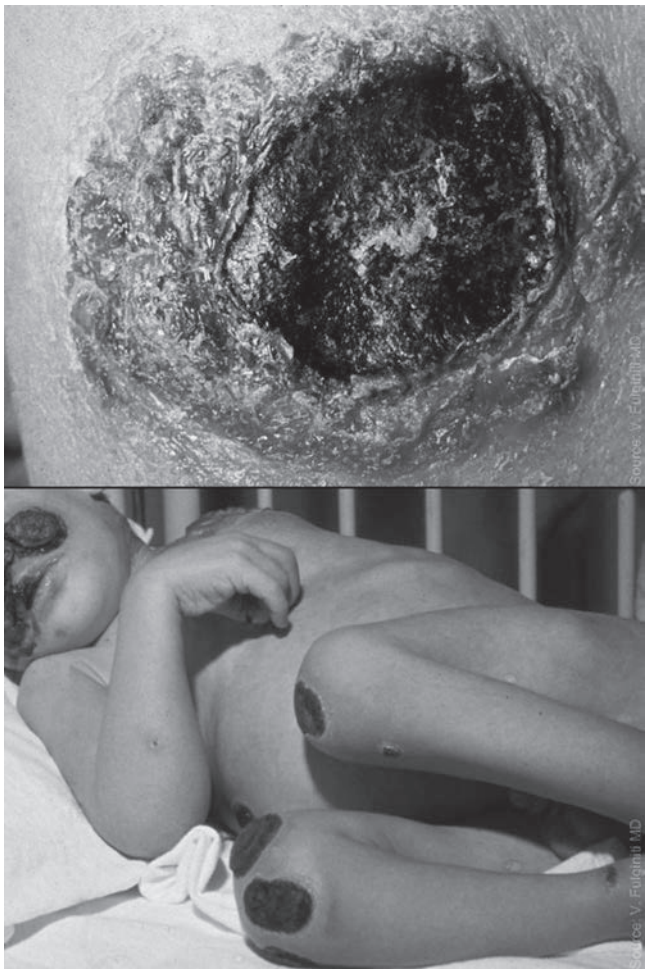

FIGURE 104-10 Progressive vaccinia: in a woman with lymphatic malignancy (*top*) and with dissemination in a child with hypogammaglobulinemia (*bottom*). (From CDC/V. Fulginiti, MD.) (*See color insert.*)

The cause of EV is thought to be from a T-cell immunomodulatory defect. Generalized vaccinia results from viremic spread of virus in presumably healthy individuals (Fig. 104-9).

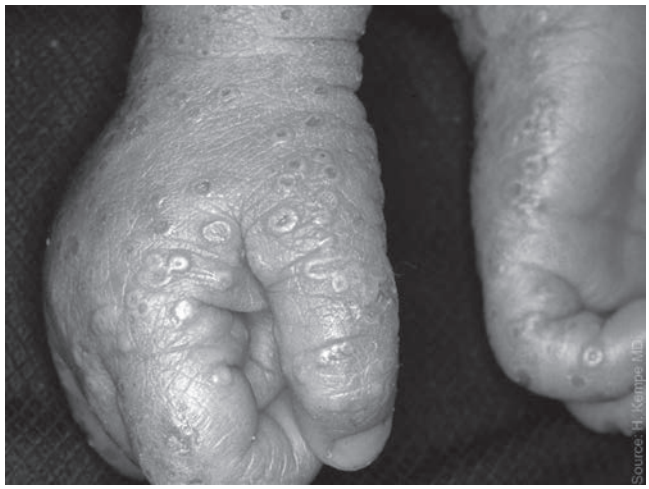

FIGURE 104-9 Generalized vaccinia: in a young boy. (From CDC/H. Kempe, MD.) (*See color insert.*)

However, some patients may have had a minor immunologic defect, most likely an antibody or B-cell deficiency. Congenital vaccinia (fetal vaccinia) is a rare event in which a fetus is directly or secondarily infected after placental or amniotic fluid infection. Congenital infection can lead to fetal or neonatal death. Progressive vaccinia (PV), also known as vaccinia gangrenosa, is the most severe complication following smallpox vaccination (Fig. 104-10). The vaccination site lesion continues to expand leaving necrotic skin behind the advancing edge, and secondary lesions may occur. The severity of PV is determined by the amount of immune deficiency; those with a profound immune defect often die despite copious amounts of intervention. Encephalitis or meningoencephalitis following vaccination has been reported. Approximately 25% of sufferers die and up to one-third of survivors will have a full spectrum of neurologic sequelae (28).

Past rates of adverse reactions gathered from a 10-statewide survey conducted in 1968 and those seen in 2002 to 2003 can be found in Table 104-3. In 1968, complication rates were higher for primary vaccinees than revaccinees: 1,253.8 per million versus 108.2 per million, respectively. With the exception of PV, all other complication rates were higher in primary vaccinees than

TABLE 104-3

Adverse Events from Smallpox (Vaccinia) Vaccination

Complication	*Number of Events/ Million Vaccinees*		*VIGIV Treatment*[a]
	1968[b]	*2002–2004*[c]	
Accidental infection	234.2	145.2	May be indicated for ocular vaccinia not involving the cornea
Eczema vaccinatum	17.0	0	May be indicated if severe
Erythema multiforme	80.0	1.5	Not indicated
Generalized vaccinia	100.7	64.4	May be indicated if severe or patient has underlying immunodeficiency
Myo/pericarditis	—	155.7	Not indicated
Other	128.6	—	Not indicated
Postvaccinial encephalitis	6.1	3.0	Not indicated
Progressive vaccinia	2.4	0	May be indicated depending on patient immune defect

[a]Recommendations from Rotz LD, Dotson DA, Damon IK, et al. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2001. *MMWR Recomm Rep* 2001;50: 1–25.
[b]Data from Lane JM, Ruben FL, Neff JM, et al. Complications of smallpox vaccination, 1968: results from ten statewide surveys. *J Infect Dis* 1970;122:303–309
[c]Data from Neff J, Modlin J, Birkhead G, et al. Monitoring the safety of a smallpox vaccination program in the United States: report of the Joint Smallpox Vaccine Safety Working Group of the Advisory Committee on Immunizations Practices and the Armed Forces Epidemiological Board. *Clin Infect Dis* 2000;46:S258–S270.

revaccinees. Inadvertent inoculation was the most common complication reported in both groups. The "other" complication category was broad in its data capture. Reports ranged from bacterial superinfection, to severe reactions to vaccination, to congenital vaccinia, to melanoma growth in a vaccination scar *(30)*. Data generated from the 2002 to 2003 US civilian and military smallpox vaccination campaigns revealed fewer adverse events than those seen in 1968 (Table 104-3). During this time period, no cases of EV, fetal vaccinia, or PV were noted in either primary or revaccinees (*25*,*31*,32). However, a case of PV was seen in 2009 in a military recruit diagnosed with leukemia shortly after vaccination *(33)*.

Previous surveillance studies, 1960s and earlier, that assessed rates for adverse events following smallpox vaccination did not include cardiac complications. Before 2003, only six cases with cardiac complications had been reported after having received smallpox vaccination. Data gathered from the recent national smallpox vaccination program suggest that myo/pericarditis occurs at a higher rate than previously seen *(34)*. From December 2002 to June 2004, the U.S. Department of Health and Human Services (DHHS) and the U.S. Department of Defense (DoD) vaccinated 667,980 persons. Eighty-three cases of suspected, probable, or confirmed cases of myo/pericarditis were indentified in DoD vaccinees and 21 among DHHS vaccinees. Most cases clustered during the first 7 to 12 days postvaccination. None of these patients had evidence of cardiac damage and <20% of either population reported persistent mild symptoms. Other cardiac events included 26 cases of ischemic cardiac disease resulting in 5 deaths and 7 cases of dilated cardiac myopathy resulting in the need for two heart transplants. While none of the reported ischemic cardiac disease cases clustered temporally with vaccination, a deferral from vaccination was given in 2003 to persons with three or more than three risk factors for ischemic heart disease (Table 104-4) (32). This deferral is still in place today.

The risk of death from smallpox vaccination was estimated at approximately one per million primary vaccinees in mortality data collected from 1959 to 1966 and 1968. The three most common causes were PV, postvaccinial encephalitis, and EV. Of the 68 individuals that died, 70.6% were primary vaccinees, 17.6% were contacts of recently vaccinated individuals, and 11.8% were revaccinees. The most common cause of death in primary vaccinees was postvaccinial encephalitis; in contacts, EV; and in revaccinees, PV. One death in a primary vaccinee was the result of Stevens–Johnson syndrome *(35)*. Five deaths occurred among DoD and DHHS vaccinees from 2002 to 2004—all from ischemic cardiac conditions (32).

Vaccinia immune globulin (VIG) contains γ-globulin fractioned from plasma of persons who have been recently vaccinated with vaccinia. VIG is used to treat some adverse reactions associated with the smallpox vaccine. This can include EV, generalized vaccinia, PV, and severe reactions to inadvertent inoculation. VIG is not recommended for the treatment of vaccinia keratitis, myo/pericarditis, mild instances of inadvertent inoculation, erythematous rashes, or postvaccinial encephalitis. The U.S. Strategic National Stockpile at the CDC stores all lots of VIG and distributes them as needed. VIG is currently the only licensed product for treatment of adverse events. Cidofovir has demonstrated antiviral activity against certain orthopoxviruses

TABLE 104-4

Cardiac Contraindication Screening Questions for Preevent Smallpox Vaccination

1. Have you ever been diagnosed by a doctor as having had any of the following:
   a. A previous heart attack (myocardial infarction)?
   b. Angina (chest pain caused by lack of blood flow to the heart)?
   c. Coronary artery disease (disease in the vessels that bring blood to the heart)?
   d. Cardiomyopathy (heart muscle becomes enlarged and does not work as it should)?
   e. Congestive heart failure?
   f. A stroke or transient ischemic attack (a "mini-stroke" that produces strokelike symptoms but no lasting damage)?
2. Do you have chest pain or shortness of breath with activity (such as walking upstairs)?
3. Are you under the care of a doctor for any other heart condition?
4. Do you have three or more than three of the following:
   a. You have been told by a doctor that you have high blood pressure?
   b. You have been told by a doctor that you have high blood cholesterol?
   c. You have a first-degree relative (e.g., mother, father, sister, or brother) who had a heart condition before the age of 50?
   d. Currently smoke cigarettes?

(Adapted from CDC Smallpox Vaccine: What You Need to Know (Vaccine Information Statement [VIS]) (Updated November 15, 2003).)

in vitro and in animal models but can only be obtained through an investigational new drug protocol. Several other antivirals are in clinical trials to determine their efficacy in treating adverse reactions (28).

HOSPITAL INFECTION CONTROL

Variola virus is viable for a considerable amount of time in the environment. As a result, a room occupied by a smallpox patient, including the objects in it, may become contaminated. Centuries ago, separate hospitals were established specifically for smallpox patients. These separate facilities limited the spread of the disease to other patients and healthcare providers. An outbreak in a German hospital resulted in secondary cases of patients on three different floors of the hospital. Transmission likely occurred via the hospital's air duct system *(36)*. However, an airborne outbreak is a rare occurrence likely due to the size of droplet nuclei. Even though droplet nuclei are expelled when a smallpox patient is breathing, talking, or coughing, experiments at the Infectious Diseases Hospital, Madras, India, determined that virus in these larger particles quickly settled closely on the floor, clothing, objects, or other linens. Virus in smaller sized particles could not be readily detected in the air even at a short distance from the patient. Only seven cases of hospital-acquired smallpox occurred in the Madras hospital that saw about 17,000 cases over a 10-year period, despite smallpox and nonsmallpox patients sharing corridors and barely 20 ft separating the wards *(10)*. However, the smallpox wards at this hospital were "open" allowing considerable air movement through them which could possibly dilute excreted virus *(37)*. Traditional hospitals served as a considerable source of transmission in outbreaks. In a summary of smallpox in Europe from 1950 to 1971, more than half of indigenous smallpox cases were acquired in a medical setting *(15)*. Hospitals and other treatment facilities should be cognizant about the risks associated with smallpox infection for staff and other patients. Plans should include comprehensive procedures that ensure the safety of smallpox and other patients and all staff that may come in contact with a smallpox patient.

There are several sources of information with detailed recommendations and instructions on healthcare and community infection control measures. The first is a consensus statement by the Working Group on Civilian Biodefense. This working group was selected to recommend medical and public health measures in the event of a release of variola (13). The second is a series of guides issued by the CDC, "CDC Smallpox Response Plan and Guidelines," and is freely available online at *http://www.bt.cdc.gov/agent/smallpox/response-plan/*. These guides cover a wide range of topics including surveillance and case reporting (Guide A), vaccination guidelines (Guide B), infection control measures for healthcare and community settings (Guide C), specimen collection (Guide D), communication plans (Guide E), and environmental control (Guide F) (38).

Designated Facilities

Preparedness for a smallpox outbreak must include plans to identify appropriate facilities to limit transmission and treat patients, including confirmed variola infections and febrile contacts. The CDC Response Plan outlines three types of facilities that should be identified, C, X, and R (Table 104-5). Type C facilities are designated for confirmed and suspect cases of smallpox; Type X facilities house febrile contacts of smallpox cases; and Type R facilities house asymptomatic contacts for observation. Guide C, Part 1 of the Response Plan has facility details and procedures for isolation and transportation of known or suspect cases (38).

Type C (C = contagious) facilities are characterized by nonshared air or ventilation systems and high particulate air filtration. Type C facilities must be equipped to maintain daily living and provide complex medical care. Type C facilities also can house vaccinated febrile contacts with a rash and atypical suspect smallpox cases. If a patient is admitted to a hospital, the ill patient should be quarantined to a negative pressure room with high particulate air filtration and transferred as soon as possible to a designated Type C facility. *All persons* entering a Type C facility must be vaccinated due to the risk of exposure. This includes suspect cases because diagnosis errors can occur. Varicella testing is recommended prior to admission to a Type C facility because varicella infection can be confused with variola (38).

TABLE 104-5

Facilities for Use in a Smallpox Emergency

Facility Type	*Purpose*	*Individuals Housed*	*Requirements*
Type C	House confirmed and suspect cases; limit exposure of susceptible individuals	• Vaccinated confirmed cases of smallpox • Vaccinated febrile contacts with rash • Vaccinated atypical suspect cases of smallpox	• Nonshared air conditioning, heating, and ventilation system • Exhausts 100% of air to the outside through a HEPA filter *or* is ≥100 yards from an occupied building or area • Has water, electricity, heating, cooling, and closed-window ventilation to maintain daily living and medical care activities • Has a telephone or intercom system • Ability to provide complex medical care • Controlled access
Type X	House febrile contacts during observation period	• Vaccinated febrile contacts without rash	• Nonshared air conditioning, heating, and ventilation system • Exhausts 100% of air to the outside through a HEPA filter *or* is ≥100 yards from an occupied building or area • Has water, electricity, heating, cooling, and closed-window ventilation to maintain daily living and medical care activities • Has a telephone or intercom system • Ability to provide basic medical care
Type R	House asymptomatic contacts for fever observation	• Asymptomatic contacts for 18 d postexposure or 14 d postvaccination • Contacts who refuse vaccination	• No strict requirements; may be person's residence

(Adapted from CDC Smallpox Response Plan and Guidelines, Guide C, Part 1.)

Type X (X = uncertain diagnosis) facilities are characterized by the same ventilation and filtration systems, but they are required to provide basic medical care rather than complex medical care. Type X facilities are designed to observe febrile contacts to see if they develop any further symptoms, particularly a rash. All febrile contacts should be treated as suspect cases, even if the fever is likely due to recent smallpox vaccination. If a rash develops in a patient housed in a Type X facility, the patient should be moved to a Type C facility for further evaluation. Fever surveillance can continue at the patient's residence (Type R facility) 5 days after being held at a Type X facility (38).

Type R (R = residential) facilities are designated for asymptomatic contacts under fever surveillance for 18 days postexposure or 14 days postsuccessful vaccination. Type R facilities are residential facilities such as the patient's home or a designated hotel. Asymptomatic contacts are permitted to continue their daily activities within 20 mi. of their residence while maintaining daily contact with a health department. Asymptomatic contacts that develop two successive fevers ≥101°F should be transported to a Type X facility (38).

Should a larger outbreak occur, patients can be cared for under home isolation and confinement. This will not be the best option for all patients, however, and the working group recommends that public health officials designate a specific hospital or standalone building for smallpox patient care, containment, and isolation from the general population (13).

Healthcare Personnel Precautions

There is a high probability for multiple transmission events before a patient is diagnosed with variola because transmission can occur at all stages of the rash illness. A patient may not be diagnosed with smallpox for 12 to 14 days postexposure; the delay in time is due to an asymptomatic period, a flu-like prodromal period, and several days to accurately recognize and diagnose the disease. Hemorrhagic smallpox, a rare form of smallpox, is particularly worrisome, as the duration of illness is very short and death often occurs within 5 or 6 days of rash onset. The hemorrhagic form may not be recognized or diagnosed until the patient is close to death and highly contagious; therefore, in the event of an outbreak, all hospital staff must be alerted to the possibility and identification of any

severe illness. Transmission may occur within a hospital by contact with respiratory droplets, and there is the likelihood, albeit lower, of transmission via contact with linens and bedding (13).

Given the transmission potential in a highly immunologically naive healthcare personnel population, the working group has recommended immediate vaccination of all hospital staff as well as patients in the event of an outbreak (13). Only healthcare workers that are vaccinated should care for suspect or confirmed smallpox patients. If there are no vaccinated healthcare workers, then a limited number of unvaccinated workers should wear N95 masks while caring for the patient (38). Vaccination should also be offered to mortuary and morgue workers who may come into contact with dead bodies. Prophylactic VIG treatment should be considered for individuals who are immunocompromised or have contraindications to live vaccinia vaccination (13).

Any person caring for smallpox patients must adhere to standard, contact, and airborne precautions. These precautions may require use of disposable gloves, gowns, masks, eye protection, and N95 respirators. These items should be discarded in biohazard waste immediately after caring for the patient (38,*39*).

Environmental Control

Variola virus has a lipid envelope and is remarkably stable when in a proteinaceous milieu. Poxviruses show high resistance to drying and have an increased temperature tolerance—a feature enhanced depending on the material in which it is found, such as crust, blood, or other excretions. When compared to other enveloped viruses, poxviruses have a lower lipid content in their envelope and a smaller quantity of carbohydrates. Although poxviruses are remarkably sensitive to commercial chemical treatment and disinfection, the reduction of lipid content makes them less sensitive to organic solvents *(40)*. The disinfectants listed in Table 104-6 are sufficient for decontamination of surface areas in smallpox patient care areas (38). In addition, quaternary ammonium compounds have been proven effective in disinfection of objects contaminated with poxviruses. A summary determining the efficacy of commercially available disinfectant formulations against poxviruses has been described elsewhere *(40)*. Reusable medical instruments and patient-care devices should be cleaned after use using previous standardized protocols then sterilized or treated with high-level disinfection depending on their reuse. Reusable medical instruments should be cleaned and sterilized (38).

Low- to intermediate-level disinfection with Environmental Protection Agency–registered chemical germicides can clean environmental surfaces frequently touched with hands, as well as floors and tabletops. Routine hospital cleaning and disinfection procedures are adequate for sanitizing nonporous surfaces such as the interior surfaces of ambulances. Fumigation is not indicated for environmental containment of variola virus. There are no special procedures or schedules for cleaning carpeted floors or furniture. A high efficiency particulate air (HEPA) filtered vacuum or commercially available furniture cleaner are adequate. Vacuum waste should be disposed of as routine solid waste (38).

Bedding and linen should be handled carefully as to not disperse any particles that may contain viable virus. A water-soluble bag is recommended for transport of linen that will be laundered in an effort to minimize environmental contamination and exposure. Personnel handling laundry should do so with appropriate personal protective equipment (PPE), including N95 respirators. Laundry should be done in an area with negative air pressure and physically separate from the area where clean laundry is dried, sorted, and folded. Standard laundry protocols may be followed. The inclusion of a chlorine bleach with hot water and a hot airdry may provide additional levels of protection (38). Alternatively, bedding and linen can be discarded in biohazard waste to be autoclaved or incinerated.

Medical waste from smallpox patients should be contained, subjected to decontamination treatment, and then discarded in accordance with currently approved methods. Human remains are often not considered anatomical or pathological waste. Barrier precautions, safe handling and disposal of embalming chemicals, proper ventilation, and environmental surface disinfection can protect mortuary personnel preparing bodies for burial or cremation.

TABLE 104-6

Chemicals Used on Environmental Surfaces for Disinfection[a]

Chemical	*Concentration*[b]
Ethyl alcohol	40%
Isopropyl alcohol	30%
Benzalkonium chloride	100 ppm
Sodium hypochlorite	200 ppm
*Ortho*phenylphenol	0.12%
Iodophor	75 ppm

[a]Inactivation after 10 min contact time at room temperature.
[b]Minimum concentration.
(Adapted from CDC Smallpox Response Plan and Guidelines, Guide F.)

CONSIDERATIONS FOR A BIOTERRORISM PLAN

Preparedness for a bioterrorism outbreak requires extensive planning by hospitals and other public health institutions. Early recognition and identification of smallpox patients is one of the first defenses a hospital has against the spread of smallpox within its walls. The last outbreak and cases of smallpox in the United States occurred in 1949 in the Lower Rio Grande Valley of Texas. The origin of the outbreak remained unknown although several cases were thought to have contracted smallpox while in the hospital from a patient admitted originally with a febrile illness. In all, eight cases and one death were reported. Smallpox was not suspected in six of the cases until the death of the fourth identified case. Several cases of smallpox were missed likely because of the prevalence of chicken pox at the time *(41)*. Similar outbreaks were seen in 1947 in New

York City and in 1950 in Glasgow, Scotland, in which a single case infected multiple people in a hospital setting before being correctly identified *(42,43)*.

Identification of smallpox today may prove even more difficult given that the majority of practicing clinicians have never seen a case of smallpox. The development of the algorithm *Evaluating Patients for Smallpox: Acute, Generalized Vesicular or Pustular Rash Protocol* by CDC was designed to help clinicians evaluate patients with suspicious rashes (*http://emergency.cdc.gov/agent/smallpox/diagnosis/evalposter.asp*). A multicenter study conducted on hospital admissions for rash or rash-like illness over a 12-month period beginning in late 2003 assessed if smallpox risk was accurately classified. Of those eligible and classified, CDC and physicians within the hospitals were in agreement 84% of the time. Discrepancies in classification were mainly due to the characteristics assigned to a patient's rash—deep seated, firm, well circumscribed, and in same stage of development. This same issue has been noted in inquiries reporting possible smallpox cases to CDC's Emergency Operations Center. Physicians may describe lesions as firm, deep seated, and in the same stage of development but evaluation of images submitted by the physicians to CDC often are interpreted otherwise. Education of physicians, other healthcare, or public health providers about the correct description of dermatological terms, smallpox diagnosis, and management may decrease this discrepancy *(44)*. To further strengthen clinician awareness on diagnosing smallpox, training efforts should be undertaken and may encompass lectures, handouts, posters, and reliable Internet resources.

The capabilities to detect and swiftly respond to a release of a biological weapon include measures that are often used to respond to naturally occurring infectious diseases or emerging infections *(45)*. This typically includes the ability to provide airborne isolation and other appropriate infection control measures. Healthcare workers with contact to patient skin, respiratory secretions, or other bodily fluids may accidently infect themselves or other patients. To prevent the spread of smallpox, and other infectious agents, healthcare workers should comply with Healthcare Infection Control Practices Advisory Committee guidelines and wear PPE such as gloves, gowns, masks, head and shoe covers, and eye protection if recommended. Regular exercises in proper donning and safe removal of PPE and healthcare worker understanding of the route of transmission can increase adherence to regulations *(46)*. Infection control measures for managing a patient with smallpox in a non–smallpox-designated facility can be found in Table 104-7.

Multiple groups and agencies must work together efficiently and effectively to isolate and contain the spread of smallpox. Hospitals, public health departments, and law enforcement agencies at local, state, and federal levels will be involved and integrated into an outbreak response. Communication across all jurisdictions will facilitate a coordinated response. There are several preevent preparedness items that are recommended by the CDC Response Plan (Table 104-8). A response plan should also include a directory of public health authorities and these resources should be readily available. This may include public health facilities, such as local or state health departments and laboratories, law enforcement at all levels, CDC Emergency Operations Center, or other resources *(47)*.

In addition to strengthening the emergency response system, hospitals should be aware of possible treatment options, create vaccine stockpiles, and maintain laboratory capabilities for diagnostic testing. There is no proven treatment for clinical smallpox. Medical management is mainly supportive and may include fluids, electrolytes, and antibiotics. Informational material about the smallpox

TABLE 104-7

Infection Control Precautions for Suspected or Confirmed Infectious Smallpox Patients in a Non–Smallpox-Designated Facility

1. Select route to transport the patient through the hospital to an airborne infection isolation room. Choose the most direct route to the room, consider ease of decontamination if required, and consider isolation from other people including use of nonpublic elevators if possible.
2. Cover patient with linen sheet and place a surgical mask (or N95 respirator) on the patient during transport through the hospital to the isolation room, or from the isolation room to other areas within the hospital, to decrease the chance of contaminating objects in the area and droplet exposure to other individuals.
3. Place the patient in an airborne infection isolation room to prevent airborne transmission to other parts of the facility.
4. Follow standard, contact, and airborne precautions while patient is isolated at the facility.
   a. Wear disposable gowns and gloves to enter contaminated areas; discard used gowns and gloves before leaving area.
   b. Wear fit-tested N95 masks.
5. All protective clothing, including sheet covering patient, should be disposed of in biohazard bags before leaving the airborne infection isolation room.
6. Restrict the number of people entering the patient's room to only those needed for patient care, investigation, and facility maintenance.
   a. Log/register all persons who enter and leave the patient's room.
7. Vaccinate all personnel caring for patient.
   a. If nonvaccinated personnel are needed to provide patient care before they are vaccinated or until vaccination is successful, temperature recordings should be taken twice daily.

(Adapted from CDC Smallpox Response Plan and Guidelines, Guide C, Part 1.)

TABLE 104-8

Preevent Preparedness Activities

Public health and law enforcement

a. Review local and state legal statutes that allow public health intervention and implementation of isolation and quarantine measures.
b. Identify personnel at local and state levels who are responsible for coordination of public health interventions.
c. Identify law enforcement personnel to enforce isolation and quarantine orders.

Facilities and maintenance

a. Identify facilities used to isolate and treat smallpox patients and febrile contacts.
b. Establish procedures to activate facilities for smallpox patients.
c. Establish procedures for controlling access to facilities.
d. Establish procedures for disposal of medical waste.
e. Establish procedures for handling and disposal of laundry.
f. Plan for food service for patients and building occupants.

Personnel

a. Identify personnel that will treat patients.
b. Identify personnel that will maintain facilities where smallpox patients will be housed.
c. Ensure that all staff who will care for smallpox personnel have been vaccinated.
d. Establish procedures to monitor the health of all personnel.
e. Establish plans for care of ill personnel.

(Adapted from CDC Smallpox Response Plan and Guidelines, Guide C, Part 1.)

vaccine should be readily available for personnel when the need arises. While orthopoxvirus testing is reserved for LRN laboratories, hospitals can rapidly rule out other causes of rash illness in low-risk patients. Specimens from high-risk patients should immediately be referred to a LRN laboratory capable of variola-specific testing prior to any other diagnostic assay. High-risk patient specimens require special collection, handling, and transport procedures. The outer surface of specimen containers should be properly decontaminated and packaged and transported within International Air Transport Association regulations. Successfully vaccinated personnel (within the last 3 years) wearing appropriate barrier protection should be involved in specimen collection before giving consideration to using unvaccinated personnel. If unvaccinated personnel must be used, they should wear a fit-tested N95 mask and have no contraindications to vaccination.

CONCLUSION

Preparations for a smallpox release should involve a coordinated effort among public health officials, state and local governments and law enforcement, treatment facilities, and healthcare personnel. Preparations require thoughtful consideration, and planning must take into account alternative responses. These include action items specific to public health and law enforcement, facilities and maintenance, and personnel who are at high risk of exposure to a smallpox patient. Given the marked decline in the number of healthcare workers receiving smallpox vaccination since 2003, hospitals must be prepared to vaccinate their personnel within a limited amount of time once a smallpox case has been detected. Additional public health control measures will incorporate surveillance, vaccination, and isolation of smallpox cases. Isolation measures may reintroduce the establishment of C, X, or R facilities to house selected groups of individuals. Hospitals and public health officials can never be overprepared for a release of variola; and existing outbreaks of other infectious diseases, particularly respiratory diseases, can be used to strengthen control practices and other response strategies.

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INDEX

Note: Page numbers followed by f indicate figures; those followed by t indicate tables.

B

C

E

F

G

H

J

K

L

N

O

P

S

T

U